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ORIGINAL RESEARCH

Exploring Causal Relationships Between Kidney Function and the Risk of Senile Cataract and Primary Open-Angle Glaucoma: A Mendelian Randomization Study and Bioinformatics Analyses

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Purpose: To explore causal relationships between kidney function and the risk of senile cataract and primary open-angle glaucoma (POAG) using Mendelian randomization (MR).

Methods: Summary statistics for kidney function traits were obtained from the CKDGen consortium to identify genetically predicted chronic kidney disease (CKD), estimated glomerular filtration rate (eGFR), and urinary albumin-to-creatinine ratio (UACR). Data on senile cataract and POAG were sourced from the FinnGen consortium. Initially, we applied the bidirectional univariate MR method (UVMR) to assess the causal effects between kidney function and the risk of senile cataract and POAG. Inverse-variance weighted method (IVW) served as the primary analysis, supplemented by weighted median and MR-Egger methods. Subsequently, multivariable MR (MVMR) was conducted to validate significant causal associations identified in UVMR. Bioinformatics analyses were conducted through enrichment analysis and a protein–protein interaction network to elucidate potential molecular mechanisms.

Results: UVMR showed that higher genetically predicted UACR was associated with an increased risk of senile cataract (IVW OR = 1.29, 95% CI: 1.05 to 1.58, P = 0.016), but no reverse causality was observed. No causal associations were found between CKD or eGFR and cataract, or between kidney function and POAG. MVMR further indicated that the associations of UACR with senile cataract remained robust after adjusting for potential confounders, including eGFR, telomere length, diabetes, hypertension, and smoking. Enrichment analysis highlighted significant associations with retinol metabolism, xenobiotic metabolism by cytochrome P450, and glycine/serine/threonine metabolism pathways.

Conclusion: Our results suggested that kidney damage, as measured by UACR, causally increased the risk of cataract, but no causal relationship was found between kidney function and POAG. This study underscores the importance of regular ophthalmic screening for individuals with albuminuria.

Keywords: senile cataract, chronic kidney disease, Mendelian randomization, primary open-angle glaucoma, urinary albumin-to-creatinine ratio

Introduction

Senile cataract and glaucoma are the two leading causes of blindness worldwide.[1] Cataract, characterized by clouding and thickening of the natural lens, accounts for the largest proportion of global blindness. It is estimated that 15.3 million individuals are blind and 78.8 million individuals have moderate-to-severe vision impairment secondary to cataract among adults aged over 50 years worldwide.[1] Glaucoma, marked by progressive damage to the optic nerve, results in vision impairment and eventually blindness. It accounts for 3.6 million cases of blindness globally.[1] The number of

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patients with glaucoma worldwide was projected to reach 111.8 million by 2040.[2] Primary open-angle glaucoma (POAG) is the most common subtype of glaucoma, in which the iridocorneal angle remains anatomically open, but aqueous humor outflow is functionally impaired. Chronic kidney disease (CKD) affects approximately 10% of the global population and imposes substantial healthcare burdens.[3] Emerging evidence suggests that kidney dysfunction may contribute to the development of various ocular diseases.[4–6] These ocular diseases share common risk factors with kidney damage, such as age, hypertension, diabetes, smoking, etc.[4] Notably, findings from observational studies remain inconsistent. Several observational studies have reported an increased risk of senile cataract among individuals with impaired kidney function,[7–11] whereas inconsistent results existed.[12] Similarly, while some studies indicated a higher prevalence of POAG in CKD patients,[13,14] others failed to confirm this relationship.[7,11,15] These discrepancies likely stem from residual confounding, reverse causation, and measurement biases inherent to observational designs.

Mendelian randomization (MR) is an epidemiological method that leverages genetic variants as instrumental variables (IVs) to infer causal relationships between exposures and outcomes. By mimicking the random allocation of controlled trials, MR mitigates confounding and reverses causation biases inherent in observational studies.[16] MR has been widely used to explore causal links between kidney function and various conditions, including cardiovascular diseases,[17–19] brain cortical structure,[20] age-related macular degeneration,[21] as well as other diseases.[22,23] However, evidence on the causal link between kidney function and risk of senile cataract and POAG is still lacking.

Given the growing public health burden of senile cataract, POAG, and CKD, it is crucial to clarify potential causal relationships between kidney function and risk of senile cataract and POAG. Using publicly available genome-wide association studies (GWAS) data, we conducted a bidirectional two-sample univariable MR (UVMR) to assess the genetic evidence for the potential causal relationship between kidney function and risk of senile cataract and POAG. To account for confounding by shared risk factors (age, diabetes, hypertension and smoking), multivariable MR (MVMR) was implemented to detect direct causal effects. Furthermore, comprehensive bioinformatics analyses, including enrichment analysis and protein–protein interaction (PPI) networks, were employed to elucidate underlying molecular mechanisms. These findings offer new insights into the causality between kidney function and risk of senile cataract and POAG, while providing a detailed exploration of the underlying mechanisms.

Materials and Methods

Study Design

Bidirectional UVMR analyses were employed to assess potential causal relationships between kidney function and both senile cataract and POAG. Similar to previous studies, CKD diagnosis, estimated glomerular filtration rate (eGFR), and urinary albumin-to-creatinine ratio (UACR) were selected as indicators of kidney function.[17,21–23] Then, we applied MVMR to assess the direct causal effect of exposure on the outcome adjusting for potential confounders based on UVMR results. A summary of the study design is provided in Figure 1.

Data Sources for Exposures and Outcomes

Publicly available GWAS summary statistics were used to identify genetic proxies for kidney function traits, senile cataract, and POAG. Summary-level data for kidney function traits were obtained from the largest GWAS to date conducted by the CKDGen Consortium. Specifically, the GWAS for CKD and eGFR were reported by Wuttke et al.[24] The CKD meta-analysis included 23 cohorts of European ancestry (n = 480,698; 41,395 cases and 439,303 controls). The meta-analysis for eGFR included 54 cohorts of European ancestry, comprising 567,460 individuals. CKD was defined as a binary outcome for eGFR <60 mL/min per 1.73 m^2[24] eGFR was calculated based on serum creatinine levels using the CKD-EPI equation for adults[25] and the Schwartz formula[26] for individuals aged <18 years. Details of the participant characteristics of enrolled cohorts for CKD and eGFR have been reported by Wuttke et al.[24] UACR summary data were obtained from another GWAS meta-analysis involving up to 547,361 individuals.[27] Details of the enrolled cohorts for UACR can be found in the original publication by Teumer et al.[27] GWAS was adjusted for sex and age.

