Observational Study

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# Hyperopia may exert a protective effect against senile cataracts

## Evidence from a Mendelian randomization study

Guoqing Wang, MM[a,b], Xianglong Yi, MD, PhD[a,b,*]

**Abstract**

Myopia has been extensively documented as a significant risk factor for cataracts; however, the relationship between hyperopia and cataract development remains poorly understood. Given the distinct refractive profiles of myopia and hyperopia, hyperopia may confer a protective effect against cataracts. In this study, we employed Mendelian randomization (MR) to examine the causal association between hyperopia and cataracts. A 2-sample MR framework was utilized to examine the causal relationship between hyperopia and cataracts, with multivariable MR implemented to account for potential confounding variables. The inverse variance weighted (IVW) method served as the primary analytical tool, complemented by multiple sensitivity analyses to ensure the robustness and reliability of the findings. Enrichment analyses were conducted to elucidate the underlying biological pathways, while Bayesian colocalization analysis pinpointed shared genetic loci that influence both hyperopia and cataracts. In our study, we found that hyperopia may exert a protective effect against cataracts (IVW odds ratio, 0.920 [95% confidence interval, 0.872–0.972]; $P = .0029$) and cataract surgery (IVW odds ratio, 0.811 [95% confidence interval, 0.754–0.873]; $P < .0001$). Multivariable MR, adjusting for confounding factors such as smoking, glaucoma, and diabetes, confirmed hyperopia's protective association with cataracts. Bayesian colocalization identified rs12193446 as a high-probability shared causal variant, while enrichment analyses revealed potential biological mechanisms linking hyperopia to cataract development. Genetic evidence suggests that higher levels of hyperopia are associated with a reduced risk of age-related nuclear cataracts, cataract extraction, and lens implants. Given the opposite refractive states of myopia and hyperopia and their opposite effects on cataracts, these findings provide new insights into the pathogenesis of age-related cataracts.

**Abbreviations:** CI = confidence interval, GO = Gene Ontology, GWAS = Genome-Wide Association Study, IVW = inverse variance weighted, KEGG = Kyoto Encyclopedia of Genes and Genomes, MR = Mendelian randomization, OR = odds ratio, SNP = single-nucleotide polymorphism.

**Keywords:** cataract, hyperopia, Mendelian randomization

## 1. Introduction

Cataracts, which cause lens opacification, are a major cause of visual impairment and blindness in the global elderly population.[1] In China, >22% of adults aged 45 to 89 suffer from cataracts.[2] Further research shows that 53% to 58% of individuals over 60 have cataracts.[3] Various previous studies have shown that myopia increases the risk of age-related cataracts.[4–6] However, hyperopia and myopia are 2 different refractive states, and the effect of hyperopia on age-related cataracts is unclear. Figuring out the effect of hyperopia on cataracts helps to understand the pathogenesis of age-related cataracts.

Cataract is a multifactorial disease associated with genetic and environmental factors.[7,8] Studies have shown that cataracts are significantly more common in patients with high myopia than in patients without high myopia.[9] The paucity of studies exploring the causal connection between cataracts and hyperopia can be attributed to the relatively lower prevalence of hyperopia compared with myopia, and the restrictive conditions of potential research scenarios. The inherent limitations of hyperopia research are primarily attributable to biases and confounding factors common in observational epidemiological studies, such as small sample sizes, population heterogeneity, reverse

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*This study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent and ethical approval are not required for Mendelian randomization studies.*

*[a] Department of Ophthalmology, First Affiliated Hospital of Xinjiang Medical University, Urumqi, China, [b] Xinjiang Medical University, Urumqi, China.*

** Correspondence: Xianglong Yi, Xinjiang Medical University, No. 393 Xinyi Road, Xinshi District, Urumqi, Xinjiang Uygur Autonomous Region 830000, China (e-mail: yixianglong1010@163.com).*



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causation, and selection biases, which obscure the causal linkage between hyperopia and cataracts.

Mendelian randomization (MR) is an analytical method utilizing the reported causal effects of genetic variants on disease outcomes.[10] The advantage of MR over traditional observational studies is that it is less susceptible to confounding factors or reverse causation.[11] MR has been extensively utilized to establish causality,[12] with applications in studies on colon cancer,[13] lung cancer,[14] and various exposure factors. In this paper, we adopt a new perspective on cataract pathogenesis through MR. To our knowledge, this is the first systematic assessment of how hyperopia affects cataract risk.

## 2. Methods

### 2.1. Study design

We employed MR design to assess the influence of exposure factors on cataract outcomes, utilizing summary statistics from independent Genome-Wide Association Studies (GWAS).[15] Hyperopia was designated as an exposure factor, with outcomes including senile incipient cataracts, senile nuclear cataracts, and procedures such as cataract extraction surgery and lens implantation. The MR approach is based on 3 core assumptions, detailed in Figure 1.[16,17] Initially, the genetic tools should demonstrate a significant correlation with the targeted biomarker. Moreover, these genetic tools ought to connect to the outcomes primarily via exposure, omitting any irrelevant biological routes. In addition, these genetic tools must not relate to any elements that could skew the relationship between exposure and outcome. Several analyses were performed utilizing the Bonferroni adjustment, and a $P$ value below $1.7 \times 10^{-2}$ (=0.05/3) was considered significant.

Due to the limited availability of GWAS databases on hyperopia and lens implantation/cataract surgery, this study primarily utilized data from the UK Biobank. However, using the UK Biobank dataset in its entirety presents the issue of sample overlap, which may influence causality. To enhance the robustness of our findings, we included data from the European Institute for Information Research for ebi-a-GCST90018814 (cataracts) and from FinnGen for finn-b-H7_CATARACTSENILE (age-related cataracts). These additional datasets were further utilized to validate the effect of hyperopia on age-related cataracts. To better assess the impact of hyperopia on cataract, we employed multivariable MR analysis to strengthen the evidence for our findings. A $P$ value of $< .05$ was considered significant in the additional cohort validation.

