

Association of Behavioral and Clinical Risk Factors With Cataract: A Two-Sample Mendelian Randomization Study

Chen Jiang,¹ Ronald B. Melles,² Poorab Sangani,³ Thomas J. Hoffmann,^{4,5} Pirro G. Hysi,⁶⁻⁸ M. Maria Glymour,⁵ Eric Jorgenson,⁹ Salil A. Lachke,^{10,11} and H el ene Choquet¹

¹Kaiser Permanente Northern California (KPNC), Division of Research, Oakland, California, United States

²KPNC, Department of Ophthalmology, Redwood City, California, United States

³KPNC, Department of Ophthalmology, South San Francisco, California, United States

⁴Institute for Human Genetics, UCSF, San Francisco, California, United States

⁵Department of Epidemiology and Biostatistics, UCSF, San Francisco, California, United States

⁶King's College London, Section of Ophthalmology, School of Life Course Sciences, London, United Kingdom

⁷King's College London, Department of Twin Research and Genetic Epidemiology, London, United Kingdom

⁸University College London, Great Ormond Street Hospital Institute of Child Health, London, United Kingdom

⁹Regeneron Genetics Center, Tarrytown, New York, United States

¹⁰Department of Biological Sciences, University of Delaware, Newark, Delaware, United States

¹¹Center for Bioinformatics and Computational Biology, University of Delaware, Newark, Delaware, United States

Correspondence: H el ene Choquet, Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94612, USA;

helene.choquet@kp.org.

Received: April 9, 2023

Accepted: June 26, 2023

Published: July 17, 2023

Citation: Jiang C, Melles RB, Sangani P, et al. Association of behavioral and clinical risk factors with cataract: A two-sample mendelian randomization study. *Invest Ophthalmol Vis Sci.* 2023;64(10):19. <https://doi.org/10.1167/iovs.64.10.19>

PURPOSE. To investigate the association of genetically determined primary open-angle glaucoma (POAG), myopic refractive error (RE), type 2 diabetes (T2D), blood pressure (BP), body mass index (BMI), cigarette smoking, and alcohol consumption with the risk of age-related cataract.

METHODS. To assess potential causal effects of clinical or behavioral factors on cataract risk, we conducted two-sample Mendelian randomization analyses. Genetic instruments, based on common genetic variants associated with risk factors at genome-wide significance ($P < 5 \times 10^{-8}$), were derived from published genome-wide association studies (GWAS). For age-related cataract, we used GWAS summary statistics from our previous GWAS conducted in the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort (28,092 cataract cases and 50,487 controls; all non-Hispanic whites) or in the UK Biobank (31,852 cataract cases and 428,084 controls; all European-descent individuals). We used the inverse-variance weighted (IVW) method as our primary source of Mendelian randomization estimates and conducted common sensitivity analyses.

RESULTS. We found that genetically determined POAG and mean spherical equivalent RE were significantly associated with cataract risk (IVW model: odds ratio [OR] = 1.04; 95% confidence interval [CI], 1.01–1.08; $P = 0.018$; per diopter more hyperopic: OR = 0.92; 95% CI, 0.89–0.93; $P = 6.51 \times 10^{-13}$, respectively). In contrast, genetically determined T2D, BP, BMI, cigarette smoking, or alcohol consumption were not associated with cataract risk ($P > 0.05$).

CONCLUSIONS. Our results provide evidence that genetic risks for POAG and myopia may be causal risk factors for age-related cataract. These results are consistent with previous observational studies reporting associations of myopia with cataract risk. This information may support population cataract risk stratification and screening strategies.

Keywords: cataract, mendelian randomization, cataract risk factors, genetic epidemiology

Cataract is a leading cause of blindness worldwide and in the United States, affecting 22% of Americans 40 years and older.¹ Surgery is the current standard of management,^{2,3} and, although cataract surgery is usually effective as measured by improvements in visual acuity,³ intraoperative or postoperative complications can occur.^{2,4,5} Twin and family studies strongly support an important role for genetic factors in cataract risk with heritability estimates up to 58%.^{6–11} Recently, we conducted a multiethnic genome-wide association study (GWAS) meta-analysis of cataract that identified 55 genetic risk loci.¹² Although this work revealed

novel genetic loci associated with cataract, there is still a need to discover the causal pathways underlying cataractogenesis.

Previous observational studies have identified clinical and behavioral risk factors for cataract, including type 2 diabetes (T2D), high blood pressure (BP), high body mass index (BMI), myopic refractive error (RE), cigarette smoking, and alcohol consumption.^{2,13–31} However, it is not clear if these observational associations represent causal risk factors. In our recent study, we estimated the pairwise genetic correlations (r_g) between cataract and more

than 700 diseases/traits from different publicly available resources/consortia and identified strong genetic correlations between cataract and several of these factors, including myopia, BMI, and cigarette smoking.¹² We also found a significant genetic correlation between cataract and glaucoma.¹² These findings suggest considerable shared genetic influences between cataract and those ophthalmic, clinical, and behavioral factors; however, the nature of the relationships remain largely unexplored.

The Mendelian randomization (MR) approach uses genetic variants to determine whether an observational association between a risk factor and an outcome is consistent with a causal effect.^{32–35} This approach leverages the random segregation of alleles that are not affected by environmental conditions. Results from MR studies are typically consistent with those of randomized controlled trials and provide, for example, evidence for drug target validation.³⁶ Although this approach has been successful in many causal inference discoveries,^{37–39} only a few MR studies evaluating whether observational associations of clinical and behavioral factors with cataract risk are consistent with causal effects have been reported.^{40–43} Furthermore, the results of prior MR studies for cataract have been inconsistent.^{42,43}

Here, we employed a two-sample MR approach⁴⁴ to assess the potential causal role of primary open-angle glaucoma (POAG), myopic RE, T2D, BP, BMI, cigarette smoking, and alcohol consumption on the risk of cataract. We compare genetic effect estimates for those exposures and cataract risk (outcome) obtained through GWAS summary statistics, in particular using our large GWAS of cataract conducted using the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort and UK Biobank.¹² The assessment of these risk factors could have public health and clinical implications for prevention and early detection of this common cause of visual disability.

METHODS

Study Design

Two-sample MR analyses were conducted to investigate the association of genetically determined POAG, myopic RE, T2D, blood pressure (i.e., systolic and diastolic), BMI, cigarette smoking (i.e., smoking initiation, cigarettes per day,

and lifetime smoking), and alcohol consumption (i.e., drinks per week) with the risk of age-related cataract. For each of the exposures, we used the lead single nucleotide variations (SNVs) previously reported as being genome-wide significant ($P < 5.0 \times 10^{-8}$) as a set of genetic instruments. Genetic instruments were then clumped using a window of 10 Mb and maximal linkage disequilibrium of $r^2 = 0.001$ between instruments to ensure that genetic variants were independent. The conceptual framework of the current MR study is reported in Figure 1, and the different datasets used for this MR study are summarized in Supplementary Table S1.