Summary-level GWAS data for senile cataract and POAG were obtained from the FinnGen consortium (https://www.r9.finngen.fi/).[28] The corresponding phenotype codes were "H7_CATARACTSENILE" (59,522 cases and

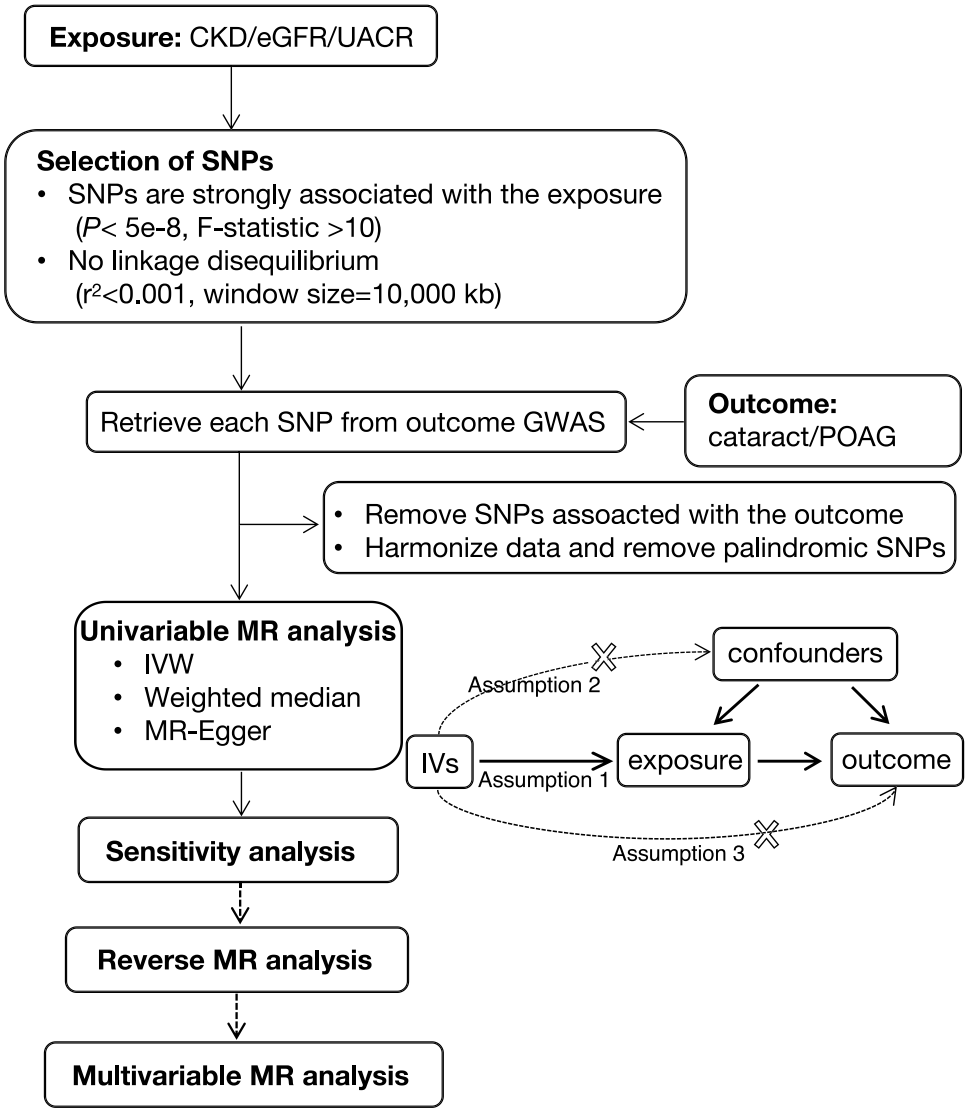

Figure 1 Flowchart of the MR analysis.
Note: The "×" represent IVs that are invalid once correlated with the outcome or potential confounders.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; POAG, primary open-angle glaucoma; IVW, Inverse variance weighted; IV, instrumental variables.

312,864 controls) and "H7_GLAUCOMA_POAG" (7756 cases and 358,375 controls), respectively. Diagnosis of senile cataract was based on ICD-10 code H25, with the mean age at the first event being 71.85 years. POAG was defined by ICD-10 code H40.1, with the mean age at first diagnosis being 67.88 years. The GWAS summary statistics were adjusted for age, sex, and 20 genetic principal components, in accordance with the FinnGen standard analysis pipeline.[28] All participants were of European ancestry.

Data Sources for Potential Confounders

Age, diabetes, hypertension and smoking are shared risk factors between kidney damage and ocular disorders.[4] Telomere length has been developed as a surrogate marker of biological age. The datasets used to assess these potential confounders include telomere length, type 1 diabetes, type 2 diabetes, hypertension and cigarettes smoked per day, all of which were retrieved from the IEU Open GWAS database (https://gwas.mrcieu.ac.uk). The corresponding GWAS IDs are as follows: telomere length: ieu-b-4879, type 1 diabetes: ebi-a-GCST90018925, type 2 diabetes: ebi-a-GCST90018926, hypertension: ukb-b-12493 and cigarettes smoked per day: ieu-b-142.

