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Mendelian Randomization Implicates Bidirectional Association between Myopia and Primary Open-Angle Glaucoma or Intraocular Pressure

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Purpose: Observational studies suggest that myopic eyes carry a greater risk of primary open-angle glaucoma (POAG); however, the evidence for this association is inconsistent. This may be the result of confounding factors that arise from myopia that complicate clinical tests for glaucoma. This study used Mendelian randomization (MR) analysis to determine genetic causal associations among myopia, glaucoma, and glaucoma-related traits that overcome the effects of external confounders.

Design: Bidirectional genetic associations between myopia and refractive spherical equivalent (RSE), POAG, and POAG endophenotypes were investigated.

Participants: Data from the largest publicly available genetic banks (n = 216,257−542,934) were analyzed.

Methods: Multiple MR models and multivariate genomic structural modeling to identify significant mediators for the relationship between myopia and POAG.

Main Outcome Measures: Genetic causal associations between myopia and POAG and POAG endophenotypes.

Results: We found consistent bidirectional genetic associations between myopia and POAG and between myopia and intraocular pressure (IOP) using multiple MR models at Bonferroni-corrected levels of significance. Intraocular pressure showed the most significant mediation effect on RSE and POAG (Sobel test, 0.13; 95% confidence interval, 0.09−0.17; $P = 1.37 \times 10^{-8}$).

Conclusions: A strong bidirectional genetic causal link exists between myopia and POAG that is mediated mainly by IOP. Our findings suggest that IOP-lowering treatment for glaucoma may be beneficial in myopic eyes, despite the challenges of establishing a clear clinical diagnosis.

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Myopia is a major global health issue with a growing disease burden. By 2050, it is estimated that almost 5 billion people will be myopic, of whom 1 billion will have high myopia.[1] Several studies indicate an association between myopia and glaucoma,[2,3] including recent meta-analyses that describe increasing odds of glaucoma with greater severity of myopia.[4,5] Higher myopia also has been associated with significantly higher intraocular pressure (IOP), which is a definitive risk factor for primary open-angle glaucoma (POAG).[6−8] In line with these reports, the World Health Organization recommends investigating glaucomatous optic neuropathy in patients with high myopia.[9] However, several studies have reported conflicting evidence about the association of myopia and glaucoma. Lee at al[10] studied on the impact of myopia on the association of long-term IOP fluctuation with glaucoma progression and suggested that additional IOP-independent mechanisms may underlie POAG risk in myopic eyes. Doshi et al[11] also found no significant association between higher degrees of myopia and glaucoma progression, which was qualified by optic disc and visual field changes. Several reasons why evidence for the myopia-glaucoma association is inconsistent can be proposed.

The presence of structural confounders such as optic disc and peripapillary deformation,[12−14] commonly seen in highly myopic eyes resulting from elongation of the eyeball, may cause the appearance of neuroretinal rim thinning that resembles glaucoma.[15−17] High myopia also is associated with abnormal circumpapillary retinal nerve fiber layer (RNFL) measurements; thus, decreased RNFL thickness may not be an effective diagnostic marker for glaucoma in patients with high myopia.[18,19] In addition, visual field

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testing may reveal deficits in patients with myopia alone, which poses as a functional confounder in routine glaucoma investigations.[20,21] Overall, it is difficult to characterize the association of myopia with glaucoma at present, especially when predicting the severity and progression of the latter. However, prompt and accurate diagnosis of glaucoma is essential to provide the appropriate treatment to improve visual prognosis.[22] This poses a challenging clinical dilemma.

We proposed that Mendelian randomization (MR) analysis, explained by Davies et al,[23] may better our understanding of the issue. Rather than investigating risk factors and the outcomes alone as outlined by observational studies, MR analysis makes use of genetic variants that are distributed independently in the population and fixed from birth to support causal inferences about the effects of the modifiable risk factors of interest.[23,24] By doing so, it overcomes unmeasured confounding that statistical adjustment cannot correct fully, which is a major limitation on the findings from observational studies.[25,26] The findings of MR studies do not have to be juxtaposed against those of traditional observational studies. In difficult situations such as the abovementioned association between myopia and glaucoma progression, if MR findings converge on similar results as observational studies and demonstrate the consistency of association, then confidence in noted associations between the two pathologic features is greater.

In the current study, we examined multiple levels of statistical evidence for the genetic correlation between myopia and glaucoma based on existing data from genome-wide association studies in both White and Asian populations. We further explored genetic associations between myopia and glaucoma-related endophenotypes, including intraocular pressure (IOP), RNFL thickness, vertical cup-to-disc ratio, optic disc area, and optic cup area.

Methods

Specific ethical approval was not required for this study because all data were obtained from sources available to the public. This research adhered to the tenets of the Declaration of Helsinki. Individual patient-level consent was not required.