GWAS Summary Statistics for Cataract

Genetic association data for cataract risk (outcome) were retrieved from our previous GWAS study conducted in the GERA cohort.¹² The GERA cohort consists of 110,266 adult members of the Kaiser Permanente Medical Care Plan, Northern California Region (KPNC), an integrated healthcare delivery system that includes ongoing longitudinal electronic health records.^{45,46} The Institutional Review Board of the Kaiser Foundation Research Institute approved all study procedures. Written informed consent was obtained from all participants. In the current study, we retrieved genetic association data from the GWAS of cataract conducted in 28,092 cataract cases and 50,487 controls (all GERA participants were of European ancestry).¹² Briefly, GERA patients with pseudophakia were diagnosed by a Kaiser Permanente ophthalmologist and were identified in the KPNC electronic health record system based on the following International Classification of Disease, Ninth Revision (ICD9) or Tenth Revision (ICD10) diagnosis codes: V43.1 (ICD-9 code) and Z96.1 (ICD-10 code). GERA cataract cases were also identified if they had a history of having a cataract surgery at KPNC. Our GERA control group included all of the non-cases. To make sure that study samples for exposures did not overlap with those for the outcome, in some MR analyses (i.e., association of POAG, BP, or BMI with cataract risk), genetic association data for cataract risk were retrieved from our previous GWAS study conducted in the UK Biobank (UKB).¹² The UKB cataract cases ($N = 31,852$ individuals of European ancestry) were defined as participants with a self-reported cataract operation (f20004 code 1435) or/and a hospital record including a diagnosis code (ICD-10: H25

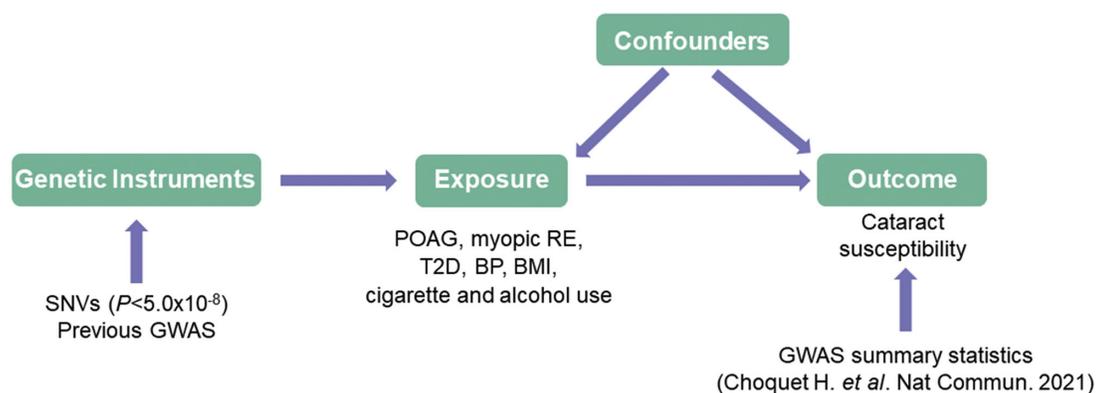


FIGURE 1. Conceptual framework of the MR study. Common genetic variants that are associated with the exposure (e.g., POAG risk) at genome-wide significance ($P < 5.0 \times 10^{-8}$) in published GWASs were used as genetic instruments. The association of those genetic instruments with the outcome (i.e., cataract risk) is only mediated through the exposure.

or H26); the UKB controls ($N = 428,084$ individuals of European ancestry) were participants who were not cases.

Genetic Instruments for POAG

Genetic association data for POAG risk (exposure) were retrieved from our recent large GWAS meta-analysis of POAG conducted by the International Glaucoma Genetics Consortium.⁴⁷ GWAS summary statistics for this study⁴⁷ have been publicly accessible via GWAS Catalog under study accession identifier GCST90011767 (corresponding to all European ancestry cohorts except UKB; $N = 15,229$ POAG cases and 177,473 controls). After clumping, a total of 46 genetic instruments for POAG were used for the MR analyses (Supplementary Table S2).

Genetic Instruments for Refractive Error

Genetic variants as instrumental variables for RE (exposure) were extracted from a GWAS conducted in 102,117 UKB participants of European ancestry with direct refraction measurement and part of our previously reported European ancestry meta-analysis.⁴⁸ In UKB, RE was measured directly using the Tomey RC 5000 Auto-Refractor Keratometer (Tomey Corporation, Aichi, Japan). The spherical equivalent was estimated as the spherical RE (UKB codes 5084 and 5085) plus half the cylindrical error (UKB codes 5086 and 5087) for each eye. The mean of spherical equivalent was then used as the outcome of the GWAS analysis.⁴⁸ After clumping, a total of 166 genetic instruments for mean spherical equivalent RE were used for the MR analyses (Supplementary Table S3).

Genetic Instruments for Type 2 Diabetes

Genetic variants as instrumental variables for T2D (exposure) were extracted from a large GWAS analysis consisting of 19,119 T2D cases and 423,698 controls, all UKB participants of European ancestry.⁴⁹ After clumping, a total of 66 genetic instruments for T2D were used for the MR analyses (Supplementary Table S4).

Genetic Instruments for Blood Pressure

Genetic variants as instrumental variables for blood pressure (exposure) were extracted from our large GWAS conducted in 80,792 GERA participants of European ancestry with systolic and diastolic blood pressure measurements.⁵⁰ After clumping, a total of 20 genetic instruments for systolic blood pressure and a total of 20 genetic instruments for diastolic blood pressure were used for the MR analyses (Supplementary Tables S5 and S6).

Genetic Instruments for BMI

Genetic variants as instrumental variables for BMI (exposure) were extracted from our large GWAS meta-analysis consisting of 315,347 individuals of European ancestry from the GERA and the Genetic Investigation of Anthropomorphic Traits consortium.⁵¹ GWAS summary statistics for this study⁵¹ were publicly accessible via the GWAS Catalog under study accession identifier GCST006368. After clumping, a total of 153 genetic instruments for BMI were used for the MR analyses (Supplementary Table S7).