Instrumental Variables Selections and Harmonization

The single nucleotide polymorphisms (SNPs) chosen as IVs have to meet three core assumptions: IVs (1) are strongly associated with the exposure, (2) are uncorrelated with known confounders, and (3) affect the outcome solely through the exposure. To select eligible IVs, we obtained the SNPs associated with each exposure at genome-wide significance ($P < 5\times10^{-8}$) and not in linkage disequilibrium (clumping $r^2 < 0.001$, clumping distance > 10,000 kb). Then, the same SNPs were extracted from the outcome GWAS, and alleles were harmonized. SNPs were excluded if they were absent in the outcome dataset or palindromic with intermediate allele frequencies.[29] The F-statistic of each instrumental SNP was calculated by the formula: $F = R^2 \times (N-2)/(1-R^2)$. R^2 was calculated with the formula: $R^2 = \frac{2\times\beta^2\times EAF\times(1-EAF)}{2\times\beta^2\times EAF\times(1-EAF)+2\times SE^2\times N\times EAF\times(1-EAF)}$. Here, R^2, EAF, β, SE, and N indicate the proportion of variance explained by a given SNP in the outcome, effect allele frequency, the genetic effect of the SNP on the exposure, standard error, and the sample size, respectively. The F-statistic is recommended to be over 10 to avoid weak genetic instruments.[29]

Mendelian Randomization Analyses

Univariable MR

We estimated the total effects of kidney function and both senile cataract and POAG using bidirectional UVMR analysis. Three methods were used to assess the causal relationship between kidney damage and risk of senile cataract and POAG, including random effects inverse variance weighted (IVW),[30] weighted median,[31] and MR-Egger.[32] IVW yields precise estimates when all IVs are valid.[30] The weighted median provides robust estimates even if up to 50% of genetic variants are invalid.[31] MR-Egger regression yields reasonable estimates even when all genetic variants are invalid IVs.[32] IVW method was the primary analysis method. Other methods were used to complement IVW in a broader set of scenarios, but are less efficient. Associations were considered significant if the IVW $P < 0.05$ and the direction of β estimates was consistent across all three methods.[29] Sensitivity analyses were conducted to assess heterogeneity and pleiotropy. Cochran's Q test was conducted to detect heterogeneity, and $P > 0.05$ was considered no heterogeneity.[33] The MR-Egger regression intercept was implemented to examine horizontal pleiotropy, and $P > 0.05$ indicated no pleiotropy.[32] The MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test was performed to reduce heterogeneity in the estimate of causal effect by removing outlier SNPs (NbDistribution = 10,000).[34] For significant estimates from UVMR, we further employed leave-one-out analyses,[29] statistical power calculations (https://sb452.shinyapps.io/power/),[35] and sensitivity analyses with a stricter instrument P threshold ($P < 1 \times 10^{-8}$) to inspect the robustness of the results.

Multivariable MR

To account for the confounders, we further applied MVMR to investigate the direct effect of the exposure on the outcome. The analytical process of MVMR refers to the previous study.[29] Briefly, the significant SNPs associated with the exposure and the potential confounders were combined to form an extended set of IVs. Duplicate SNPs and those in linkage disequilibrium (clumping $r^2 < 0.001$, clumping distance > 10,000 kb) were excluded. The selected SNPs were then extracted from the outcome GWAS dataset, and alleles were harmonized. In MVMR, the multivariate IVW method was employed.

All MR analyses were conducted using R packages TwoSampleMR, MRPRESSO and MendelianRandomization in the R software (version 4.3.1). Effect estimates were reported as β values when the outcome was continuous (eGFR and UACR) and converted to odds ratio (OR) when the outcome was dichotomous (CKD, cataract and POAG).

Functional Annotation and Bioinformatics Analyses

Functional mapping and annotation of target SNPs were performed using the FUMA GWAS platform (https://fuma.ctglab.nl/).[29] Two mapping strategies were applied: positional mapping (within 10 kb of genes) and eQTL mapping based on eQTLGen cis-eQTLs, GTEx v8 kidney and EyeGEx datasets. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were conducted using the Bioinformatics online platform (https://www.bioinformatics.com.cn), with mapped genes as input. PPI network was built via the STRING version 12.0 online website (https://string-db.org/) and Cytoscape software version 3.10.3.[36,37]

Results

Bidirectional UVMR Estimates

In the forward UVMR analyses, after excluding SNPs with linkage disequilibrium and palindromic sequences, 19~166 SNPs were retained as IVs for different kidney function traits with the F-statistics ranging from 29.57 to 458.97, suggesting minimal bias from weak instruments. Five SNPs (rs10224002, rs1458038, rs3925584, rs77924615, rs881858) overlapped in CKD and eGFR. Five SNPs (rs1047891, rs2068888, rs3850625, rs4410790, rs78444298) overlapped in eGFR and UACR. There was no overlap between CKD and UACR. Details of IVs as well as their F-statistics were documented in Tables S1-S3. As presented in Table 1, IVW estimates indicated that higher genetically predicted UACR was significantly associated with an increased risk of senile cataract (OR=1.29, 95% CI: 1.05 to 1.58, P = 0.016). Consistent results were obtained using the weighted median method (OR=1.29, 95% CI: 1.02 to 1.65, P = 0.036). Directionally consistent results were observed in MR-Egger analysis, although the significance was attenuated to null (OR=2.11, 95% CI: 0.91 to 4.88, P = 0.090). In contrast, no significant association was found between genetically predicted UACR and POAG. CKD and eGFR were not associated with either senile cataract or POAG (Table 1). Scatter plots illustrated the SNP-specific effects of kidney function traits (CKD, eGFR, and UACR) on senile cataract and POAG, with colored lines representing causal estimates from different MR methods (Figure 2A-F).

In the reverse MR analyses, IVs were successfully extracted for senile cataract and POAG, with the number of SNPs ranging from 28 to 34 (Tables S4 and S5). The F-statistics of these IVs ranged from 29.98 to 251.15, indicating strong instruments. No overlapped SNPs were detected between senile cataract and POAG. Our analysis did not reveal any significant causal effects of senile cataract or POAG on kidney function traits (Table S6). Corresponding scatter plots displayed the SNP-specific effects of cataract/POAG on kidney function traits (Figure 2G–L).