Study Samples

Genome-Wide Association Study Dataset for Refractive Error. Genetic associations for myopia were obtained from genome-wide association study (GWAS) summary statistics in the meta-analysis by Hysi et al.[27] A total of 542 934 individuals of European descent were included in this meta-analysis, which combined 5 independent studies: 2 separate groups of UK Biobank (UKB) participants (UKB 1 and 2 groups), the Genetic Epidemiology Research in Adult Health and Aging Study, the 23andMe personal genomics company customer base, and the Consortium for Refractive Error and Myopia (CREAM) Study.

Associations for myopia were assessed on refractive spherical equivalent (RSE) in diopters in the UKB 1 (102 117 individuals), the Genetic Epidemiology Research in Adult Health and Aging Study (34 998 individuals), and the CREAM (34 079 individuals) cohorts, whereas the analysis of the UKB 2 and 23andMe groups relied on categorical definitions of myopic status (108 956 people with myopia and 70 941 people without myopia in the UKB 2 group; 106 086 self-reported people with myopia and 85 757 people without myopia from the 23andMe group). Therefore, we converted the z scores reported by Hysi et al[27] into β coefficients to standardize associations with myopia in our study based on RSE.

The association statistics (β coefficient and standard error [SE]) from the meta-analysis by Hysi et al[27] for all lead single-nucleotide polymorphisms (SNPs) are shown in Tables S1 and S2 (available at www.aaojournal.org). However, the summary statistics from this GWAS meta-analysis, containing the z score, P value, and allele frequency for each genetic variant, excluded the 23andMe cohort because of data restrictions. Therefore, in the MR analyses of myopia on POAG, we selected instrumental variables (IVs) based on lead SNPs that came from a meta-analysis of all 542 934 participants, but in the inverse MR analysis, the genetic instruments were based on 351 091 participants from the other 4 cohorts without 23andMe individuals.

Burgess and Davey Smith[28] reported that SE multiplied by $\sqrt{MAF(1-MAF)}$, where MAF is the minor allelic frequency, should be a constant for all variants, assuming that the sample size is the same for all variants. We calculated the average value of this expression over the UKB 1, Genetic Epidemiology Research in Adult Health and Aging Study, and CREAM Study cohorts in terms of every 391 lead SNPs, and then calculated the average value across 391 lead SNPs as an estimate of the constant (0.007878) in diopters. Then, we computed SE for all available genetic variants in summary statistics based on allele frequency. β coefficients were estimated by z score multiplied by SE and represent diopter changes in refractive error per additional copy of risk allele.

The CREAM-EUR (Consortium for Refractive Error and Myopia - European Cohort),[29] a meta-analysis including 44 192 individuals of European descent, and CREAM-ASN (Consortium for Refractive Error and Myopia - Asian cohort),[30] a meta-analysis comprising 8376 individuals of Asian descent, were used for sensitivity testing. For both studies, β coefficients represent diopter changes in refractive error per copy of the risk allele.

Genome-Wide Association Study Dataset for Primary Open-Angle Glaucoma. Genome-wide association study summary results for POAG according to International Classification of Diseases, Ninth and Tenth Revision, codes were obtained from the International Glaucoma Genetics Consortium (IGGC).[31] In brief, a meta-analysis of 19 studies was conducted on a total of 16 677 patients and 199 580 control participants of European descent. Independent genome-wide significant SNPs and their summary statistics were provided in Supplementary Datasets 1 and 2 from Gharahkani et al.[31] We used 6935 patients and 46 523 control participants of Asian descent from the IGGC study for sensitivity testing (see details next).

Genome-Wide Association Study Dataset for Intraocular Pressure and Other Glaucoma Endophenotypes. We obtained summary statistics for IOP in participants from the UKB of European descent. The GWAS results for corneal-compensated IOP were available for left eyes (field identifier, 5262; n = 76 510) and right eyes (field identifier, 5254; n = 76 630), separately, from the Neale laboratory.[32] We also downloaded GWAS summary statistics for glaucoma endophenotypes from studies in European populations, including vertical cup-to-disc ratio,[33] RNFL thickness,[34] optic cup area,[35] and optic disc area.[35]

Heritability and Genetic Correlation

We used a linkage disequilibrium score regression (LDSC) model[36,37] to estimate SNP heritability (the proportion of the phenotypic variance of a trait that can be explained by common genetic variants) and pairwise genetic correlation among RSE, POAG, and glaucoma endophenotypes. We reformatted summary

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statistics to the precomputed linkage disequilibrium scores based on the 1000 Genomes European reference data and kept only genetic variants overlapping with a HapMap 3 SNP list provided by the LDSC model, which includes common SNPs, usually of high quality, in genotyping and imputation processes.