To establish the associations between single-nucleotide polymorphisms (SNPs) and genes, we first annotated each SNP based on its genomic position. For each SNP, we defined an extended range by expanding 10,000 base pairs upstream and downstream from its location (with the range adjustable as needed). Using the Ensembl Gene database, we obtained a list of genes located within these extended regions, including each gene's Ensembl Gene ID, gene name, and Entrez Gene ID. At this stage, we filtered the genes associated with each SNP and compiled the relevant information into a data frame named gene_list. To avoid redundancy, we removed duplicate entries, ensuring that each gene was listed only once. After compiling the list of relevant genes, we performed Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses. In addition, we conducted a Disease Gene Network enrichment analysis to identify associations between disease-associated genes and relevant biological pathways. GO Enrichment Analysis: We performed GO enrichment analysis on the Entrez Gene IDs of the genes using the enrichGO function, with significance thresholds set at $P$ value and $q$ value $< .05$. All GO domains, including biological processes, molecular functions, and cellular components, were considered in the analysis. KEGG Enrichment Analysis: we conducted KEGG pathway enrichment analysis on the same gene set using the enrich KEGG function, with significance thresholds set at $P$ value and $q$ value $< 1$. The aim was to identify the involvement of these genes in cellular signaling, metabolic processes, and other critical biological pathways.

To explore the hypothesized protective role of hyperopia in age-related cataract development, a Bayesian colocalization analysis was performed using the coloc package to identify shared genetic loci associated with both conditions. The hyperopia

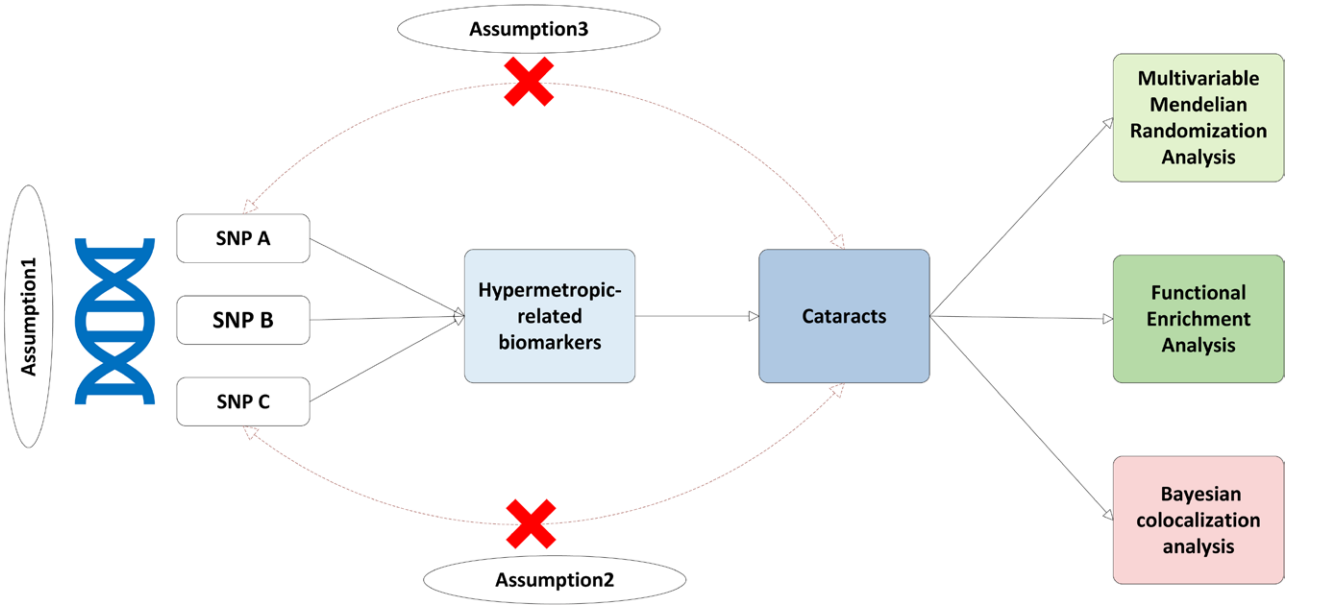


**Figure 1.** Illustration depicting the fundamental ideas and underlying assumptions of MR. Assumption 1: the genetic instruments should exhibit a robust and dependable association with the specified biomarker of interest. Assumption 2: the genetic instruments should directly associate with the outcome solely through the exposure, without mediation by any unrelated biological pathways. Assumption 3: the genetic instruments must not be linked with any confounding factors that might affect the relationship between the exposure and the outcome. MR=Mendelian randomization.

dataset, derived from the UK Biobank (ukb-b-18189), included 19,050 cases and 441,486 controls, whereas the cataract dataset, obtained from the European Bioinformatics Institute (European Bioinformatics Institute; GCST90018814), comprised 39,519 cases and 452,358 controls. These findings offer compelling evidence for shared genetic determinants, thereby underscoring the need for additional genetic and mechanistic investigations into the relationship between hyperopia and cataracts.

Table 1 presents a comprehensive overview of the summary statistics derived from the GWAS for cataract-related traits, encompassing critical parameters such as sample size, data sources, and pivotal statistical metrics.

### 2.2. GWAS summary statistics for hyperopia and cataracts

The OpenGWAS repository (https://gwas.mrcieu.ac.uk/) hosted by the MRC Integrated Epidemiology Unit includes a comprehensive GWAS summary dataset focused on hyperopia and cataracts. Given the unclear association between various forms of age-related cataracts and hyperopia, the Royal Research Council Integrated Epidemiology Unit dataset for hyperopia integration (ukb-b-18189),[18,19] enrolling a total of 460,536 participants of European descent, served as an exposure variable. Characteristics linked to age-related cataracts were also incorporated in this analysis, featuring age-related initial cataracts (dataset ukb-b-2285; n = 463,010), age-related nuclear cataracts (dataset ukb-b-3095; n = 463,010), and cataract extraction surgery combined with intraocular lens implantation (dataset ukb-b-6266; n = 462,933) as outcomes. When validated with additional datasets, the exposure data remained ukb-b-18189, while the outcome data were ebi-a-GCST90018814 for cataracts (n = 491,877) and finn-b-H7_CATARACTSENILE for senile cataracts (n = 216,362).We chose only genetic variants achieving genome-wide significance ($P < 5 \times 10^{-8}$) for MR analysis.