The MR-Egger intercept test indicated no horizontal pleiotropy (Tables 1 and S6). Cochran's Q test revealed heterogeneity in most comparisons, except for the associations between genetically predicted CKD and cataract, and between cataract/POAG and CKD (Tables 1 and S6). Heterogeneity in our study is acceptable as the random-effects IVW was the main MR method. After potential outlier SNPs pruning from MR-PRESSO, the overall pattern of results

Table 1 Mendelian Randomization Estimates from Genetically Predicted Kidney Function Traits on Senile Cataract and POAG

Exposure	Outcome	Methods	No. of SNPs	OR (95%CI)	P	Cochran_P	Intercept_P
CKD	Cataract	IVW	19	1.02 (0.98, 1.07)	0.329	0.341	0.452
		MR-Egger	19	0.98 (0.87, 1.10)	0.755		
		WM	19	1.02 (0.96, 1.09)	0.553		
eGFR	Cataract	IVW	166	1.08 (0.64, 1.81)	0.777	<0.001	0.859
		MR-Egger	166	1.20 (0.33, 4.40)	0.783		
		WM	166	1.03 (0.52, 2.03)	0.925		
UACR	Cataract	**IVW**	**45**	**1.29 (1.05, 1.58)**	**0.016**	0.008	0.243
		MR-Egger	45	2.11 (0.91, 4.88)	0.090		
		WM	**45**	**1.29 (1.02, 1.65)**	**0.036**		
CKD	POAG	IVW	19	0.95 (0.81, 1.11)	0.550	<0.001	0.566
		MR-Egger	19	0.85 (0.57, 1.28)	0.451		
		WM	19	0.97 (0.83, 1.13)	0.684		
eGFR	POAG	IVW	166	1.75 (0.57, 5.35)	0.330	<0.001	0.716
		MR-Egger	166	1.08 (0.06, 17.97)	0.960		
		WM	166	1.94 (0.45, 8.40)	0.378		
UACR	POAG	IVW	45	1.05 (0.64, 1.75)	0.824	<0.001	0.695
		MR-Egger	45	1.60 (0.19, 13.11)	0.665		
		WM	45	0.88 (0.51, 1.53)	0.658		

Notes: Bold values indicate statistical significance at P < 0.05 in the MR analysis.

Abbreviations: SNP, single nucleotide polymorphism; OR: odds ratio; CI: confidence intervals; WM: weighted median; IVW: inverse-variance weighted; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; UACR: urinary albumin-to-creatinine ratio; POAG: primary open-angle glaucoma.

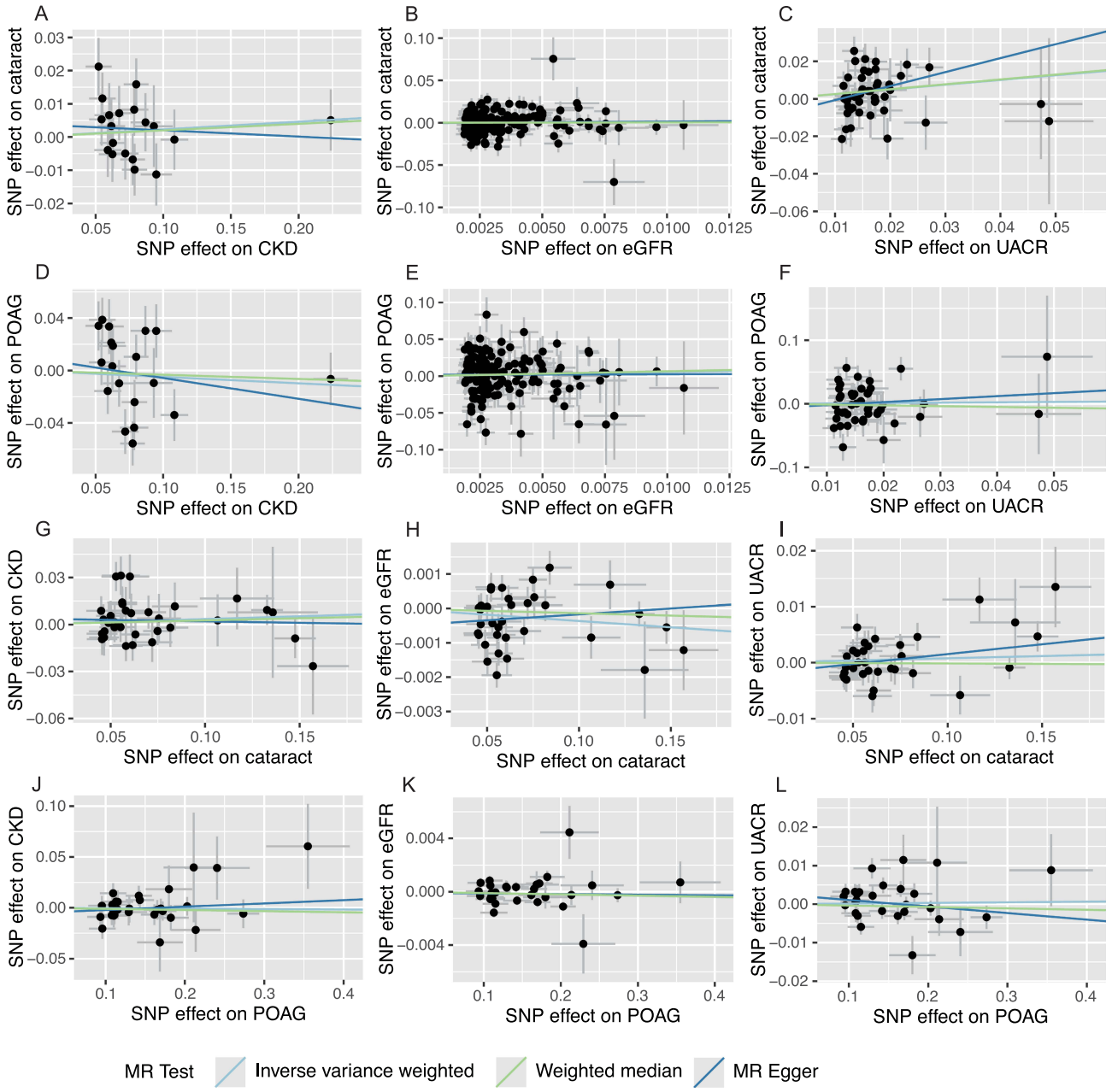

Figure 2 Scatter plots of MR analyses assessing causal relationships between kidney function traits and the risk of cataract and POAG. (**A**–**C**) CKD, eGFR, and UACR on cataract; (**D**–**F**) CKD, eGFR, and UACR on POAG; (**G**–**I**) cataract on CKD, eGFR, and UACR; (**J**–**L**) POAG on CKD, eGFR, and UACR.
Abbreviations: POAG, primary open-angle glaucoma; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

remained consistent (Table S7). Notably, the causal effect of UACR on senile cataract remained significant after outlier correction (OR = 1.33, 95% CI: 1.10 to 1.61, P = 0.004) (Figure 3).