Mendelian Randomization Analyses for Myopia and Glaucoma

Multiple MR models were used in our study to address potential issues with violation of assumptions. We used 6 MR methods to investigate the putative causal relationship between myopia and POAG, including inverse variance weighting,[38] MR-Egger,[39] generalized summary data-based MR,[40] weighted median model,[41] weighted mode-based estimator,[42] and causal analysis using summary effect estimates (CAUSE)[43] models. Ideally, a causal model assumes that all genetic instruments are valid and no pleiotropy, which refers to the effect of the genetic variant on multiple pathways affecting the outcome, exists. Inverse variance weighting assumes no measure error for IVs and 0-average uncorrelated pleiotropy, that is, the overall effect of genetic variants acting directly on the outcome is 0. We reported results for both unpenalized and penalized random-effects inverse variance weighting models based on the first-order term from the Δ expansion of variance for the ratio estimate. Mendelian randomization-Egger assumes that all IVs are valid and requires that any pleiotropic effects act directly on the outcome. The intercept test, which is estimated as part of the MR-Egger analysis, assesses the evidence of the existence of uncorrelated pleiotropy if the intercept term is significantly different from 0. We applied a penalty for MR-Egger model to downplay the contribution of outliers. Generalized summary data-based MR assumes no correlated pleiotropy that arises from shared biological pathways involving unmeasured confounders of both exposure and outcome and implements the heterogeneity in dependent instrument outlier method to identify and exclude genetic instruments that are likely to have large uncorrelated pleiotropic effects. The weighted median model has the ability to identify true causality if up to 50% of IVs are invalid by measuring the weighted medium value of the IV ratios. Similarly, the weighted mode-based model splits IVs into multiple groups based on their estimated effect and uses only the largest group of IVs to estimate causal effect. The estimator is robust even if most IVs are invalid. These two methods also are capable of accounting for some degree of pleiotropy regardless of types.

The aforementioned MR models rely on strong assumptions and may lead to false conclusions when nonzero pleiotropy exists. Therefore, we separately used the CAUSE model, which is capable of accounting for both correlated and uncorrelated pleiotropy, by including a large set of pruned SNPs (linkage disequilibrium $r^2 < 0.01$) with a P value threshold of 1×10^{-3} and clump distance of 500 kb, and distinguishes between causal and sharing models (i.e., one with correlated pleiotropy) by implementing a Bayesian model comparison approach.

We implemented bidirectional MR analyses using all 6 models to test for any causal relationship between myopia and POAG (Table 1). Our methods for the selection of IVs are provided in the Supplemental Material (available at www.aaojournal.org).

Sensitivity Tests

We conducted several types of sensitivity analyses (Table 1) to test the robustness of our results. First, we further excluded SNPs with ambiguous alleles, that is, A/T or G/C from our original selection of IVs, resulting in 331 nonambiguous IVs for MR analyses of myopia on POAG and 47 IVs for MR of POAG on myopia. Second, we assessed the causal effect of myopia on POAG using summary statistics in European participants from the CREAM cohort, where myopia was defined as RSE in diopters, without requiring transformation of z score statistics.[29] A total of 24 IVs were included in these MR models. Third, we investigated the causal relationship between myopia and POAG in Asian populations using GWAS data of CREAM-ASN and control participants of Asian descent from the IGGC. The forward and inverse MR analyses for myopia-POAG and POAG-myopia included 30 and 9 IVs, respectively.

Mendelian Randomization Analyses for Intraocular Pressure and Other Glaucoma Endophenotypes

We also tested bidirectional casual associations of RSE on IOP and other glaucoma endophenotypes, including vertical cup-to-disc ratio, RNFL, optic cup area, and optic disc area. All samples were of European ancestry. The analysis for myopia-IOP contained 2 GWAS datasets for IOP from UKB (left and right eye, separately).[32] Forward analyses were based on 408 independent IVs that showed genome-wide significance for RSE. The inverse analyses contained a set of independent instrumental SNPs that were determined from clumping analyses implemented in PLINK version 1.90, using parameters $r^2 = 0.01$, 500-kb windows, and $P = 5 \times 10^{-8}$. All 6 MR models were applied to test bidirectional causal effects. An additional requirement for the generalized summary data-based MR model was that at least 10 IVs were used to achieve sufficient test power.

Genomic Structural Equation Modelling

Genomic structural equation modeling (SEM) enables the investigation of multivariate genetic architecture to offer novel insights into relationships across multiple phenotypes using summary statistics that were not measured in the same samples. It is unbiased by sample overlap and sample size imbalances.[44,45] We proceeded with genomic SEM to explore the mediation effect of glaucoma endophenotypes in the path between RSE and POAG. We included optic cup area and optic disc area but excluded vertical cup-to-disc ratio from genomic SEM to avoid model convergence problems that may arise because of the high correlation among them. First, we reformatted GWAS summary statistics and retained only shared SNPs with the Hapmap 3 SNP list. We made a genomic SEM that consists of indirect pathways of 4 mediators—namely, IOP, RNFL thickness, optic cup area, and optic disc area—and covariance between mediators. We also trained a saturated model that demonstrated a direct pathway from RSE to POAG (Fig S1, available at www.aaojournal.org). The product of standardized factor loadings within an indirect path measures the mediation effect. We used the Sobel method to construct a 95% confidence interval (CI) of mediation effect and to obtain P values (Supplemental Material).[46]