### 2.3. MR analysis and sensitivity analysis

MR analysis between hyperopia and relevant features associated with cataracts was performed using the TwoSampleMR, v0.5.11 R package (R Foundation for Statistical Computing, Vienna, Austria).[20] The criteria set for selecting genetic instruments for each trait included: $P < 5 \times 10^{-8}$; linkage disequilibrium $r2 < .001$; and a linkage disequilibrium distance exceeding 10,000 kb. The principal technique employed to evaluate the association between hyperopia and senile cataracts was the inverse variance weighting (IVW) method.[21] For the sensitivity analysis, 3 supplementary methods were employed using the TwoSampleMR R package,[22] These methods include MR Egger regression, the weighted median approach, and the weighted mode technique. These methods were specifically selected to tackle horizontal pleiotropy. Consequently, the results of the MR analysis were considered significant if the IVW method identified a correlation ($P < .017$) and all 4 MR techniques indicated effects in the same direction.

To further examine the robustness of these associations, we analyzed the effects of potential horizontal pleiotropy. In addition, we performed extensive sensitivity analyses employing techniques such as the Mendelian randomization-Pleiotropy-Residual Sum and Outlier Test (MR-PRESSO) test, Egger intercept, leave-one-out analysis, heterogeneity tests, and the Steiger test.

***2.3.1. Ethical approval.*** This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was waived for this study as it utilized publicly available summary-level data from GWAS and did not involve direct human subject participation.

***2.3.2. Informed consent.*** Informed consent was not required for this study as it utilized de-identified, publicly available data

## 3. Results

### 3.1. The effect of hyperopia on age-related nuclear cataracts

Genetically predicted hyperopia was observed to have a significant and inverse correlation with the occurrence of senile nuclear cataracts and the frequency of cataract surgeries or intraocular lens implantations. IVW (odds ratio [OR], 0.920 [95% confidence interval [CI], 0.872–0.972]; $P = .0029$), MR-Egger (OR, 0.919 [95% CI, 0.304–2.778]; $P = .894$), the weighted median technique (OR, 0.927 [95% CI, 0.868–0.900]; $P = .0235$), and the weighted mode approach (OR, 0.935 [95% CI, 0.847–1.033]; $P = .280$). The trend of hyperopia's effect consistently indicates a protective role against age-related nuclear cataracts. Figure 2 presents a scatter plot illustrating the extent of the effect linking hyperopia with senile nuclear cataracts as demonstrated by the MR study. The IVW findings continued to be statistically significant even after the application of the Bonferroni correction ($P < .017$).

To assess the robustness and dependability of the causal linkage between hyperopia and senile nuclear cataracts, we undertook a comprehensive sensitivity analysis. The Egger intercept was minimal (intercept < 0.0001) with a $P$ value exceeding 0.017, indicating a lack of significant evidence for directional horizontal pleiotropy effects. Furthermore, the MR-PRESSO test revealed no horizontal pleiotropic outliers distorting these findings. The global test registered a $P$ value above .017 ($P = .518$). Heterogeneity tests further confirmed an absence of significant heterogeneity in both the IVW and MR-Egger approaches. $P$ values of .476 for the IVW approach and .287 for the MR-Egger approach both exceeded .017. A leave-one-out analysis was performed, and no outlier was identified. We also evaluated the reverse model, estimating the impact of senile nuclear cataracts on hyperopia. For the senile nuclear cataract dataset (ukb-b-3095), no instrumental variables were chosen when the $P$ value fell below $5 \times 10^{-8}$ during the genetic instrument selection phase. However, setting the $P$ value threshold to $1 \times 10^{-5}$ resulted in the selection of 8 SNPs,

**Table 1**

**Description of Genome-Wide Association Study summary statistics for cataracts traits.**

| Traits | Accession Number* | Sample sizes | Number of SNPs | Population ethnicity | Study |
|---|---|---|---|---|---|
| Senile incipient cataract | ukb-b-2285 | 463,010 | 9,851,867 | European | Backman et al[17] |
| Senile nuclear cataract | ukb-b-3095 | 463,010 | 9,851,867 | European | Backman et al[17] |
| Cataract extraction/lens implant | ukb-b-6266 | 462,933 | 9,851,867 | European | Mitchell[15,17] |
| Senile cataract | finn-b-H7_CATARACTSENILE | 216,362 | 16,380,461 | European | Mitchell[18] |
| Cataract | ebi-a-GCST90018814 | 491,877 | 24,163,031 | European | Mitchell[18] |

SNP=single-nucleotide polymorphism.

*The GWAS summary dataset of cataract features was obtained from the MRC IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/).