To validate the robustness of significant findings from the bidirectional MR analyses, we conducted leave-one-out analyses, statistical power calculations, and re-analyzed with a more stringent instrument P threshold ($P < 1 \times 10^{-8}$). Leave-one-out analysis for the association between UACR and senile cataract indicated the estimates were not biased by a single SNP (Figure S1). Power calculation estimated that we had 99.2% statistical power to detect a 29% increase in senile cataract risk per SD increase in the UACR. When applying a stricter instrument P threshold, 34 SNPs were retained for UACR, and the MR estimates remained robust (Figure 3). The Cochran's Q test suggested no heterogeneity (P = 0.078) and the MR-Egger intercept suggested no pleiotropy (P=0.713). These results further supported that genetically predicted UACR causally increased the risk of senile cataract.

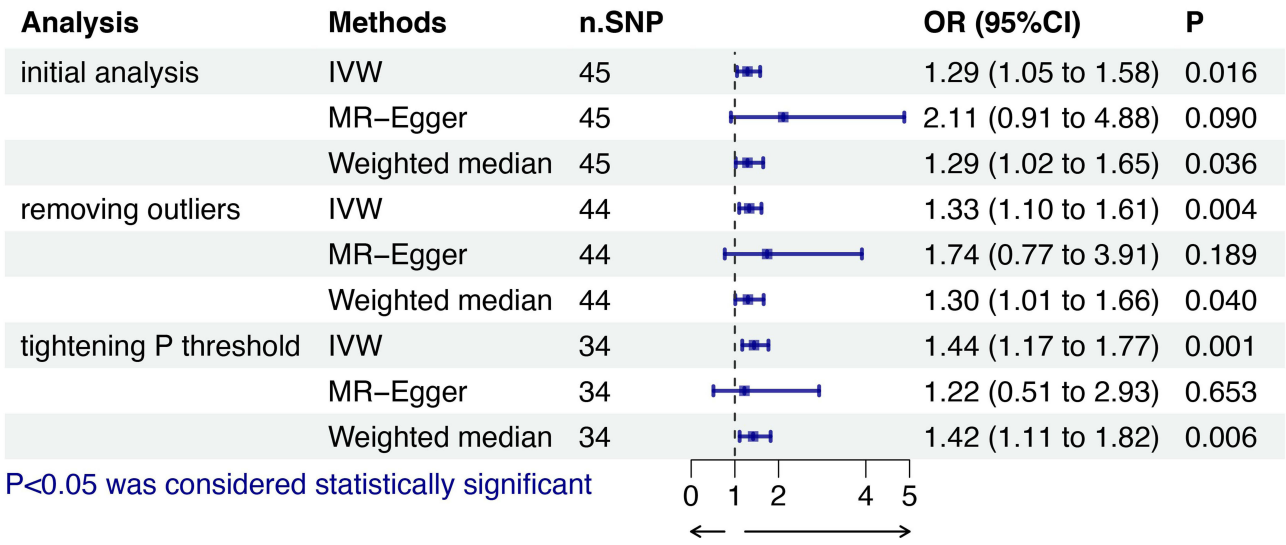

Figure 3 Mendelian randomization estimates for UACR on senile cataract after removing the outlier or tightening the instrument P threshold.
Abbreviation: IVW, Inverse variance weighted.

MVMR Analyses

To investigate the independent effects of UACR, MVMR was applied to identify the independent causal effects of UACR on senile cataract. Controlling for eGFR, the association between UACR and cataract remained statistically significant (OR = 1.27, 95%CI: 1.03 to 1.56, P=0.023). Similarly, the causal effects were not substantially changed with adjustment for telomere length (OR = 1.35, 95% CI: 1.08 to 1.67, P = 0.008), type 1 diabetes (OR = 1.33, 95% CI: 1.07 to 1.65, P = 0.010), type 2 diabetes (OR = 1.29, 95% CI: 1.04 to 1.59, P = 0.020), hypertension (OR = 1.32, 95% CI: 1.10 to 1.58, P = 0.003) and cigarettes smoked per day (OR = 1.29, 95% CI: 1.04 to 1.61, P = 0.021) (Table 2).

Enrichment Analyses

The 45 independent SNPs in UCAR were mapped to FUMA to obtain 241 genes (Table S8). GO enrichment analysis revealed that the mapped genes were significantly enriched in biological processes related to hyaluronan metabolic process, cellular response to xenobiotic stimulus, glycosylation, and cell–cell recognition (Figure 4A). KEGG pathway analysis identified enrichment in retinol metabolism, glycine/serine/threonine metabolism, and xenobiotic metabolism by cytochrome P450 (Figure 4B). Furthermore, PPI analysis via the STRING database revealed a densely interconnected network (Figure 4C). Visualization in Cytoscape (Figure 4D) identified six key hub genes, TGFB1, MUC1, CYP2A6, SCARB2, ITIH4, and BDNF, which may play central roles in mediating the link between UACR and senile cataract.

Table 2 MVMR Analyses of Causal Effects of UACR on Senile Cataract Using IVW Method

Confounders	No. of SNPs	OR (95% CI)	P
eGFR	203	1.27 (1.03, 1.56)	0.023
Telomere length	130	1.35 (1.08, 1.67)	0.008
Type 1 diabetes	58	1.33 (1.07, 1.65)	0.010
Type 2 diabetes	173	1.29 (1.04, 1.59)	0.020
Hypertension	84	1.32 (1.10, 1.58)	0.003
Cigarettes smoked per day	60	1.29 (1.04, 1.61)	0.021

Abbreviations: UACR, urinary albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval; IVW, inverse-variance weighted.