Genetic Instruments for Cigarette Smoking

Genetic variants as instrumental variables for cigarette smoking initiation (ever having smoked regularly vs. never) and amount smoked (number of cigarettes per day) were extracted from the most recent GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) study.⁵² GWAS summary statistics for smoking initiation and amount smoked analyses⁵² included 805,431 and 326,497 individuals of European ancestry, respectively. Those GWAS summary statistics are publicly accessible at <https://conservancy.umn.edu/handle/11299/241912>. We also used genetic variants as instrumental variables for lifetime smoking (represented by an index that captures smoking status, duration, heaviness, and cessation) from a GWAS conducted in 462,690 UKB participants of European ancestry.⁵³ GWAS summary statistics for this study⁵³ were publicly accessible via the GWAS Catalog under study accession identifier GCST009096. After clumping, a total of 231 genetic instruments for smoking initiation, 47 for cigarettes per day, and 121 for lifetime smoking were used for the MR analyses (Supplementary Tables S8–S10).

Genetic Instruments for Alcohol Consumption

Genetic variants as instrumental variables for alcohol consumption (i.e., number of drinks per week as the exposure) were extracted from the most recent GSCAN study.⁵² GWAS summary statistics corresponding to the drinks per week analysis⁵² included 619,011 individuals of European ancestry, after removing GERA participants. After clumping, a total of 93 genetic instruments for drinks per week were used for the MR analyses (Supplementary Table S11).

Two-Sample MR Analyses

All analyses were conducted in the R V.4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) using the TwoSampleMR package.⁴⁴ This package makes causal inference about an exposure on an outcome using GWAS summary statistics, generates linkage disequilibrium pruning of exposure SNVs and harmonizes exposure and outcome datasets. We used the inverse-variance weighted (IVW) method as our primary source of MR estimates. This IVW method essentially translates to a weighted regression of SNV outcome effects on SNV-exposure effects where the intercept is constrained to zero. Moreover, we reported the estimations from MR weighted median, weighted mode, and Mendelian randomization–Egger (MR-Egger). Further, leave-one-SNV-out analyses were conducted (Supplementary Tables S12–S21).

Sensitivity Analyses

The potential effect of pleiotropy was evaluated by the regression intercept from the MR-Egger method,⁵⁴ and Cochran Q tests were used to evaluate the presence of global heterogeneity among the effects of the genetic instruments.⁵⁵ The MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) method^{55,56} was also used to provide an MR estimate that is robust against the presence of heterogeneity among SNV effects and to re-assess the MR estimate after excluding outlier SNVs. Finally, we applied the MR-Steiger method,⁵⁷ which removes variants from the analysis if their association with the outcome is stronger than that with the exposure.⁵⁵

Multivariable MR for POAG Adjusting for the Effect of RE on Cataract Risk

Recent MR studies^{37,58} suggested that lower (more myopic) RE is associated with POAG risk. Moreover, some genetic loci exhibited pleiotropic effects with RE/myopia, POAG, and cataract.¹² Because these relationships can potentially bias the relationship between POAG and cataract, we conducted a multivariable MR analysis^{59,60} to adjust for the potential effect of RE. Genetic variants as instrumental variables for mean spherical equivalent RE were extracted from a GWAS conducted in 59,094 GERA non-Hispanic white participants.³⁷ Single nucleotide polymorphisms (SNPs) achieving genome-wide significance for each trait (e.g., RE, POAG) were included in the multivariable MR analysis. After clumping, a total of 43 genetic instruments were used for the multivariable MR analysis adjusting for the effect of RE. The multivariable MR analysis was performed by jointly fitting the SNP-POAG and SNP-RE effect sizes simultane-

ously in the regression model on the SNP-ataract association. The multivariable MR analysis was conducted using the `mv_multiple()` function available in the `TwoSampleMR` package in R curated in the MR-Base platform.⁴⁴

RESULTS

MR Analyses Identify Association of Ophthalmic Conditions With Cataract Risk

To investigate whether genetically determined POAG and myopic RE increase the risk of cataract, we conducted two-sample MR analyses. We found that genetically determined POAG was significantly associated with cataract risk (IVW model: OR = 1.04; 95% CI, 1.01–1.08; $P = 0.018$) (Table, Fig. 2, Supplementary Tables S12 and S22). We also found evidence for a causal effect of RE on cataract risk, as a more negative mean spherical equivalent RE was associ-

TABLE. MR Results of the Associations of Genetically Predicted Risk Factors With Cataract

Exposure (Source)	Outcome	Genetic Instruments, <i>n</i>	MR Method	OR (95% CI)	<i>P</i>	Detected Outlier SNV Via MR-PRESSO
POAG (IGGC)	Cataract (UKB)	46	IVW	1.04 (1.01–1.08)	0.018	—
POAG (IGGC)	Cataract (UKB)	44	MR-PRESSO model	1.03 (1.00–1.07)	0.044	rs6475604; rs33912345
Myopic RE (UKB)	Cataract surgery (GERA)	166	IVW	0.92 (0.89–0.93)	6.51 × 10⁻¹³	—
Myopic RE (UKB)	Cataract surgery (GERA)	165	MR-PRESSO model	0.92 (0.90–0.94)	9.29 × 10⁻¹²	rs429358
T2D (UKB)	Cataract surgery (GERA)	66	IVW	1.00 (0.96–1.04)	0.96	—
T2D (UKB)	Cataract surgery (GERA)	66	MR-PRESSO model	1.00 (0.96–1.04)	0.96	NA
SBP (GERA)	Cataract (UKB)	20	IVW	1.00 (0.99–1.01)	0.68	—
SBP (GERA)	Cataract (UKB)	20	MR-PRESSO model	1.00 (0.99–1.01)	0.68	NA
DBP (GERA)	Cataract (UKB)	20	IVW	1.00 (0.99–1.02)	0.36	—
DBP (GERA)	Cataract (UKB)	20	MR-PRESSO model	1.01 (0.99–1.02)	0.37	NA
BMI (GIANT + GERA)	Cataract (UKB)	153	IVW	0.94 (0.87–1.03)	0.18	—
BMI (GIANT + GERA)	Cataract (UKB)	152	MR-PRESSO model	0.95 (0.88–1.03)	0.25	rs889398
Cigarette smoking initiation (GSCAN)	Cataract surgery (GERA)	231	IVW	1.15 (0.98–1.34)	0.08	—
Cigarette smoking initiation (GSCAN)	Cataract surgery (GERA)	231	MR-PRESSO model	1.15 (0.98–1.34)	0.08	NA
Cigarettes per day (GSCAN)	Cataract surgery (GERA)	47	IVW	1.06 (0.90–1.25)	0.51	—
Cigarettes per day (GSCAN)	Cataract surgery (GERA)	47	MR-PRESSO model	1.06 (0.90–1.25)	0.51	NA
Lifetime smoking (UKB)	Cataract surgery (GERA)	121	IVW	1.07 (0.83–1.37)	0.62	—
Lifetime smoking (UKB)	Cataract surgery (GERA)	121	MR-PRESSO model	1.07 (0.83–1.37)	0.62	NA
Alcohol drinks/week (GSCAN)	Cataract surgery (GERA)	93	IVW	0.86 (0.71–1.04)	0.12	—
Alcohol drinks/week (GSCAN)	Cataract surgery (GERA)	92	MR-PRESSO model	0.90 (0.74–1.08)	0.27	rs62641967