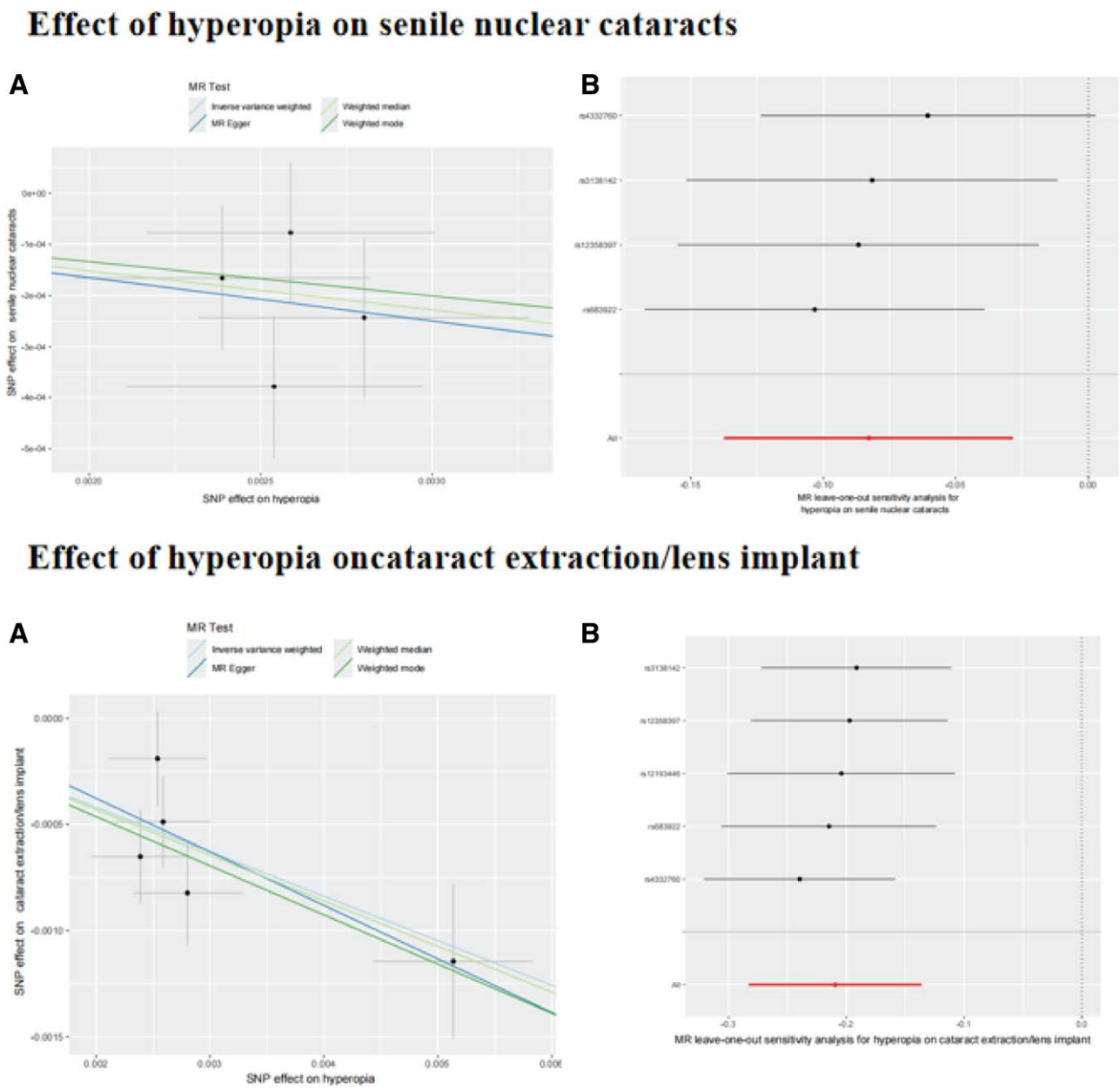


**Figure 2.** Effect of hyperopia on senile nuclear cataracts and cataract extraction/lens implantation. (A) Scatterplot illustrating the MR analysis of the causal impact of hyperopia on senile cataracts.[12] The slope of each line represents the MR effect as estimated by different approaches. (B) Exclusion analysis assessing the causal impact of hyperopia levels on senile cataracts. MR=Mendelian randomization.

and a MR analysis was conducted utilizing these SNPs. The results obtained indicated no observed associations, as all MR models registered *P* values above .017. To determine the explained variance of instrumented SNPs on both exposure and outcome, the Steiger test was utilized for directionality assessments of exposure and outcome.[23] The findings indicated that the variance in exposure significantly exceeded that in the outcome; the Staiger test direction was TRUE, with a *P* value below .001, suggesting an absence of reverse causality between exposure and outcome. Overall, these results corroborate the causal link between hyperopia and senile nuclear cataracts.

Table 2 examines how hyperopia affects different types of cataracts, including nuclear and incipient cataracts, as well as its connection to cataract surgery and lens implantation outcomes. The results are presented using key statistical measures like ORs and CIs, offering a clear picture of these relationships.

### *3.2. The effect of hyperopia on cataract extraction/lens implant*

Moreover, a correlation has been noted between the degree of hyperopia and cataract surgery, with the IVW method indicating that elevated levels of hyperopia are significantly linked to a decreased risk of cataract surgery (OR, 0.811 [95% CI, 0.754–0.873]; *P* < .0001). The remaining 3 MR methods—MR-Egger, weighted median, and weighted mode—also produced consistent outcomes. The MR-Egger approach demonstrated an OR of 0.777, with a 95% CI ranging from 0.565 to 1.069, and a *P* value of .218. The weighted median technique produced an OR of 0.807, with a 95% CI between 0.728 and 0.893, and a *P* value of <.0001. Finally, the weighted mode technique resulted in an OR of 0.793, with a 95% CI spanning 0.689 to 0.914, and a *P* value of .033.

The leave-one-out analysis shows that there were no outliers. The Egger intercept computation showed no substantial evidence

**Table 2**

**Effect of hyperopia on different types of cataracts and cataract extraction/lens implant.**

| Outcome | SNPs | Methods | OR | 95% CI | *P* value |
|---|---|---|---|---|---|
| Senile incipient cataract | 3 | Inverse variance weighted | 0.978 | 0.933–1.024 | .338 |
| | | MR-Egger | 0.435 | 0.111–1.707 | .44 |
| | | Weighted median | 0.986 | 0.928–1.047 | .648 |
| | | Weighted mode | 0.998 | 0.929–1.071 | .958 |
| Senile nuclear cataract | 4 | Inverse variance weighted | 0.920 | 0.872–0.972 | .0029* |
| | | MR-Egger | 0.919 | 0.304–2.778 | .894 |
| | | Weighted median | 0.927 | 0.868–0.990 | .0235 |
| | | Weighted mode | 0.935 | 0.847–1.033 | .280 |
| Cataract extraction/lens implant | 5 | Inverse variance weighted | 0.811 | 0.754–0.873 | <.0001* |
| | | MR-Egger | 0.777 | 0.565–1.069 | .218 |
| | | Weighted median | 0.807 | 0.728–0.893 | <.0001* |
| | | Weighted mode | 0.793 | 0.689–0.914 | .033 |