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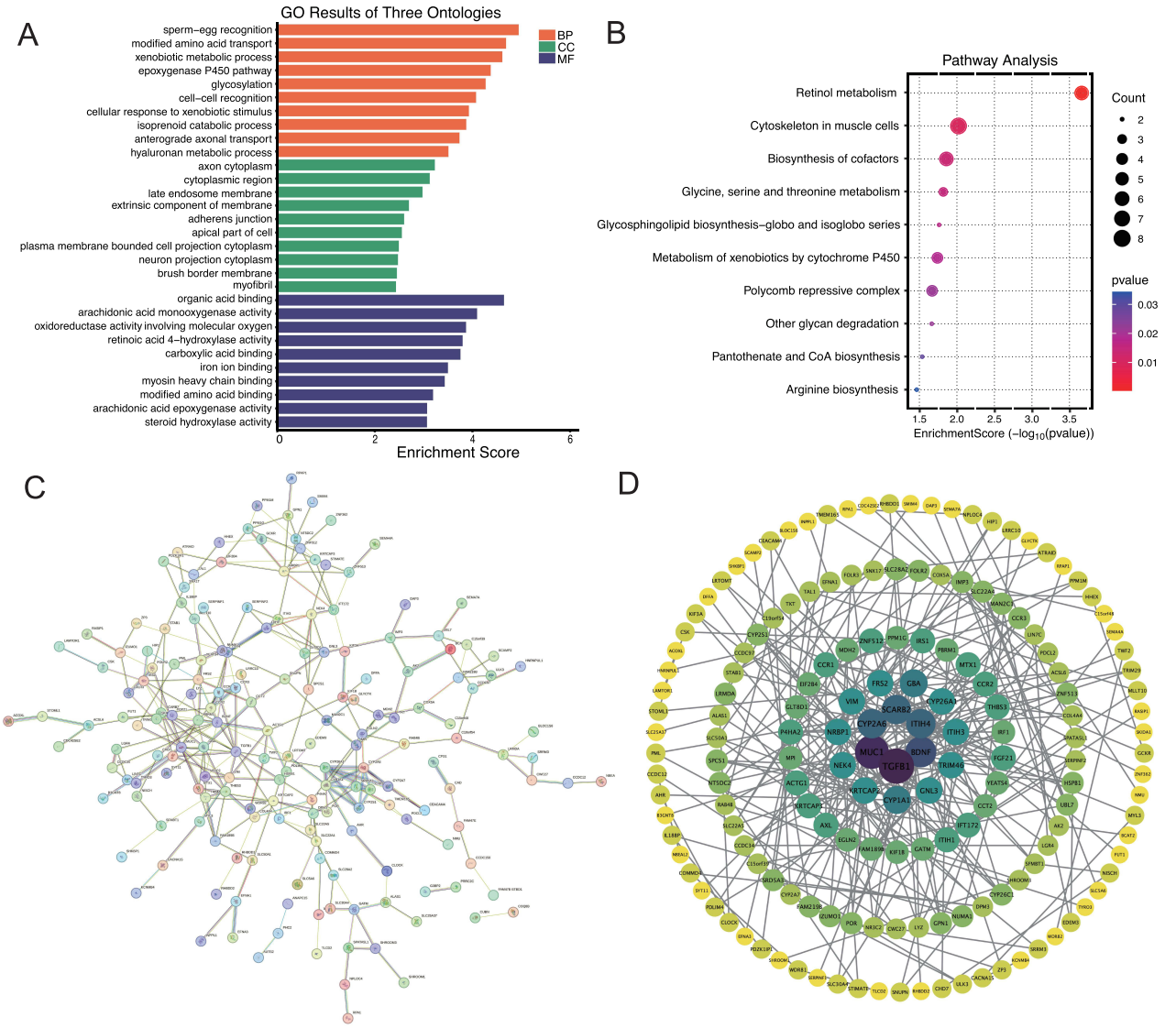

Figure 4 Integrated bioinformatics analyses. (**A**) GO enrichment analysis. (**B**) KEGG enrichment analysis. (**C**) PPI network in STRING database. (**D**) Visualization of PPI network in Cytoscape.
Abbreviations: GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPI, Protein–protein interaction.

Discussion

To the best of our knowledge, this is the first study using the MR method to explore the causal connections between kidney function traits (CKD, eGFR, and UACR) and risk of senile cataract and POAG. Our results supported a causal association between UACR and senile cataract, but not in the reverse direction. No significant causal association was found between kidney function and POAG. The causal link between UACR and senile cataract were robust through a comprehensive set of sensitivity analyses. Furthermore, our MVMR analyses confirmed that UACR is causally associated with an increased risk of senile cataract after adjusting for age, diabetes, hypertension, and smoking, ensuring that these factors did not confound the observed relationship.

Previous observational studies investigating the relationship between kidney function and cataract have yielded inconsistent results. The Blue Mountains Eye Study II, which followed 3654 participants for five years, found no significant association between serum creatinine or eGFR and the incidence of various cataract subtypes.[12] Similarly, our MR analysis revealed no causal link between CKD (defined as eGFR < 60 mL/min/1.73m²) or eGFR and senile cataract. In contrast, Rim et al analyzed 1758 sociodemographically matched subjects extracted from a longitudinal national database and found that

patients undergoing hemodialysis for end-stage renal disease had a higher probability of receiving cataract surgery during an 11-year follow-up.[7] Recently, a longitudinal population-based retrospective case–control study in Sweden showed that CKD patients have an increased risk of developing cataract.[8] UACR had been incorporated into Kidney Disease: Improving Global Outcomes criteria for CKD diagnosis as a biomarker of glomerular filtration barrier damage.[38] Our results supported the higher UACR as a causal risk factor of cataract. Even moderate elevations in UACR predict poorer health outcomes, independently of the glomerular filtration rate.[39] The reason UACR, but not eGFR, was found to have a causal relationship with senile cataract may be attributed to the distinct pathophysiological aspects of eGFR and UACR. The increased UACR indicates microvascular dysfunction or systemic inflammation, which could directly contribute to cataract pathogenesis.