Note: In the current study, we retrieved genetic association data from the GWAS of cataract conducted in 28,092 cataract cases and 50,487 controls; all GERA participants were of European ancestry.¹² However, to make sure that study samples for exposures did not overlap with those for the outcome, in some MR analyses (i.e., association of POAG, BP, or BMI with cataract risk), genetic association data for cataract risk were retrieved from our previous GWAS study conducted in the UK Biobank.¹² Abbreviations: *n*, number of genetic instruments after clumping; MR, Mendelian randomization; OR, odds ratio; CI, confidence interval; SNV, single nucleotide variation; POAG, primary open-angle glaucoma; IGGC, International Glaucoma Genetics Consortium; UKB, UK Biobank; IVW, inverse-variance weighted; RE, refractive error; GERA, Genetic Epidemiology Research on Adult Health and Aging; T2D, type 2 diabetes; SBP, systolic blood pressure; DBP, diastolic blood pressure; GIANT, Genetic Investigation of Anthropomorphic Traits; GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine use. Highlighted in bold *P*-values are significant ($P < 0.05$) *P*-values.

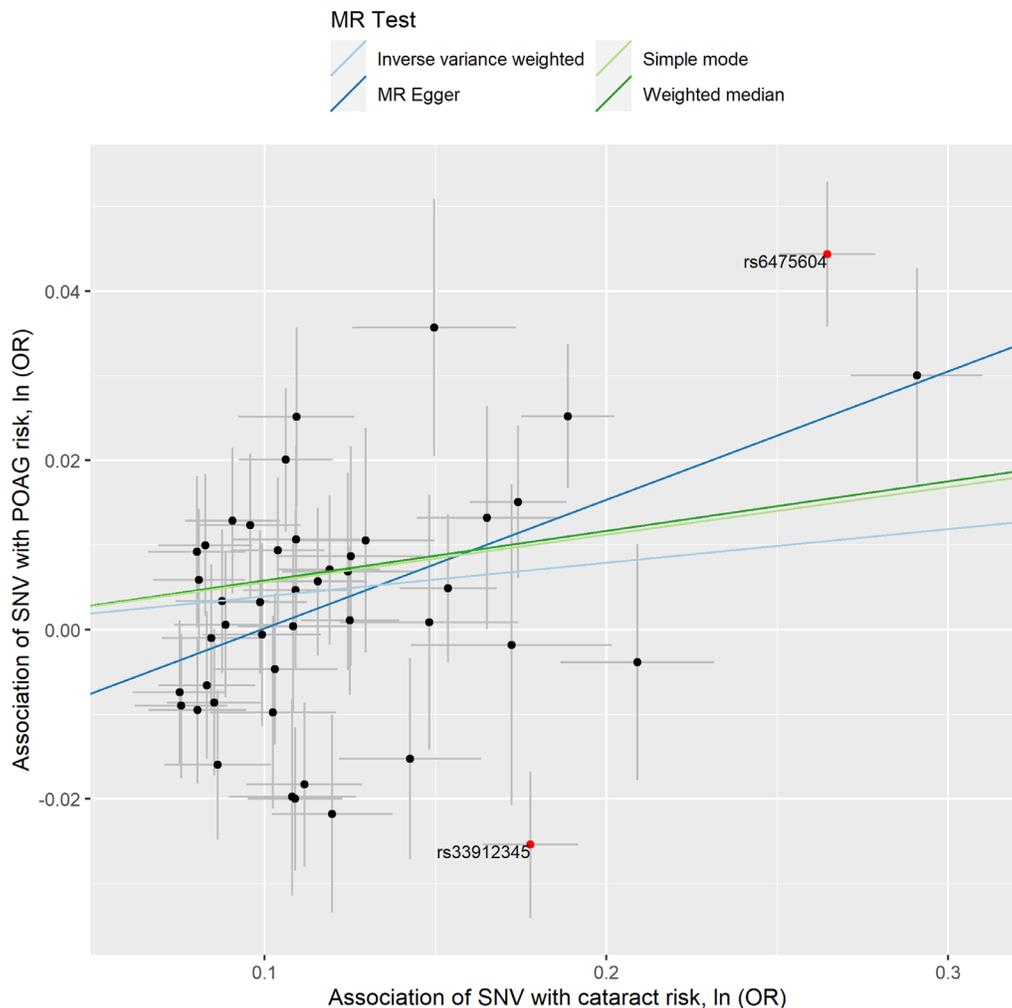


FIGURE 2. Association of POAG-associated variants with the risk of cataract. The x-axis shows 46 genetic instruments for POAG and their effect size estimates (ORs) with POAG. The y-axis shows the association of the same variants with cataract risk. The MR IVW regression line is plotted. The outlier genetic variants rs6475604 and rs33912345 detected by the MR-PRESSO model are labeled in red.

ated with an increased risk of cataract (IVW model: OR per diopter more hyperopic mean spherical equivalent = 0.92; 95% CI, 0.89–0.93; $P = 6.51 \times 10^{-15}$) (Table, Fig. 3, Supplementary Tables S13 and S23).

As significant heterogeneity amongst the effects of the genetic instruments was detected using the computed Cochran Q statistics (POAG: $Q = 97.3$, $P = 1.03 \times 10^{-5}$; myopic RE: $Q = 214.98$, $P = 0.0054$), we conducted a MR-PRESSO model to identify potential outliers for POAG and myopic RE. After excluding outlier genetic variants (i.e., SNVs rs6475604 at *CDKN2B-AS1* and rs33912345 at *SLX6* for POAG, and SNV rs429358 at *APOE* for myopic RE) as the source of most of the observed heterogeneity, genetically determined POAG and RE were confirmed to be associated with cataract risk (Table). MR-Steiger results showed that the selected SNVs were valid instruments for the exposures and that the causal estimates were oriented in the expected direction.

Because recent MR studies suggested that lower (more myopic) RE is associated with POAG risk,^{37,58} we also conducted a multivariable MR analysis to assess the association of POAG with cataract risk after adjusting for the effect

of RE. The association of POAG with cataract risk was similar after the adjustment of RE (OR = 1.05; 95% CI, 1.00–1.10; $P = 0.030$).

Association of Clinical Risk Factors With Cataract Risk

Genetically determined T2D was not associated with an increased risk of cataract (OR = 1.00; 95% CI, 0.96–1.04; $P = 0.96$) (Table, Supplementary Fig. S1, Supplementary Tables S14 and S24). Similarly, we observed no association between increased genetically determined BMI or systolic and diastolic blood pressures and the risk of cataract using two-sample MR analyses (Table, Supplementary Figs. S2–S4, Supplementary Tables S15–S17 and S25–S27).