CI=confidence interval, MR=Mendelian randomization, OR=odds ratio, SNP=single-nucleotide polymorphism.
*Significance was defined as $P < .05$.

for a directed-level multidirectional effect (intercept = 0.00013, <0.001; *P* value = .803, >0.017). The MR-PRESSO test indicated that the *P* value for the original MR analysis stood at .0046, with no outliers detected in the adjusted MR analysis. The MR-PRESSO Global Test produced a *P* value of .551, above the significance threshold of .017, suggesting an absence of horizontal pleiotropy. The heterogeneity test, including Cochran Q test for IVW and MR-Egger, recorded *P* values of .293 and .431, respectively, both exceeding .017, indicating no heterogeneity. An absence of association was observed when evaluating the impact of cataract extraction or lens implantation on hyperopia through inverse modeling. The IVW approach demonstrated no causal link between cataract extraction/lens implantation and hyperopia ($P = .850$). Outcomes from the other 3 MR approaches (MR-Egger, weighted median, and weighted mode) aligned. The MR-Egger approach had a *P* value of .616, the weighted median approach a *P* value of .784, and the weighted mode approach a *P* value of .750. The aforementioned outcomes suggest that neither cataract extraction nor lens implantation affects hyperopia. The Steiger test was conducted for each SNP, revealing that the variance in hyperopia exposure significantly surpassed that in the cataract extraction/lens implant outcome. The Staiger test outcomes were TRUE, with a *P* value below .001. In conclusion, data from all sensitivity analyses reinforce our initial conclusions. Based on stringent criteria (IVW $P < .017$, with all 4 MR approaches consistently oriented), no significant association was detected between senile incipient cataracts and hyperopia.

### 3.3. The effect of hyperopia on cataract in the validation cohort

In the validation cohort, analyses using the UK Biobank data and the Finnish dataset showed significant results for the IVW method (OR, 0.000092 [95% CI, 0.0000013–0.0066]; $P = .000019$). The other 3 MR methods—MR-Egger, weighted median, and weighted mode—also yielded consistent results, as shown in Figure 3. Specifically, the analysis of the IVW method on the UK Biobank and European Bioinformatics Institute datasets yielded similar results (OR, 0.00014 [95% CI, 0.0000023–0.0088]; $P = .000025$), as shown in Figure 3. These findings suggest that hyperopia remains protective against age-related cataracts. Table 3 employs ORs and 95% CIs to elucidate the association between hyperopia and cataract across diverse cohorts.

### 3.4. Hyperopia and multivariable MR results

After adjusting for common factors affecting cataract, including type 2 diabetes, body mass index, smoking, glaucoma, etc, through multivariable MR, the effect of hyperopia on senile cataract remains robust. However, after adjusting for all these confounding factors, the protective effect of hyperopia and the harmful effect of smoking are no longer significant. The *P* value for hyperopia is .2146, and the *P* value for ever smoked is .6765. Results as shown in Table 4

### 3.5. SNP annotation result

We initially connected to the Ensembl SNP dataset (ENSEMBL_MART_SNP) using the useMart function. This dataset, provided by Ensembl, is a specialized resource for obtaining annotation information related to SNPs. The specific dataset selected was the human genome SNP dataset (hsapiens_snp). The results are presented in Table 5 and visualized in Figure 4.

### 3.6. GO, KEGG, Disease Gene Network enrichment results[24]

GO Enrichment Key Pathway: Integrin-Mediated Signaling, the analysis shows significant enrichment in integrin-mediated signaling pathways, including "positive regulation of integrin-mediated signaling pathway" and "regulation of integrin-mediated signaling pathway." Integrin signaling is crucial for cell adhesion and extracellular matrix interactions, both of which help maintain lens transparency and structural integrity. This suggests that genes in integrin pathways may contribute to the observed protective effect against cataracts by supporting cellular adhesion and lens health. In Figure 5. KEGG Pathway Enrichment Analysis, PI3K-Akt Signaling Pathway: this pathway is critical in regulating cell survival, growth, and metabolism. Its enrichment suggests that genes associated with this pathway may contribute to cellular maintenance processes relevant to lens health. Focal Adhesion and Cytoskeleton Regulation: enrichment in pathways such as "Focal adhesion" and "Regulation of actin cytoskeleton" indicates roles in cell adhesion and cytoskeletal organization, both crucial for maintaining lens transparency and structural support. Key Enriched Diseases and Traits: Ocular Conditions: The top enriched terms, including "Abnormality of refraction," "Refractive Errors," "Myopia," and "Severe Myopia," suggest a strong association between the identified genes and various refractive eye conditions. This aligns with the study focus on hyperopia (farsightedness) and cataract risk, indicating potential shared genetic pathways.

### 3.7. Bayesian colocalization analysis

Among the SNPs analyzed, rs12193446 demonstrated an exceptionally high posterior probability for colocalization,