Statistical Software

PLINK version 1.90[47] was used to perform clumping analyses with 1000 Genomes phase 3 of the European population as a reference panel. Generalized summary data-based MR analysis was performed using the R package gsmr version 1.0.9 developed by the (Genome-wide Complex Trait Analysis) GCTA team,[48] where we set the minimum number of independent genome-wide significant SNPs required as 10. We calculated linkage disequilibrium correlation matrix for genetic variants using 1000 Genomes phase 3 reference data with matched populations. The heterogeneity in the dependent instrument outlier approach was applied to remove SNPs that act directly on outcome because of

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Table 1. Summary of Study Cohorts, Number of Instrumental Variables, and Mendelian Randomization Analyses Performed

Exposure	Outcome	Population	No. of Instrumental Variables	Inverse Variance Weighting	MR-Egger	Weighted Median	Weighted Mode-Based Estimator	Generalized Summary Data based Mendelian Randomization	Causal Analysis Using Summary Effect Estimates
Main MR analyses									
RSE (Hysi; n = 542 934*)	POAG (IGGC; n = 216 257*)	European	408	✓	✓	✓	✓		✓†
POAG (IGGC; n = 216 257*)	RSE (Hysi; n = 351 091*)	European	57	✓	✓	✓	✓	✓	✓
Sensitivity MR analyses									
RSE (CREAM_EUR; n = 44 192*)	POAG (IGGC; n = 216 257*)	European	24	✓	✓	✓	✓	✓	NA‡
RSE (CREAM_ASN; n = 8376*)	POAG (IGGC; n = 46 523*)	Asian	30	✓	✓	✓	✓	✓	✓
POAG (IGGC; n = 46 523*)	RSE (CREAM_ASN; n = 8376*)	Asian	9	✓	✓	✓	✓	✓	✓

CREAM = Consortium for Refractive Error and Myopia; CREAM_ASN = Consortium for Refractive Error and Myopia - Asian cohort; CREAM_EUR = Consortium for Refractive Error and Myopia - European cohort; IGGC = International Glaucoma Genetics Consortium; Hysi = Hysi et al[27]; MR = Mendelian randomization; POAG = primary open-angle glaucoma (case-control); RSE = refractive spherical equivalent.

*Number of samples in the genome-wide association studies.

†CAUSE analysis used summary statistics on a total of 351,091 Europeans without 23andMe cohort in Hysi's paper.

‡Genome-wide summary statistics were not available.

pleiotropy. The CAUSE model was implemented by R package CAUSE version 1.2.0.0335. We used R package MendelianRandomization version 0.5.1 to perform the other 4 MR models. We applied R package GenomicSEM version 0.0.5 for mediation analysis. Bonferroni thresholds were determined based on the number of MR models used in each analysis and were set as $P \leq 8.33 \times 10^{-3}$ (0.05/6).

Results

Genetic Correlation among Myopia, Primary Open-Angle Glaucoma, and Glaucoma Endophenotypes

We applied LDSC modeling to estimate SNP heritability (Table 2) for RSE as an indicator of myopia and POAG. The heritability was 18% (95% CI, 17%−18%) for RSE and was 26% (95% CI, 22%−30%) for POAG. We then estimated the bivariate genetic correlation (Table 2) between RSE and POAG ($rg = 0.16$; $P = 4.81 \times 10^{-10}$). The intercept of genetic covariance between RSE and POAG was 0.02 (SE, 0.007), suggesting a mild sample overlap between RSE and POAG datasets. We further estimated pairwise genetic correlation among RSE, POAG, and multiple glaucoma endophenotypes using the bivariate LDSC method. Intraocular pressure was significantly genetically correlated with RSE ($rg = 0.18$; $P = 8.91 \times 10^{-10}$; Table S3, available at www.aaojournal.org). We also found strong genetic correlations between IOP and POAG ($rg = 0.67$; $P = 1.95 \times 10^{-47}$) and between optic cup area and POAG ($rg = 0.56$; $P = 1.35 \times 10^{-30}$). The Bonferroni-corrected P value threshold was set at 3.33×10^{-3} for 15 pairwise comparisons of all 6 glaucoma endophenotypes.

Genetic Associations of Variants with Disease Outcomes

We conducted bidirectional MR analyses to investigate causal associations between myopia and POAG, with the rationale that consistent and significant results across different models reveal robust relationships (Table 1). Multiple MR models (n = 6) were used to identify consistent trends in our study. Using data from European populations, myopia showed a causal association with POAG risk in most of our MR models, and vice versa in some models, at a Bonferroni-corrected threshold of significance ($P \leq 8.33 \times 10^{-3}$, based on 0.05/6; Table 4). These trends persisted with the removal of ambiguous IVs. The CAUSE model, which considers a separate question of whether it is possible to distinguish a causal association from a sharing model with correlated pleiotropy, also found significant bidirectional associations ($P < 0.05$) between myopia and POAG ($P = 0.024$ for RSE-POAG and $P = 0.019$ for inverse analysis; Tables S5 and S6, available at www.aaojournal.org). On applying sensitivity tests to determine the causal effect of myopia on POAG from the CREAM cohort without transformation of z score statistics, the causal association of myopia on POAG still held true at a statistically significant level ($P = 0.05$), whereas MBE and generalized summary data-based MR models reached the Bonferroni correction threshold ($P \leq 8.33 \times 10^{-3}$; Table S7, available at www.aaojournal.org). However, our observations in Asian populations from the IGGC and CREAM cohorts showed consistent trends with the findings in European populations, although this did not reach statistical significance (Table S5).