Association of Behavioral Risk Factors With Cataract Risk

We found no evidence that cigarette smoking traits (i.e., smoking initiation, amount smoked, and lifetime smoking) or alcohol consumption (i.e., drinks per week) had a causal

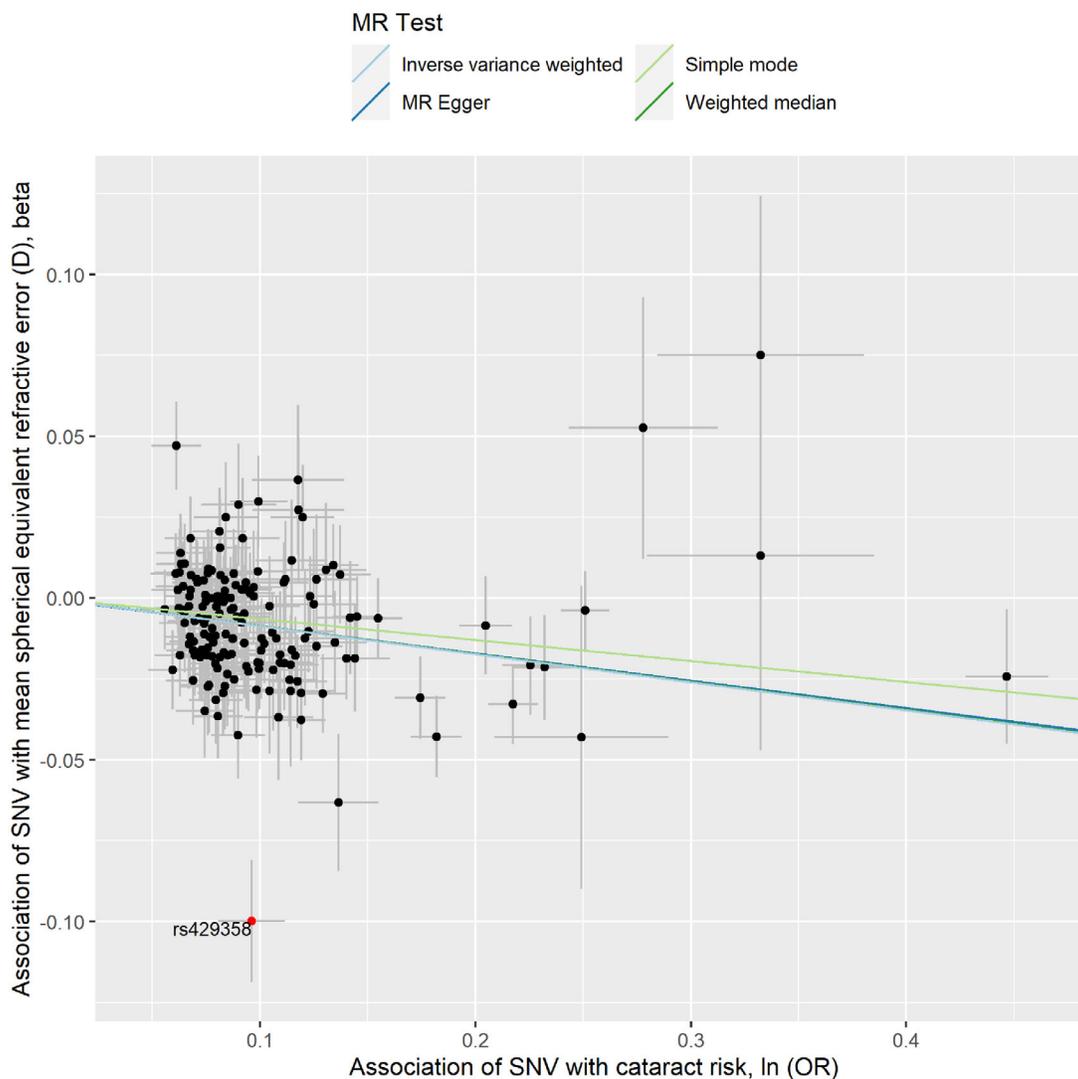


FIGURE 3. Association of refractive error-associated variants with the risk of cataract. The *x*-axis shows 166 genetic instruments for mean spherical equivalent RE and their effect size estimates (betas) with RE. The *y*-axis shows the association of the same variants with cataract risk. The MR IVW regression line is plotted. The outlier genetic variant rs429356 detected by the MR-PRESSO model is labeled in red.

association with the risk of cataract using two-sample MR analyses (Table, Supplementary Figs. S5–S8, Supplementary Tables S18–S21 and S28–S31).

DISCUSSION

This study leveraged a MR framework to investigate the associations of clinical and behavioral factors with the risk of cataract. We found genetic evidence for a potential causal effect of POAG on cataract risk. Consistent with previous observational studies, we also found genetic evidence for a potential causal association between myopic RE and cataract risk. Those associations were robust in sensitivity analyses that address significant heterogeneity among the effects of the genetic instruments. Further, although multiple tests were conducted, the causality of myopic RE on cataract would clearly stand multiple testing correction. In contrast, we found no evidence for association of genetically determined T2D, BP, and BMI with cataract risk. In addition, we did not find evidence for associations with genetic

predilections for cigarette smoking or alcohol consumption on cataract risk.

Our results are consistent with previous observational studies that have consistently reported RE or myopia as a risk factor for cataract.^{14,18,20,22,24,27,29,30,61,62} The first indication was from a study that measured axial thickness of human lenses that suggested that individuals presenting with axial myopia may have a higher likelihood of cataract detected at earlier ages.²⁸ Using MR methods, we found genetic evidence that myopic RE was associated with an increased risk of cataract. Although the mechanisms behind this association are not entirely clear, prior works, especially from animal models, have attempted to provide potential biological explanations.^{63–66} Lipid peroxidation is thought to play a key role in cataractogenesis, especially in retinal degenerative disease and myopia.^{63–65} In addition, oxidative damage to lens proteins has been shown to influence myopic cataractogenesis,⁶⁶ and the pathways involved in oxidative stress response are associated with cataracts in high myopia.^{67,68} Recently, a study in mouse models reported the

dysregulation of the MAF–transforming growth factor- β 1–crystallin axis as an underlying mechanism leading to an increased lens size in highly myopic eyes.⁶⁹ Finally, a comparative analysis of microarray expression patterns between human lens epithelia from high myopic eyes with that of emmetropic (normal refractive eye) controls suggests alterations in mitogen-activated protein kinase (MAPK) signaling and calcium signaling pathways in abnormal lens growth.⁷⁰ Thus, the pathways described above should be investigated further to advance knowledge on the mechanisms commonly relevant to cataract and myopia.