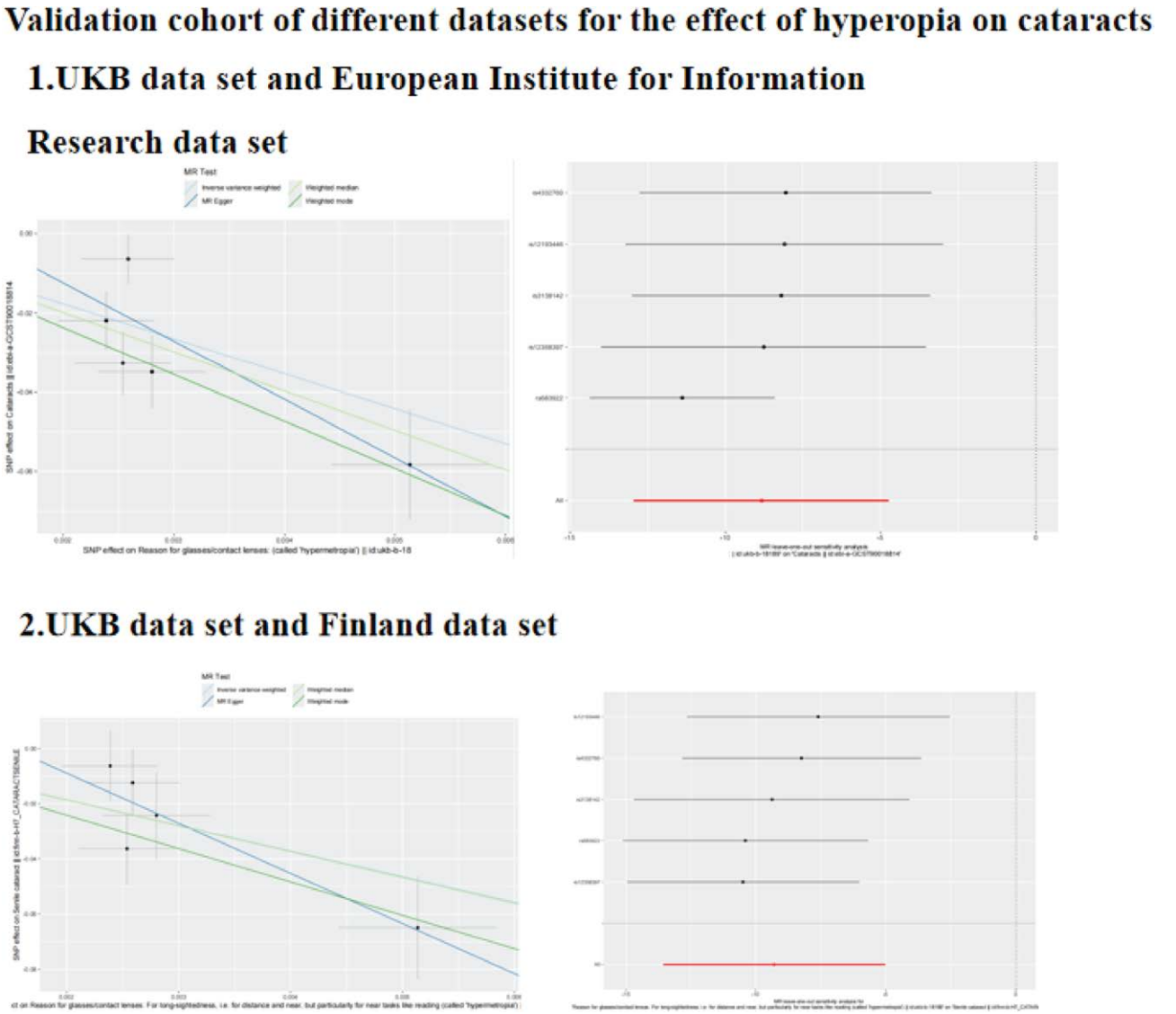


**Figure 3.** The outcomes of 2-sample Mendelian randomization analyses across distinct cohorts are presented, highlighting the robustness and generalizability of the findings.

**Table 3**

**Validation cohort of different datasets.**

| Validation cohort: Mendelian randomization analysis across different datasets | | | | | |
|---|---|---|---|---|---|
| Senile cataract | 5 | Inverse variance weighted | 0.000092 | 0.0000013–0.00660 | .0000197* |
| | | MR-Egger | <0.0001 | <0.000001–0.035 | .0958 |
| | | Weighted median | 0.00008 | <0.000001–0.0193 | .000695 |
| | | Weighted mode | 0.000005 | <0.000001–0.021 | .0450 |
| Cataract | 5 | Inverse variance weighted | 0.00014 | 0.0000023–0.0088 | .000025* |
| | | MR-Egger | 0.00000040 | <0.000001–72.45 | .226 |
| | | Weighted median | 0.000048 | 0.000001–0.0023 | <.0001 |
| | | Weighted mode | 0.0000071 | <0.000001–0.0577 | .055 |

MR=Mendelian randomization.

*Significance was defined as $P < .05$.

with an SNP.PP. H4 value of ≈0.99998. This finding suggests that rs12193446 may serve as a shared causal locus for both hyperopia and cataracts. The high posterior probability of colocalization provides robust evidence that rs12193446 influences both traits via a shared genetic mechanism. The remaining SNPs, including rs12358397, rs3138142, rs4332760, and rs683922, exhibited significantly lower posterior probabilities for colocalization, with SNP.PP. H4 values approaching zero. The low probability of colocalization indicates that these SNPs do not influence both traits through a shared causal pathway, suggesting independent effects on hyperopia and cataracts. The log Approximate Bayes Factor for rs12193446 was substantially higher (28.94) compared with the other SNPs, further corroborating its robust association with both traits. This evidence

**Table 4**

**Multivariate Mendelian randomization result.**

| | Exposure | | Outcome | | *P* value | OR | 95% CI | |
|---|---|---|---|---|---|---|---|---|
| Model 1 | Hypermetropia | ukb-b-18189 | Cataract | ebi-a-GCST90018814 | <.00001* | 0.0148 | 0.0004 | 0.5188 |
| | Type 2 diabetes | ukb-b-10753 | | | .0203 | 10.9074 | 5.6164 | 21.1831 |
| Model 2 | Hypermetropia | ukb-b-18189 | Cataract | ebi-a-GCST90018814 | .0065 | 0.1260 | 0.0283 | 0.5606 |
| | BMI | ukb-b-19953 | | | <.00001 | 1.1916 | 1.1349 | 1.2511 |
| Model 3 | Hypermetropia | ukb-b-18189 | Cataract | ebi-a-GCST90018814 | .0003* | 0.0001 | <0.00001 | 0.0173 |
| | Glaucoma | ukb-d-H40 | | | .0007 | 2,457,242,913.8172 | 9546.2779 | 632,502,299,130,844.0000 |
| Model 4 | Hypermetropia | ukb-b-18189 | Cataract | ebi-a-GCST90018814 | .0001 | 0.0057 | 0.0004 | 0.0797 |
| | Ever smoked | ukb-b-20261 | | | .0128* | 1.4331 | 1.0794 | 1.9026 |
| Model 5 | Type 2 diabetes | ukb-b-10753 | Cataract | ebi-a-GCST90018814 | <.00001 | 7.7253 | 4.5449 | 13.1312 |
| | Hypermetropia | ukb-b-18189 | | | .2146 | 0.3703 | 0.0771 | 1.7779 |
| | BMI | ukb-b-19953 | | | .0399 | 1.0632 | 1.0028 | 1.1271 |
| | Ever smoked | ukb-b-20261 | | | .6765 | 1.0739 | 0.7684 | 1.5007 |
| | Glaucoma | ukb-d-H40 | | | .0071 | 272.5799 | 4.6011 | 16,148.3079 |