KEGG pathway enrichment analysis revealed several critical pathways potentially linking UACR to senile cataract, notably retinol metabolism, xenobiotic metabolism by cytochrome P450, and glycine/serine/threonine metabolism. Retinol metabolism plays a vital role in visual function and antioxidant defense;[40] its disruption may exacerbate oxidative stress within the lens, thereby promoting cataractogenesis.[41] The enrichment of cytochrome P450–related pathways aligns with experimental evidence showing that CYP450 inhibition delays cataract onset, while CYP450 induction accelerates it in animal models.[42] In addition, glycine/serine/threonine metabolism is essential for glutathione biosynthesis, a major antioxidant in the lens. Deficiency in glutathione exacerbates crystallin oxidation, a known contributor to cataract formation.[43] These pathways collectively implicate oxidative stress and metabolic dysregulation as shared mechanisms underlying both kidney damage and cataract formation. Although oxidative stress is also implicated in POAG, our MR analysis did not support a causal role of UACR in POAG. The pathophysiology of POAG is multifactorial, with elevated intraocular pressure being a major risk factor. It involves a complex interplay of mechanisms such as mechanical stress, vascular insufficiency, extracellular matrix remodeling, excitotoxicity, oxidative damage, and immune dysregulation, collectively leading to retinal ganglion cell loss and optic nerve injury.[44] On the other hand, the lens, largely composed of crystalline proteins from terminally differentiated, organelle-deficient fiber cells, is highly vulnerable to oxidative damage.[45] Thus, systemic oxidative stress may be sufficient to induce cataract in a susceptible tissue like the lens, yet inadequate to initiate POAG without additional glaucoma-risk factors.

The strengths of our study include the utilization of large-scale genetic data within an MR framework, which enhances the robustness of causal inference. Additionally, the implementation of multiple sensitivity analyses further reinforces the credibility of the association between genetically predicted UACR and the risk of cataract. Nonetheless, several limitations should be acknowledged. First, the definition of CKD was solely based on reduced eGFR derived from serum creatinine, without incorporating albuminuria measurement. Second, the enrolled participants were all European, and hence, it should be cautious when generalizing our MR results to other ethnicities and races. Third, the limited GWAS datasets restricted our ability to perform stratified analyses on specific cataract subtypes. Fourth, although we applied MVMR and multiple-sensitivity analyses to mitigate the impact of directional pleiotropy, the possibility of residual pleiotropy cannot be entirely excluded. Lastly, MR estimates reflect associations of lifelong, cumulative genetic risk, which differ from associations observed in conventional observational studies that assess risk at a given period.

Conclusion

This is the first bidirectional MR analysis to explore associations between CKD, eGFR, UACR, and risk of senile cataract and POAG among European populations. Our MR estimates suggested that UACR causally increases the risk of senile cataract, but not in the reverse direction. No causal effects between kidney function and POAG were observed. The association between UACR and senile cataract remained robust after adjustment for age, diabetes, hypertension, and smoking. These results underscore the value of regular ophthalmological screening in individuals with albuminuria to facilitate early detection and intervention.

Ethics Statement

This study utilized publicly available GWAS summary data, and no individual-level data were used. In accordance with national legislative guidelines, specifically items 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects promulgated on February 18, 2023, in China, this study is exempt from the requirement for ethical approval.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Steinmetz JD, Bourne RRA, Briant PS; GBD 2019 Blindness and Vision Impairment Collaborators, Vision Loss Expert Group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the right to sight: an analysis for the global burden of disease study. *Lancet Glob Health*. 2021;9(2):e144–160. doi:10.1016/S2214-109X(20)30489-7
2. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040. *Ophthalmology*. 2014;121(11):2081–2090. doi:10.1016/j.ophtha.2014.05.013
3. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. *Lancet*. 2021;398(10302):786–802. doi:10.1016/s0140-6736(21)00519-5
4. Wong CW, Wong TY, Cheng CY, Sabanayagam C. Kidney and eye diseases: common risk factors, etiological mechanisms, and pathways. *Kidney Int*. 2014;85(6):1290–1302. doi:10.1038/ki.2013.491
5. Liu W, Guo R, Huang D, et al. Co-occurrence of chronic kidney disease and glaucoma: epidemiology and etiological mechanisms. *Surv Ophthalmol*. 2023;68(1):1–16. doi:10.1016/j.survophthal.2022.09.001
6. Kanbay M, Guldan M, Ozbek L, Copur S, Mallamaci F, Zoccali C. Unveiling the intricacies of chronic kidney disease: from ocular manifestations to therapeutic frontiers. *Eur J Clin Invest*. 2025;55(1):e14324. doi:10.1111/eci.14324
7. Rim TH, Yoon CY, Park HW, Chung EJ. Association between starting hemodialysis for end-stage renal disease and incident cataract surgery: a 12-year nationwide cohort study. *Invest Ophthalmol Vis Sci*. 2016;57(3):1112–1119. doi:10.1167/iovs.15-18276
8. Ballester Dolz P, Ålander K, Smedberg P, et al. Eye diseases in chronic kidney disease: a nationwide longitudinal case-control study in Sweden. *Clin Exp Ophthalmol*. 2025;53(2):209–217. doi:10.1111/ceo.14464
9. Liu YT, Hung TY, Lee YK, Huang MY, Hsu CY, Su YC. Association between chronic kidney disease and risk of cataract: a nationwide retrospective cohort study. *Am J Nephrol*. 2017;45(6):524–531. doi:10.1159/000475555
10. Huang CY, Lee JI, Chang CW, et al. Chronic kidney disease and its association with cataracts: a cross-sectional and longitudinal study. *Front Public Health*. 2022;10:1029962. doi:10.3389/fpubh.2022.1029962
11. Wong CW, Lamoureux EL, Cheng CY, et al. Increased burden of vision impairment and eye diseases in persons with chronic kidney disease- a population-based study. *EBioMedicine*. 2016;5:193–197. doi:10.1016/j.ebiom.2016.01.023
12. Huynh SC, Kifley A, Strippoli GF, Mitchell P. Is renal impairment a predictor of the incidence of cataract or cataract surgery? Findings from a population-based study. *Ophthalmology*. 2005;112(2):293–300. doi:10.1016/j.ophtha.2004.09.014
13. Ro JS, Moon JY, Park TK, Lee SH. Association between chronic kidney disease and open-angle glaucoma in South Korea: a 12-year nationwide retrospective cohort study. *Sci Rep*. 2022;12:3423. doi:10.1038/s41598-022-07190-8
14. Fyc N, Hjjmd S, Tan BKJ, et al. Bidirectional association between glaucoma and chronic kidney disease: a systematic review and meta-analysis. *eClinicalMedicine*. 2022;49:101498. doi:10.1016/j.eclinm.2022.101498
15. Tham YC, Tao Y, Zhang L, et al. Is kidney function associated with primary open-angle glaucoma? Findings from the Asian Eye Epidemiology Consortium. *Br J Ophthalmol*. 2020;104(9):1298–1303. doi:10.1136/bjophthalmol-2019-314890
16. Li TL, Fu ML, Wang LH, et al. Causal characteristics of immune cells associated with aortic dissection: a Mendelian randomisation analysis. *Eur Cardiol*. 2025;20:e07. doi:10.15420/ecr.2024.44
17. Kelly DM, Georgakis MK, Franceschini N, Blacker D, Viswanathan A, Anderson CD. Interplay between chronic kidney disease, hypertension, and stroke: insights from a multivariable mendelian randomization analysis. *Neurology*. 2023;101(20):e1960–e1969. doi:10.1212/WNL.0000000000207852
18. Gaziano L, Sun L, Arnold M, Bell S, Cho K, Kaptoge SK. Mild-to-moderate kidney dysfunction and cardiovascular disease: observational and Mendelian randomization analyses. *Circulation*. 2022;146(20):1507–1517. doi:10.1161/CIRCULATIONAHA.122.060700
19. Hu C, Li Y, Qian Y, Wu Z, Hu B, Peng Z. Kidney function and cardiovascular diseases: a large-scale observational and Mendelian randomization study. *Front Immunol*. 2023;14:1190938. doi:10.3389/fimmu.2023.1190938
20. Chen X, Kong J, Pan J, et al. Kidney damage causally affects the brain cortical structure: a Mendelian randomization study. *eBioMedicine*. 2021;72:103592. doi:10.1016/j.ebiom.2021.103592
21. Hou Y, Liu Q, Xiao Z, Li Y, Tian X, Wang Z. Association between chronic kidney disease and age-related macular degeneration: a Mendelian randomization study. *Front Aging Neurosci*. 2024;16:1399666. doi:10.3389/fnagi.2024.1399666