The current study also determined that genetically determined POAG increased the risk of cataract. These findings built on our previous genetic investigations that reported a significant positive genetic correlation between glaucoma and cataract risk.¹² Further, oxidative stress and endoplasmic reticular stress have been implicated in both vision disorders.⁷¹ Future investigations are needed to understand the shared molecular biology pathways involved between POAG and cataract.

In this study, our MR estimates did not indicate a potential causal association for T2D and the risk of cataract. Our results are consistent with recent MR studies on the association between T2D and cataract risk.^{42,43} Although a prior MR study found no evidence of causal relationship between T2D and cataract risk in Europeans, a causal effect of T2D on the development of cataract was observed in East Asians.⁴² Moreover, a recent MR study found no evidence for a causal effect of T2D on cataract risk in the UK Biobank study but detected significant association between the two diseases in the FinnGen consortium.⁴³ Further studies in larger samples of European and non-European populations are required to clarify the potential effect of T2D on cataract risk.

We also found no evidence of causal association between higher systolic or diastolic blood pressure and cataract risk. Although hypertension has been related to incident cataract in observational studies,^{20–22} a recent MR study found limited evidence for a causal effect of SBP on cataract risk.⁴³ Similarly, in our current MR study, we found no evidence of a causal association between higher BMI and cataract risk. Although obesity (or higher BMI) has been reported to be associated with an increased risk of cataract surgery,¹⁵ recent MR studies on the association of obesity or BMI with cataract risk are conflicting.^{40,43} Although higher genetically determined BMI was associated with an increased risk of cataract in the FinnGen consortium,⁴³ obesity was not causally associated with age-related cataract in the Blue Mountains Eye Study or in the UK Biobank study.^{40,43} Additional MR studies using many more genetic instruments and larger samples may elucidate the potential effect of BMI on cataract risk.

Many observational studies have consistently reported the association of cigarette smoking with cataract risk,^{13–15,20,23} suggesting that this lifestyle exposure might be a modifiable risk factor for cataract, and a causal effect of smoking initiation on cataract risk has been identified in recent MR studies.^{41,45} In contrast, our results provide no genetic evidence of a potential causal association of cigarette smoking with cataract risk, even if a large number of genetic instruments derived from the recent and large GSCAN study⁵² were used for some exposures (i.e., smoking initiation or amount smoked). Further investigations are required to understand the reasons for those inconsistent results.

The effect of alcohol consumption on cataract risk seem to differ according to the trait tested (i.e., drinker status, moderate vs. heavy alcohol consumption among drinkers, and type of alcohol beverage).^{16,17,25} In a meta-analysis study, Gong and colleagues¹⁶ reported that heavy alcohol consumption significantly increased the risk of cataract, whereas moderate consumption may be protective. Those findings were reinforced by a recent observational study that found a lower risk of undergoing cataract surgery with low to moderate alcohol consumption, especially wine consumption.²⁵ More recently, a MR study found no evidence for a causal effect of alcohol consumption (drinks per week) on cataract risk in either the FinnGen consortium or the UK Biobank study.⁴³ Similarly, although we used a large number of genetic instruments for this lifestyle exposure (drinks per week), our current MR estimates did not indicate a potential causal association for alcohol consumption with cataract risk.

Our study has important strengths. Our two-sample MR analyses were performed using independent and large GWAS summary statistics for both exposures and outcomes. This allowed us to evaluate the association of behavioral and clinical risk factors with the risk of cataract using strong genetic instruments that consist of multiple SNVs across the genome previously reported as genome-wide significant in large samples. We found similar results using different MR methods, especially MR-PRESSO, which is a robust method for sensitivity analysis that excludes outlier SNVs for which horizontal pleiotropic effect can be observed. Finally, for all of the MR analyses, the two samples tested represented the same ethnic group (i.e., European ancestry individuals), enabling comparisons between exposures and outcomes and ensuring the validity of causal estimates.

Our study also has limitations. First, although we used summary statistics from the largest GWAS of cataract conducted to date,¹² the number of cataract cases (i.e., mainly patients who underwent cataract surgery) is limited compared to the number of cases used in MR studies for other outcomes. Future GWAS studies of cataract could focus on more statistically powerful cataract outcomes, such as age of cataract diagnosis or age at cataract surgery. Those outcomes could then be used in future MR studies that could provide additional important insights into the causal pathways underlying cataractogenesis. Second, subtypes of cataract were not available in the GERA and UK Biobank cohorts when we conducted our previous GWAS study.¹² Future MR studies using other cohorts will determine whether genetically determined POAG and myopic RE are also associated with specific cataract subtypes (i.e., nuclear, cortical, or subcapsular) and the extent to which these potential specific causal associations display shared pathways across subtypes. Third, the generalizability of our findings might not be applicable to non-European ancestry populations, due to the previously observed (and above-mentioned) inconsistent associations between genetically determined T2D and cataract between East Asians and Europeans.⁴² Future investigations could address this limitation as genetic data in other ethnic groups become more available.

Our findings support the use of POAG and myopic RE as ophthalmic metrics to help stratify risk of cataract in the general population. Understanding which factors increase risk of cataract could not only help identify high-risk individuals but also help develop preventative strategies.

CONCLUSIONS

Using a two-sample MR approach, our study supports previous observational studies showing that myopic RE is a risk factor for cataract. Our study also provides evidence that genetically determined POAG increased the risk of cataract. Altogether, clarifying the nature of the relationships between those ophthalmic conditions and cataract could open new avenues of investigation into the specific mechanisms underlying this leading cause of blindness.

Acknowledgments

The authors are grateful to the Kaiser Permanente Northern California members who have generously agreed to participate in the Kaiser Permanente Research Program on Genes, Environment, and Health. Support for participant enrollment, survey completion, and biospecimen collection for the RPGEH was provided by the Robert Wood Johnson Foundation, the Wayne and Gladys Valley Foundation, the Ellison Medical Foundation, and Kaiser Permanente Community Benefit Programs. Genotyping of the GERA cohort was funded by a grant from the National Institute on Aging, National Institute of Mental Health, and National Institute of Health Common Fund (RC2 AG036607). This work was also supported by grants from the National Eye Institute (R01 EY033010 to HC and SAL; R01 EY027004 to HC).