CI=confidence interval, BMI=body mass index, OR=odds ratio.

*Significance was defined as $P < .05$.

**Table 5**

**Identification of SNPs through 2-sample Mendelian randomization for hyperopia and cataracts across different datasets**

| SNP | Chromosome | Position | Variant type | Allele | Associated gene(s) |
|---|---|---|---|---|---|
| rs12193446 | 6 | 129498893 | Intron_variant | A/G | *LAMA2*, *ARHGAP18* |
| rs12358397 | 10 | 77307295 | Intron_variant | A/G/T | *ANO2* |
| rs12368397 | 12 | 5658831 | Intron_variant | G/T | *RDH5*, *BLOC1S1* |
| rs3138142 | 12 | 55721801 | Synonymous_variant | C/A/T | *RDH5*, *BLOC1S1*, *CD63* |
| rs4332760 | 16 | 7412044 | Intron_variant | C/G | *ITGA7* |
| rs683922 | 15 | 34716475 | NA | T/C | NA |

NA=missing or unavailable data in the dataset, SNP=single-nucleotide polymorphism.

strengthens the conclusion that rs12193446 is likely a shared causal variant, whereas the remaining SNPs exhibit negligible colocalization signals.

## 4. Discussion

Myopia increases the risk of age-related cataracts, which has been confirmed in many previous studies.[9,25] Myopia is defined as parallel light rays passing through the eye's refractive system and focusing in front of the retina in a state of relaxed accommodation.[26] Hyperopia is defined as parallel light rays passing through the eye's refractive system and focusing behind the retina in a relaxed state of accommodation.[27,28]Myopia and hyperopia have opposite refractive states,[29] the effect of hyperopia on age-related cataracts is unclear and may reduce the risk of cataracts. Therefore, our study, which used MR, provides evidence to support a causal relationship between higher levels of hyperopia and a lower risk of senile nuclear cataract and cataract surgery or lens implantation.

Myopia is a type of refractive error, and in recent years, myopia patients have become more common among adolescents due to the increasing prevalence of myopia.[30] Myopia increases the risk of and prevalence of cataracts. Myopia affects cataracts through multiple mechanisms. A team of researchers previously used MR to study the causal effect of myopia on cataracts and showed that myopia increases the risk of cataracts, which is at the genetic level.[31] Lipid peroxidation,[32] oxidative damage to lens proteins,[33] oxidative stress,[34] up-regulation of some genes, and altered cellular signaling pathways are a number of mechanisms by which myopia affects cataract.[35] The study indicated that hyperopia affects cataracts differently than myopia, demonstrating an inverse relationship between the 2 conditions. This observation suggests substantial differences between hyperopic and myopic patients, which include not only refractive status but also genetic, metabolic, and developmental aspects. Consequently, comprehensive research is imperative to validate these distinctions and understand their implications. Notably, our current findings indicate that hyperopia is a protective factor for age-related cataracts and cataract surgery, suggesting that increased levels of hyperopia may reduce the risk of age-related nuclear cataracts. In this study, we found that higher levels of hyperopia were associated with a lower risk of senile nuclear cataracts, but that the level of hyperopia did not have a significant effect on the risk of early senile cataracts. This may be related to the fact that there are fewer effective genetic tools for early age-related cataracts, and it is important in clinical practice to decrease the incidence of myopia and thus the risk of age-related cataracts by avoiding increases in myopia as much as possible, including regular eye exams and necessary outdoor exercise.

Hyperopia Reduces the Risk of Age-Related Nuclear Cataracts, Providing New Perspectives for Future Research on Age-Related Cataracts, these interesting results raise questions about how and why hyperopia affects age-related nuclear cataracts. Some of the possibilities considered include, first, reduced choroidal blood flow in myopic patients; a study in children found that myopic eyes had thinner baseline choroid and lower baseline choroidal blood perfusion compared with hyperopic eyes. In addition, myopic eyes were more likely to experience choroidal thinning and reduced blood perfusion after accommodation.[36] Second, the vascular density of the deep retinal capillary plexus was significantly lower in myopic eyes than in hyperopic eyes.[37] These changes in blood perfusion to the eye may account for the different effects of myopia and hyperopia on cataracts.

This study focuses primarily on cataracts and offers additional insights into the causal role of hyperopia. Previous studies have shown a genetic susceptibility to hyperopia[38] and cataracts,[39] which provided the conditions for MR studies. This study's use of the MR approach to