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Table 2. Heritability and Genetic Correlation between Refractive Spherical Equivalent and Primary Open-Angle Glaucoma

	Heritability		Genetic Correlation		
Trait	h^2	Standard Error	Coefficient	Standard Error	P Value
RSE*	0.18	0.01	0.16	0.03	$\mathbf{4.81 \times 10^{-10}}$
POAG†	0.26	0.02			

POAG = primary open angle glaucoma; RSE = refractive spherical equivalent. Boldface indicates statistical significance.
*Summary statistics for RSE based on 351 091 European individuals (without 23andMe cohort) in the study by Hysi et al, 2020.[27]
†Summary statistics for POAG based on 216 257 European individuals from Gharakhani et al, 2021.[31]

Association between Myopia and Glaucoma Endophenotypes

We also examined causal associations between myopia and several glaucoma endophenotypes, including IOP, vertical cup-to-disc ratio, RNFL, optic cup area, and optic disc area. We found a significant bidirectional causal association between myopia and IOP (Bonferroni-corrected $P \leq 8.33 \times 10^{-3}$) in many of the MR models tested (Table 8) but not in any of the other glaucoma endophenotypes (Table S9, available at www.aaojournal.org). The causal relationship of myopia on optic disc area exhibited consistent and significant results in the 6 MR models, whereas the CAUSE model did not support the evidence of a causal model outperforming a sharing model in this case ($P = 0.32$; Table S6). In the inverse analysis, no evidence was found of the existence of a causal effect of optic disc area on myopia.

In view of the lack of detailed information on IOP handling in the UKB dataset, we performed an updated GWAS meta-analysis for IOP in the European population combining 93 543 UKB participants and 31 269 participants from Bonnemaijer et al[33] using a more stringent selection process to exclude eyes with a history of refractive surgery, glaucoma treatment with laser therapy or surgery, cornea graft surgery, and trauma. We further adjusted IOP data by multiplying 1.3 for participants reporting IOP-lowering medication, based on methods described by Khawaja et al[49] and Hysi et al.[50] We repeated the MR analyses to examine the association between myopia and IOP using the revised GWAS data. Our updated analyses show similar trends to those we reported previously, even after applying stricter selection criteria in handling IOP data (Table S10, available at www.aaojournal.org).

Multivariate Genomic Structural Modeling

Using multivariate genomic SEM, we investigated multivariate genetic architecture and quantified the indirect effect between RSE to POAG involving IOP, RNFL thickness, optic cup area, and optic disc area, with consideration of the covariance among 4 glaucoma endophenotypes. The standardized genomic SEM model showed a good fit for our data (chi-square, 3.98; Akaike information criterion, 43.98; comparative fit index, 0.99; and standardized root mean square residual, 0.01). According to the Sobel test, IOP showed the most significant mediation effect (0.13; 95% CI, 0.09−0.17; $P = 1.37 \times 10^{-8}$) on RSE and POAG compared with RNFL ($P = 0.81$), optic cup area ($P = 0.89$), and optic disc area ($P = 0.89$; Fig 2). Assuming the genomic SEM matrix does not exclude other critical pathways underlying this relationship, our findings suggest that the causal effect from myopia on POAG is mainly mediated by IOP.

Discussion

In this study, we examined causal associations between myopia and POAG using an extensive set of variables obtained from several of the largest genetic databases known at present. Separate datasets were used to derive summary statistics on genetic associations of myopia and POAG and to derive their causal relationship using various models of MR analyses that consider both standard and alternative assumptions of the MR method applied. Overall, our results highlighted a bidirectional causal association between myopia and POAG. In addition, we found that IOP had a significant bidirectional genetic causal association with myopia. Mendelian randomization analyses also showed that myopia had a causal effect on optic disc area, although the converse relationship of the effect on optic disc area on myopia did not hold true. Using genomic SEM, we confirmed the role of IOP as a key mediator in the causal association between myopia and POAG.

Our study suggests that good evidence exists for a consistent association between genetic risk factors for myopia in relationship to both POAG and IOP, in the absence of potential confounders. The association between myopia and glaucoma prevalence and risk of progression has been described previously, although the clinical definition of glaucoma in a myopic eye remains challenging because of the wide variation in optic nerve head morphologic features seen in myopia. Different mechanisms have been proposed to underlie the association between myopia and glaucoma, such as lamina cribrosa elongation and thinning arising from axial elongation and optic disc enlargement, leading to a steeper translaminar pressure gradient because of the decreased distance between the intraocular compartment and the retrobulbar compartment of the eye.[51,52] It has been suggested that this steeper trans−lamina cribrosa pressure gradient may predispose glaucomatous injury to retinal ganglion cell axons.[53,54] Our findings support the association between myopia and optic disc area, although we did not find any causal associations between optic disc area and POAG. Myopic axial elongation also may lead to biomechanical[55] and ischemic[56] processes that cause retinal thinning, including RGC layers. Notably, these theories also have been proposed to underlie glaucoma pathogenesis.[57] The converse directional association between POAG and myopia also is an intriguing prospect. It is possible that the structural changes seen at the optic nerve head in POAG are mediated by raised IOP, which contributes to lengthening of the posterior pole, resulting in a myopic shift. In support of this, several population-based studies indeed have shown that higher myopia is associated significantly with higher IOP.[6,7,58−61] Our observations further confirm possible associations between these pathogenic processes underlying both myopia and POAG.