Disclosure: **C. Jiang**, None; **R.B. Melles**, None; **P. Sangani**, None; **T.J. Hoffmann**, None; **P.G. Hysi**, None; **M.M. Glymour**, None; **E. Jorgenson**, None; **S.A. Lachke**, None; and **H. Choquet**, None

References

- Congdon N, Vingerling JR, Klein BE, et al. Prevalence of cataract and pseudophakia/aphakia among adults in the United States. *Arch Ophthalmol*. 2004;122(4):487–494.
- Liu YC, Wilkins M, Kim T, Malyugin B, Mehta JS. Cataracts. *Lancet*. 2017;390(10094):600–612.
- Davis G. The evolution of cataract surgery. *Mo Med*. 2016;113(1):58–62.
- Day AC, Donachie PH, Sparrow JM, Johnston RL, Royal College of Ophthalmologists' National Ophthalmology Database. The Royal College of Ophthalmologists' National Ophthalmology Database study of cataract surgery: report 1, visual outcomes and complications. *Eye (Lond)*. 2015;29(4):552–560.
- Hong AR, Sheybani A, Huang AJ. Intraoperative management of posterior capsular rupture. *Curr Opin Ophthalmol*. 2015;26(1):16–21.
- Heiba IM, Elston RC, Klein BE, Klein R. Genetic etiology of nuclear cataract: evidence for a major gene. *Am J Med Genet*. 1993;47(8):1208–1214.
- Hammond CJ, Snieder H, Spector TD, Gilbert CE. Genetic and environmental factors in age-related nuclear cataracts in monozygotic and dizygotic twins. *N Engl J Med*. 2000;342(24):1786–1790.
- Hammond CJ, Duncan DD, Snieder H, et al. The heritability of age-related cortical cataract: the twin eye study. *Invest Ophthalmol Vis Sci*. 2001;42(3):601–605.
- Congdon N, Broman KW, Lai H, et al. Nuclear cataract shows significant familial aggregation in an older population after adjustment for possible shared environmental factors. *Invest Ophthalmol Vis Sci*. 2004;45(7):2182–2186.
- Sanfilippo PG, Hewitt AW, Hammond CJ, Mackey DA. The heritability of ocular traits. *Surv Ophthalmol*. 2010;55(6):561–583.
- Yonova-Doing E, Forkin ZA, Hysi PG, et al. Genetic and dietary factors influencing the progression of nuclear cataract. *Ophthalmology*. 2016;123(6):1237–1244.
- Choquet H, Melles RB, Anand D, et al. A large multiethnic GWAS meta-analysis of cataract identifies new risk loci and sex-specific effects. *Nat Commun*. 2021;12(1):3595.
- Beltrán-Zambrano E, García-Lozada D, Ibáñez-Pinilla E. Risk of cataract in smokers: a meta-analysis of observational studies. *Arch Soc Esp Ophthalmol (Engl Ed)*. 2019;94(2):60–74.
- Chang JR, Koo E, Agron E, et al. Risk factors associated with incident cataracts and cataract surgery in the Age-Related Eye Disease Study (AREDS): AREDS report number 32. *Ophthalmology*. 2011;118(11):2113–2119.
- Floud S, Kuper H, Reeves GK, Beral V, Green J. Risk factors for cataracts treated surgically in postmenopausal women. *Ophthalmology*. 2016;123(8):1704–1710.
- Gong Y, Feng K, Yan N, Xu Y, Pan CW. Different amounts of alcohol consumption and cataract: a meta-analysis. *Optom Vis Sci*. 2015;92(4):471–479.
- Hiratsuka Y, Ono K, Murakami A. Alcohol use and cataract. *Curr Drug Abuse Rev*. 2009;2(3):226–229.
- Hugosson M, Ekström C. Prevalence and risk factors for age-related cataract in Sweden. *Ups J Med Sci*. 2020;125(4):311–315.
- Li L, Wan XH, Zhao GH. Meta-analysis of the risk of cataract in type 2 diabetes. *BMC Ophthalmol*. 2014;14:94.
- Mukesh BN, Le A, Dimitrov PN, et al. Development of cataract and associated risk factors: the Visual Impairment Project. *Arch Ophthalmol*. 2006;124(1):79–85.
- Tan JS, Wang JJ, Mitchell P. Influence of diabetes and cardiovascular disease on the long-term incidence of cataract: the Blue Mountains eye study. *Ophthalmic Epidemiol*. 2008;15(5):317–327.
- Tang Y, Wang X, Wang J, et al. Risk factors of age-related cataract in a Chinese adult population: the Taizhou Eye Study. *Clin Exp Ophthalmol*. 2018;46(4):371–379.
- Ye J, He J, Wang C, et al. Smoking and risk of age-related cataract: a meta-analysis. *Invest Ophthalmol Vis Sci*. 2012;53(7):3885–3895.
- Younan C, Mitchell P, Cumming RG, Rochtchina E, Wang JJ. Myopia and incident cataract and cataract surgery: the blue mountains eye study. *Invest Ophthalmol Vis Sci*. 2002;43(12):3625–3632.
- Chua SYL, Luben RN, Hayat S, et al. Alcohol consumption and incident cataract surgery in two large UK cohorts. *Ophthalmology*. 2021;128(6):837–847.
- Brown NA, Hill AR. Cataract: the relation between myopia and cataract morphology. *Br J Ophthalmol*. 1987;71(6):405–414.
- Chang MA, Congdon NG, Bykhovskaya I, Munoz B, West SK. The association between myopia and various subtypes of lens opacity: SEE (Salisbury Eye Evaluation) project. *Ophthalmology*. 2005;112(8):1395–401.
- Hoffer KJ. Axial dimension of the human cataractous lens. *Arch Ophthalmol*. 1993;111(7):914–918.
- Pan CW, Cheng CY, Saw SM, Wang JJ, Wong TY. Myopia and age-related cataract: a systematic review and meta-analysis. *Am J Ophthalmol*. 2013;156(5):1021–1033.e1.
- Pan CW, Cheung CY, Aung T, et al. Differential associations of myopia with major age-related eye diseases: the Singapore Indian Eye Study. *Ophthalmology*. 2013;120(2):284–291.
- Ang MJ, Afshari NA. Cataract and systemic disease: a review. *Clin Exp Ophthalmol*. 2021;49(2):118–127.
- Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32(1):1–22.