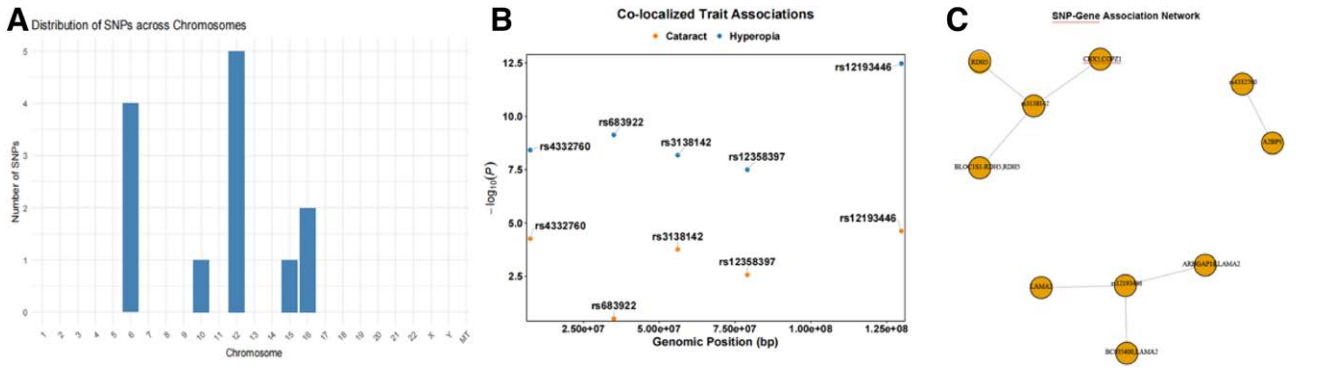


**Figure 4.** (A) Presents a bar chart depicting the distribution of identified SNPs across multiple chromosomes. (B) Presents the findings of a Bayesian colocalization analysis, conducted using datasets "ebi-a-GCST90018814" (cataracts) and "ukb-b-18189" (hyperopia), which explored the shared genetic loci between hyperopia (farsightedness) and cataracts, thereby providing insights into the potential genetic overlap between these conditions. The analysis pinpointed specific loci exhibiting significant genetic associations for both hyperopia and cataracts, indicating a shared genetic basis between the 2 conditions. (C) Depicts a network diagram elucidating the relationships between SNPs and their corresponding genes. SNP=single-nucleotide polymorphism.

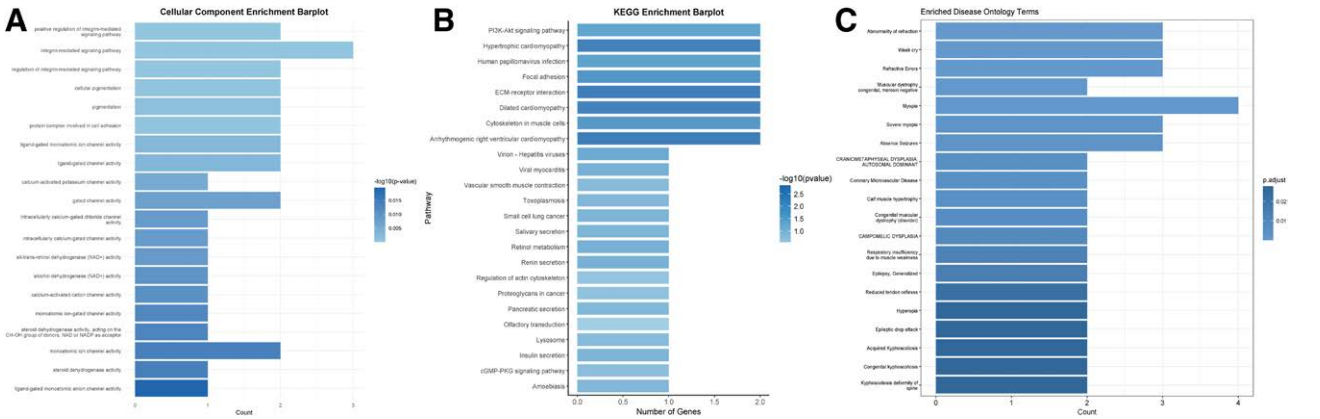


**Figure 5.** (A and B) Present the results of GO and KEGG enrichment analyses, which were employed to elucidate the molecular pathways implicated in hyperopia and age-related cataracts.[24] (C) Depicts a bar plot summarizing the results of a DGN enrichment analysis, which identifies diseases or traits exhibiting significant correlations with genes mapped from SNPs. Each bar represents a specific disease or trait, with the length of the bar proportional to the number of genes linked to the corresponding disease. The intensity of the color, determined by the adjusted *P* value (p.adjust), reflects the degree of statistical significance, with darker shades representing higher significance (i.e., lower adjusted *P* values). DGN=Disease Gene Network, G0=Gene Ontology, KEGG=Kyoto Encyclopedia of Genes and Genomes, SNP=single-nucleotide polymorphism.

assess large-scale datasets using accepted protocols is one of its main strengths. When compared with conventional research, the MR methodology is less susceptible to biases resulting from reverse causality or confounding variables.[15] However, there are some limitations to this study. First, our study only included participants of European descent, necessitating further investigation to determine the applicability of our findings to other ethnic groups. Second, due to the cross-sectional nature of this research, a long-term follow-up study is necessary to fully understand the impact of hyperopia on the risk and progression of age-related nuclear cataract and cataract extraction/lens implantation. Third, the effect of hyperopia on the senile cataract has not been studied experimentally, and further laboratory investigations are needed. Eventually, our study reveals that hyperopia could predict senile cataract, underscoring its significant research and clinical potential.

In conclusion, our study demonstrates a causal link between higher levels of hyperopia and lower risks of senile cataract. Moreover, higher hyperopia levels also decrease the risk of cataract extraction or a lens implant. These observations provide new perspectives to study the pathogenesis of senile cataract, and the reduction of the risk of senile cataract by hyperopia needs to be further explained by subsequent studies.

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## Author contributions

**Conceptualization:** Guoqing Wang, Xianglong Yi.
**Data curation:** Guoqing Wang, Xianglong Yi.
**Validation:** Guoqing Wang, Xianglong Yi.
**Visualization:** Guoqing Wang, Xianglong Yi.
**Writing – original draft:** Guoqing Wang.
**Writing – review & editing:** Guoqing Wang.
**Formal analysis:** Guoqing Wang, Xianglong Yi.
**Funding acquisition:** Guoqing Wang, Xianglong Yi.
**Investigation:** Guoqing Wang, Xianglong Yi.
**Methodology:** Guoqing Wang, Xianglong Yi.
**Project administration:** Guoqing Wang, Xianglong Yi.

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