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Table 4. Summary of Bidirectional Mendelian Randomization Analyses for Myopia and Primary Open-Angle Glaucoma in European Populations

Mendelian Randomization Method	Refractive Spherical Equivalent as Exposure and Primary Open-Angle Glaucoma as Outcome				Primary Open-Angle Glaucoma as Exposure and Refractive Spherical Equivalent as Outcome			
	408 Instrumental Variables		*331 Nonambiguous Instrumental Variables*		*57 Instrumental Variables*		*47 Nonambiguous Instrumental Variables*	
	Odds Ratio (95% Confidence Interval)	*P Value*	*Odds Ratio (95% Confidence Interval)*	*P Value*	*β Coefficient (95% Confidence Interval)*	*P Value*	*β Coefficient (95% Confidence Interval)*	*P Value*
Penalized IVW	1.04 (1.03–1.05)	**6.48×10^{-12}**	1.04 (1.03–1.05)	**1.71×10^{-10}**	0.06 (0.003–0.12)	4.10×10^{-2}	0.09 (0.02–0.15)	**7.86×10^{-3}**
Unpenalized IVW	1.05 (1.03–1.07)	**1.36×10^{-10}**	1.05 (1.03–1.06)	**2.83×10^{-8}**	0.15 (0.02–0.28)	1.94×10^{-2}	0.17 (0.02–0.31)	2.24×10^{-2}
MR-Egger	1.04 (1.01–1.07)	**7.14×10^{-3}**	1.03 (0.997–1.07)	6.96×10^{-2}	0.33 (0.17–0.50)	**5.28×10^{-5}**	0.24 (0.08–0.40)	**3.05×10^{-3}**
Intercept	1 (0.995–1.004)	**0.88**	1 (0.996–1.01)	0.68	−0.02 (−0.04 to −0.01)	1.10×10^{-2}	−0.01 (−0.03 to 0.01)	0.17
Weighted median	1.05 (1.03–1.06)	**9.60×10^{-8}**	1.05 (1.03–1.07)	**8.00×10^{-7}**	0.07 (−0.01 to 0.15)	7.00×10^{-2}	0.11 (0.03–0.19)	1.00×10^{-2}
MBE	1.04 (1.02–1.05)	**1.52×10^{-8}**	1.03 (1.02–1.05)	**4.01×10^{-6}**	0.12 (0.07–0.17)	**8.97×10^{-7}**	0.15 (0.10–0.21)	**1.53×10^{-8}**
GSMR*	1.04 (1.03–1.05)	**6.67×10^{-14}**	1.04 (1.03–1.05)	**1.49×10^{-12}**	0.09 (0.04–0.13)	**2.48×10^{-4}**	0.10 (0.05–0.15)	**1.03×10^{-4}**

GSMR = generalized summary data-based Mendelian randomization; IVW = inverse variance weighting model; MBE = weighted mode-based estimator; MR = Mendelian randomization.
*GSMR models used 377, 309, 44, and 36 instrumental variables in order. Bonferroni-corrected threshold of significance was $P \leq 8.33 \times 10^{-3}$ indicated in bold typeface based on 0.05/6.

Our observations regarding the presence of a strong bidirectional causal association between myopia and IOP also have potential clinical implications in terms of managing patients with suspected glaucoma who also have high myopia. A recent study that comprehensively characterized visual field changes in a large cohort of high-myopia eyes without maculopathy suggested that 10.8% of patients with high myopia showed glaucoma-like visual field defects.[62] However, only a fraction of these individuals showed raised IOP with neuroretinal rim changes that clearly corresponded to their visual field test results. The remaining participants with glaucoma-like visual field defects and normal IOP remain a challenging group of patients for whom to establish a clear diagnosis of glaucoma, especially in the presence of myopic optic disc changes that prevent accurate assessment of the neuroretinal rim. Our current findings highlight the association between myopia and IOP, which may suggest that pre-emptive glaucoma treatment in patients with suspected glaucoma who also have high myopia could have the dual benefit of modulating myopia progression and preventing glaucoma onset.