33. Swerdlow DI, Kuchenbaecker KB, Shah S, et al. Selecting instruments for Mendelian randomization in the wake of genome-wide association studies. *Int J Epidemiol.* 2016;45(5):1600–1616.
34. Paternoster L, Tilling K, Davey Smith G. Genetic epidemiology and Mendelian randomization for informing disease therapeutics: conceptual and methodological challenges. *PLoS Genet.* 2017;13(10):e1006944.
35. Davey Smith G, Paternoster L, Relton C. When will Mendelian randomization become relevant for clinical practice and public health? *JAMA.* 2017;317(6):589–591.
36. Mokry LE, Ahmad O, Forgetta V, Thanassoulis G, Richards JB. Mendelian randomisation applied to drug development in cardiovascular disease: a review. *J Med Genet.* 2015;52(2):71–79.
37. Choquet H, Khawaja AP, Jiang C, et al. Association between myopic refractive error and primary open-angle glaucoma: a 2-sample Mendelian randomization study. *JAMA Ophthalmol.* 2022;140(9):864–871.
38. Han X, Ong JS, An J, et al. Association of myopia and intraocular pressure with retinal detachment in European descent participants of the UK Biobank Cohort: a Mendelian randomization study. *JAMA Ophthalmol.* 2020;138(6):671–678.
39. Kuan V, Warwick A, Hingorani A, et al. Association of smoking, alcohol consumption, blood pressure, body mass index, and glycemic risk factors with age-related macular degeneration: a Mendelian randomization study. *JAMA Ophthalmol.* 2021;139(12):1299–1306.
40. Tan AG, Kifley A, Flood VM, et al. Evaluating the associations between obesity and age-related cataract: a Mendelian randomization study. *Am J Clin Nutr.* 2019;110(4):969–976.
41. Larsson SC, Burgess S. Appraising the causal role of smoking in multiple diseases: A systematic review and meta-analysis of Mendelian randomization studies. *EBioMedicine.* 2022;82:104154.
42. Zhang H, Xiu X, Xue A, et al. Mendelian randomization study reveals a population-specific putative causal effect of type 2 diabetes in risk of cataract. *Int J Epidemiol.* 2022;50(6):2024–2037.
43. Yuan S, Wolk A, Larsson SC. Metabolic and lifestyle factors in relation to senile cataract: a Mendelian randomization study. *Sci Rep.* 2022;12(1):409.
44. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. *eLife.* 2018;7:e34408.
45. Kvale MN, Hesselton S, Hoffmann TJ, et al. Genotyping informatics and quality control for 100,000 subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. *Genetics.* 2015;200(4):1051–1060.
46. Banda Y, Kvale MN, Hoffmann TJ, et al. Characterizing race/ethnicity and genetic ancestry for 100,000 subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. *Genetics.* 2015;200(4):1285–1295.
47. Gharahkhani P, Jorgenson E, Hysi P, et al. Genome-wide meta-analysis identifies 127 open-angle glaucoma loci with consistent effect across ancestries. *Nat Commun.* 2021;12(1):1258.
48. Hysi PG, Choquet H, Khawaja AP, et al. Meta-analysis of 542,934 subjects of European ancestry identifies new genes and mechanisms predisposing to refractive error and myopia. *Nat Genet.* 2020;52(4):401–407.
49. Mahajan A, Taliun D, Thurner M, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet.* 2018;50(11):1505–1513.
50. Hoffmann TJ, Ehret GB, Nandakumar P, et al. Genome-wide association analyses using electronic health records identify new loci influencing blood pressure variation. *Nat Genet.* 2017;49(1):54–64.
51. Hoffmann TJ, Choquet H, Yin J, et al. A large multiethnic genome-wide association study of adult body mass index identifies novel loci. *Genetics.* 2018;210(2):499–515.
52. Saunders GRB, Wang X, Chen F, et al. Genetic diversity fuels gene discovery for tobacco and alcohol use. *Nature.* 2022;612(7941):720–724.
53. Wootton RE, Richmond RC, Stuijzand BG, et al. Evidence for causal effects of lifetime smoking on risk for depression and schizophrenia: a Mendelian randomisation study. *Psychol Med.* 2020;50(14):2435–2443.
54. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol.* 2015;44(2):512–525.
55. Burgess S, Davey Smith G, Davies NM, et al. Guidelines for performing Mendelian randomization investigations. *Wellcome Open Res.* 2019;4:186.
56. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet.* 2018;50(5):693–698.
57. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS Genet.* 2017;13(11):e1007081.
58. Chong RS, Li H, Cheong AJY, et al. Mendelian randomization implicates bidirectional association between myopia and primary open-angle glaucoma or intraocular pressure. *Ophthalmology.* 2023;130(4):394–403.
59. Sanderson E, Davey Smith G, Windmeijer F, Bowden J. An examination of multivariable Mendelian randomization in the single-sample and two-sample summary data settings. *Int J Epidemiol.* 2019;48(3):713–727.
60. Burgess S, Thompson SG. Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. *Am J Epidemiol.* 2015;181(4):251–260.
61. Leske MC, Wu SY, Nemesure B, Hennis A, Barbados Eye Studies Group. Risk factors for incident nuclear opacities. *Ophthalmology.* 2002;109(7):1303–1308.
62. Lim R, Mitchell P, Cumming RG. Refractive associations with cataract: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci.* 1999;40(12):3021–3026.
63. Simonelli F, Nesti A, Pensa M, et al. Lipid peroxidation and human cataractogenesis in diabetes and severe myopia. *Exp Eye Res.* 1989;49(2):181–187.
64. Micelli-Ferrari T, Vendemiale G, Grattagliano I, et al. Role of lipid peroxidation in the pathogenesis of myopic and senile cataract. *Br J Ophthalmol.* 1996;80(9):840–843.
65. Zigler JS, Jr, Bodaness RS, Gery I, Kinoshita JH. Effects of lipid peroxidation products on the rat lens in organ culture: a possible mechanism of cataract initiation in retinal degenerative disease. *Arch Biochem Biophys.* 1983;225(1):149–156.
66. Boscia F, Grattagliano I, Vendemiale G, Micelli-Ferrari T, Altomare E. Protein oxidation and lens opacity in humans. *Invest Ophthalmol Vis Sci.* 2000;41(9):2461–2465.
67. Zhu XJ, Zhou P, Zhang KK, et al. Epigenetic regulation of α A-crystallin in high myopia-induced dark nuclear cataract. *PLoS One.* 2013;8(12):e81900.
68. Zhu X, Li D, Du Y, He W, Lu Y. DNA hypermethylation-mediated downregulation of antioxidant genes contributes to the early onset of cataracts in highly myopic eyes. *Redox Biol.* 2018;19:179–189.
69. Zhu X, Du Y, Li D, et al. Aberrant TGF- β 1 signaling activation by MAF underlies pathological lens growth in high myopia. *Nat Commun.* 2021;12(1):2102.

70. Lai W, Wu X, Liang H. Identification of the potential key genes and pathways involved in lens changes of high myopia. *Int J Gen Med.* 2022;15:2867–2875.
71. Babizhayev MA. Biomarkers and special features of oxidative stress in the anterior segment of the eye linked to

lens cataract and the trabecular meshwork injury in primary open-angle glaucoma: challenges of dual combination therapy with *N*-acetylcarnosine lubricant eye drops and oral formulation of nonhydrolyzed carnosine. *Fundam Clin Pharmacol.* 2012;26(1):86–117.