22. Ren J, Huang Q, Lie X, Tong X, Yao Q, Zhou G. Kidney damage on fertility and pregnancy: a Mendelian randomization. *PLoS One*. 2023;18(7): e0288788. doi:10.1371/journal.pone.0288788
23. Tan Y, Huang Z, Li H, et al. Association between psoriasis and renal functions: an integration study of observational study and Mendelian randomization. *Biomedicines*. 2024;12(1):249. doi:10.3390/biomedicines12010249
24. Wuttke M, Li Y, Li M, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet*. 2019;51 (6):957–972. doi:10.1038/s41588-019-0407-x
25. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604–612. doi:10.7326/0003-4819-150-9-200905050-00006
26. Schwartz GJ, Schneider MF, Maier PS, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. *Kidney Int*. 2012;82(4):445–453. doi:10.1038/ki.2012.169
27. Teumer A, Li Y, Ghasemi S, et al. Genome-wide association meta-analyses and fine-mapping elucidate pathways influencing albuminuria. *Nat Commun*. 2019;10(1):4130. doi:10.1038/s41467-019-11576-0
28. Kurki MI, Karjalainen J, Palta P, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature*. 2023;613 (7944):508–518. doi:10.1038/s41586-022-05473-8
29. Li P, Liu X, Wu L, Dong L, Zhou J, Song Z. Thyroid function and brain structure: insight from a Mendelian randomization study. *Neuroendocrinology*. 2025;115(1):60–71. doi:10.1159/000542955
30. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37(7):658–665. doi:10.1002/gepi.21758
31. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304–314. doi:10.1002/gepi.21965
32. 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. doi:10.1093/ije/dyv080
33. Corlin L, Ruan M, Tsilidis KK, et al. Two-sample Mendelian randomization analysis of associations between periodontal disease and risk of cancer. *JNCI Cancer Spectr*. 2021;5(3):pkab037. doi:10.1093/jncics/pkab037
34. 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. doi:10.1038/s41588-018-0099-7
35. Burgess S, Davey SG, Davies NM, et al. Guidelines for performing Mendelian randomization investigations: update for summer 2023. *Wellcome Open Res*. 2023;4:186. doi:10.12688/wellcomeopenres.15555.3
36. Szklarczyk D, Kirsch R, Koutrouli M, et al. The STRING database in 2023: protein-protein. association networks and functional enrichment analyses for any sequenced genome of interest. *Nucleic Acids Res*. 2023;51(D1):D638–D646. doi:10.1093/nar/gkac1000
37. Shannon P, Markiel A, Ozier O, et al. Cytoscape: a software environment for integrated models. of biomolecular interaction networks. *Genome Res*. 2003;13(11):2498–2504. doi:10.1101/gr.1239303
38. Stevens PE, Levin A, Disease K, Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158(11):825–830. doi:10.7326/0003-4819-158-11-201306040-00007
39. Grams ME, Coresh J, Woodward M, et al. Writing Group for the CKD Prognosis Consortium. Estimated glomerular filtration rate, albuminuria, and adverse outcomes: an individual-participant data meta-analysis. *JAMA*. 2023;330(13):1266–1277. doi:10.1001/jama.2023.17002.
40. Choi YJ, Kwon JW, Jee D. The relationship between blood vitamin A levels and diabetic retinopathy: a population-based study. *Sci Rep*. 2024;14 (1):491. doi:10.1038/s41598-023-49937-x
41. Kulbay M, Wu KY, Nirwal GK, Bélanger P, Tran SD. Oxidative stress and cataract formation: evaluating the efficacy of antioxidant therapies. *Biomolecules*. 2024;14(9):1055. doi:10.3390/biom14091055
42. Patel DV, Gandhi TR, Patel KV, et al. Targeting CYP450 modulation to decrease the risk of induced cataract in the experimental model. *Indian J Ophthalmol*. 2010;58(6):471–475. doi:10.4103/0301-4738.71676
43. Lim JC, Jiang L, Lust NG, et al. Minimizing oxidative stress in the lens: alternative measures for elevating glutathione in the lens to protect against cataract. *Antioxidants*. 2024;13(10):1193. doi:10.3390/antiox13101193
44. Ekici E, Moghimi S. Advances in understanding glaucoma pathogenesis: a multifaceted molecular approach for clinician scientists. *Mol Aspects Med*. 2023;94:101223. doi:10.1016/j.mam.2023.101223
45. Ho MC, Peng YJ, Chen SJ, Chiou SH. Senile cataracts and oxidative stress. *J Clin Gerontol Geriatr*. 2010;1(1):17–21. doi:10.1016/j.jcgg.2010.10.006