Through the use of MR analysis, we were able to consider multiple independent genetic variants that alter myopia risk at distinct locations on the genome to evaluate their association with glaucoma risk in the absence of environmental or behavioral confounders that impede traditional observational studies. We considered a wide range of updated MR analyses methods that allow for weaker, or alternative, assumptions compared with earlier models, such as inverse variance weighting,[38] including nonzero average directional uncorrelated pleiotropy (MR-Egger),[39] allowance for greater percentages of invalid IVs (weighted median and MBE),[41,42] and existence of both correlated and uncorrelated horizontal pleiotropy (CAUSE).[43] In addition, summary statistics were obtained from the most current, largest sources of genetic data in an attempt to address the question of causality as thoroughly as possible.

Our findings generally concur with a recent study by Choquet et al,[63] who also demonstrated common genetic cause between myopia and POAG. However, several distinctions exist. First, we included genetic data from 23andMe and the CREAM Study consortium and also investigated causal associations between myopia and glaucoma in Asian cohorts. Second, we assumed that IOP and vertical cup-to-dis ratio may exert both confounder and mediator effects on the association between myopia and glaucoma. Third, we further examined the potential mediation effects of various glaucoma endophenotypes using multivariable genomic structural equation modelling. The results of our analyses suggest that IOP has a complex role in mediating the bidirectional causal association between myopia glaucoma that is not limited to an external confounding effect.

However, our findings should be interpreted in due consideration of their limitations. Our approach was unable to indicate a single causative gene for glaucoma risk in myopic eyes, which would require further phenotypic characterization using transgenic biological models. An increased understanding of the functional properties of specific genetic variants may suggest explanations for the

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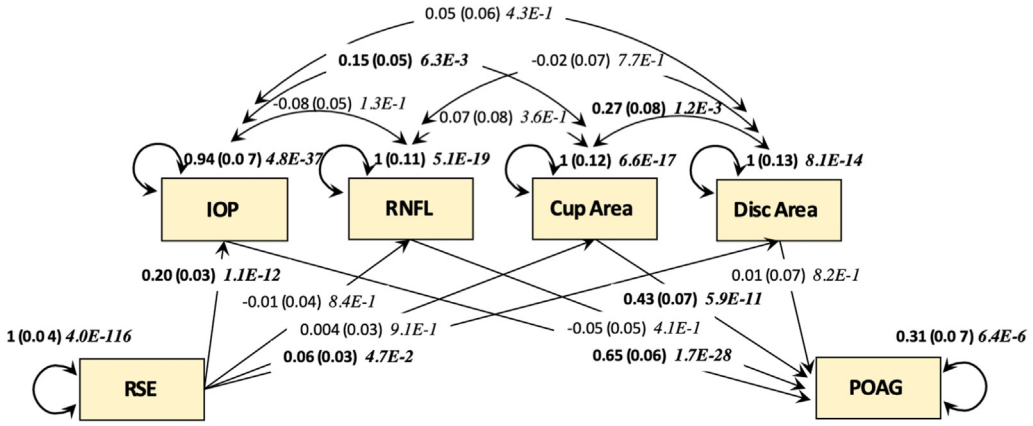
Table 8. Summary of Bidirectional Mendelian Randomization Analyses between Myopia and Intraocular Pressure

	Effect (95% Confidence Interval)	*P* Value	Effect (95% Confidence Interval)	*P* Value
Forward MR: RSE as exposure and IOP as outcome				
Exposure cohort	Hysi (n = 542 934)			
Outcome cohort	UKB left eye (n = 76 510)		UKB right eye (n = 76 630)	
No. of IV	408		408	
Penalized IVW	0.06 (0.04–0.08)	**2.54×10^{-10}**	0.06 (0.04–0.08)	**1.59×10^{-10}**
Unpenalized IVW	0.07 (0.05–0.09)	**1.94×10^{-9}**	0.06 (0.04–0.08)	**2.30×10^{-7}**
MR-Egger	0.06 (0.01–0.11)	3.09×10^{-2}	0.02 (−0.03 to 0.07)	4.72×10^{-1}
Intercept	0.001 (−0.01 to 0.01)	0.85	0.01 (−0.002 to 0.02)	0.11
Weighted median	0.07 (0.04–0.09)	**1.29×10^{-6}**	0.06 (0.03–0.09)	**9.28×10^{-6}**
MBE	0.06 (0.04–0.09)	**7.52×10^{-9}**	0.05 (0.03–0.07)	**4.38×10^{-6}**
GSMR	0.05 (0.04–0.07)	**1.17×10^{-9}**	0.06 (0.04–0.08)	**1.72×10^{-12}**
Inverse MR: IOP as exposure and RSE as outcome				
Exposure cohort	UKB left eye (n = 76 510)		UKB right eye (n=76 630)	
Outcome cohort	Hysi (n = 351 091)			
No. of IV	29		44	
Penalized IVW	0.15 (0.08–0.22)	**2.39×10^{-5}**	0.12 (0.06–0.18)	**6.24×10^{-5}**
Unpenalized IVW	0.07 (−0.01 to 0.16)	8.57×10^{-2}	0.15 (0.06–0.23)	**6.30×10^{-4}**
MR-Egger	−0.02 (−0.12 to 0.08)	7.02×10^{-1}	0.14 (−0.04 to 0.32)	1.19×10^{-1}
Intercept	0.03 (0.01–0.05)	**6.00×10^{-3}**	−0.003 (−0.04 to 0.03)	0.88
Weighted median	0.001 (−0.07 to 0.07)	9.94×10^{-1}	0.16 (0.09–0.24)	**1.24×10^{-5}**
MBE	0.08 (0.04–0.12)	**1.70×10^{-4}**	0.16 (0.12–0.21)	**4.13×10^{-14}**
GSMR	0.08 (0.04–0.13)	**2.50×10^{-4}**	0.11 (0.06–0.15)	**7.25×10^{-6}**

GSMR = generalized summary data-based Mendelian randomization; IOP = intraocular pressure; IV = instrumental variable; IVW = inverse variance weighting model; MBE = weighted mode-based estimator; MR = Mendelian randomization; RSE = refractive spherical equivalent; SEM = structural equation modeling; SNP = single nucleotide polymorphism; UKB = UK Biobank; Hysi = Hysi et al.[27]
In the forward analysis, GSMR models included 379 380 and 388 IVs for 3 cohorts, respectively. In the inverse analysis, GSMR models included 12, 17, and 9 IVs for 3 cohorts, respectively. Bonferroni-corrected significance was $P \leq 8.33 \times 10^{-3}$ indicated in boldface.

associated disease risk. Furthermore, we did not examine genetic associations with other structural markers of myopic severity such as myopic macular degeneration or peripapillary atrophy. A sample overlap of up to 6.7% was detected in the myopia and glaucoma databases from the UKB; however, we believe that this will not have a major impact on our findings in view of the statistical strength of our observations (up to $P = 10^{-10}$). Detailed information on



χ^2	*df*	*P*	AIC	CFI	SRMR
3.98	1	0.046	43.98	0.99	0.01

Figure 2. Genomic structure equation modelling (SEM) included a direct path from refractive spherical equivalent (RSE) to primary open-angle glaucoma (POAG), indirect pathways involving 4 glaucoma endophenotypes, and covariance between endophenotypes. The standardized factor loadings, standard error (in parentheses), and *P* values (in italics) are presented. Significant coefficients that have $P < 0.05$ appear in boldface. We reported multiple evaluation matrices, including chi-square statistics (χ^2), Akaike information criterion (AIC), comparative fit index (CFI), and standardized root mean square residual (SRMR). IOP = intraocular pressure; RNFL = retinal nerve fiber layer thickness.

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IOP handling also was not available from the UKB GWAS; however, after repeating the MR modelling with updated GWAS meta-analyses results, using data from UKB and Bonnemaijer et al[33] with more stringent IOP handling, we found similar trends. Although our sensitivity analyses showed that our conclusions held true in European eyes, they were not significant in Asian eyes. This may be because of the relatively smaller size of the Asian cohorts, resulting in modest statistical power and the limited ability to derive robust IVs for MR analysis. Epidemiologic studies have reported that Asian eyes have lower IOP than Western eyes, although considerably higher rates of normal-tension glaucoma.[64–66] Therefore, myopia-associated glaucoma in Asian eyes also may arise from IOP-independent mechanisms such as ethnic-specific differences in blood pressure variability. Larger sample sizes are required to probe possible genetic causal associations between myopia and glaucoma in Asian eyes with greater certainty. However, given the wide prevalence of myopia in Asia especially among young individuals, the effect of ethnicity on the interplay between myopia and glaucoma is an important question that remains to be answered.

In conclusion, we have reported genetic evidence that myopia is a causal factor for POAG and vice versa. The observed common genetic causal link between myopia and glaucoma pathogenesis suggests that potential treatments to halt myopia could be beneficial in modulating the risk of glaucoma risk. Furthermore, we also showed evidence that the effect of myopia on glaucoma is mediated by IOP. This may imply possible therapeutic benefits of IOP-lowering treatment on alleviating retinal ganglion cell injury associated with progressive myopic optic neuropathy, even in the absence of a clear clinical diagnosis of glaucoma, which is often challenging to establish in myopic eyes.

Footnotes and Disclosures

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Author Contributions:

Conception and design: Chong, Li, Cheong, Cheng

Analysis and interpretation: Chong, Li, Fan, Koh, Cheng

Data collection: Chong, Li, Cheng

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Overall responsibility: Chong, Li, Cheong, Fan, Koh, Raghavan, Nongpiur, Cheng

Abbreviations and Acronyms:
CAUSE = causal analysis using summary effect estimates; **CI** = confidence interval; **CREAM** = Consortium for Refractive Error and Myopia; **GWAS** = genome-wide association study; **IGGC** = International Glaucoma Genetics Consortium; **IOP** = intraocular pressure; **IV** = instrumental variable; **LDSC** = linkage disequilibrium score regression; **MR** = Mendelian randomization; **POAG** = primary open-angle glaucoma; **RNFL** = retinal nerve fiber layer; **RSE** = refractive spherical equivalent; **SE** = standard error; **SEM** = structural equation modeling; **SNP** = single nucleotide polymorphism; **UKB** = UK Biobank.

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