Genes & Nutrition

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Exploring causal relationships between circulating micronutrients and age-related eye diseases: a Mendelian randomization study

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Abstract

Background With the global population aging, age-related eye diseases (AREDs) such as senile cataract (SC), age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy (DR) are becoming increasingly significant public health concerns. The rising prevalence of AREDs underscores the urgent need for effective prevention and treatment strategies. This study aimed to explore the causal relationships between circulating micronutrients (CMs) and AREDs.

Methods A bidirectional two-sample Mendelian randomization (MR) analysis was conducted using genetic variants as instrumental variables to assess the effects of fifteen CMs (vitamin A, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E, folate, carotene, copper, calcium, iron, magnesium, potassium, selenium, zinc) on AREDs. Data were sourced from large-scale genome-wide association studies (GWAS). The primary analytical method employed was inverse-variance weighted (IVW), supplemented by sensitivity analyses to confirm the robustness of the results.

Results The MR analysis revealed significant protective effects of selenium against SC (OR = 0.961, 95% CI = 0.932–0.991, $P = 0.012$) and DR (OR = 0.927, 95% CI = 0.870–0.987, $P = 0.019$). Furthermore, higher genetically predicted magnesium levels were associated with a reduced risk of AMD (OR = 0.679, 95% CI = 0.515–0.895, $P = 0.006$). However, no significant causal relationships were observed between the other CMs and glaucoma or other AREDs.

Conclusions These findings provided valuable insights into the complex interplay between CMs and AREDs, offering potential pathways for developing targeted nutritional interventions and public health strategies to mitigate the risk of these debilitating conditions.

Keywords Age-related eye diseases, Circulating micronutrients, Mendelian randomization, Senile cataract, Age-related macular degeneration, Diabetic retinopathy

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Introduction

According to estimates from the Global Burden of Disease Study, in 2020, approximately 295 million people worldwide will suffer from moderate to severe visual impairment [1]. With an aging global population, age-related eye diseases (AREDs), mainly including senile cataract (SC), age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy (DR), are major public health challenges [2, 3]. These diseases can lead to severe visual impairment and blindness, seriously affecting the quality of life [3]. As the global population ages, the prevalence of AREDs is expected to increase, highlighting the urgent need for effective prevention and treatment strategies [4]. Therefore, it is very important to identify risk factors for AREDs and develop targeted interventions.

The pathogenesis of AREDs is intrinsically linked to the aging process, which is characterized by oxidative damage and chronic low-grade inflammation within ocular tissues [4–7]. Emerging research highlights the significant role of micronutrients, owing to their antioxidative and anti-inflammatory properties, in maintaining ocular health [8–11]. For example, a population-based epidemiological study has demonstrated that elevated serum levels of vitamin A are associated with a reduced risk of diabetic retinopathy [10]. Iron accumulation in the retina, a hallmark of aging, may contribute to the development of retinal disorders such as AMD [12]. Moreover, insufficient dietary calcium intake has been strongly associated with an increased risk of AMD [13]. The formulation used in the ARED Study, which includes vitamins C, E, β-carotene, zinc, and copper, has been shown to reduce the risk of progression to late-stage AMD by 25% over five years [14]. In addition, adequate dietary intake of calcium, potassium, and magnesium may confer protective benefits against glaucoma, offering a basis for the development of targeted preventive strategies [15]. Furthermore, evidence from systematic reviews indicates that supplementation with B-group vitamins may have a beneficial effect on reducing cataract incidence [8]. Observational studies suggest that individuals who consume diets rich in antioxidant vitamins (such as carotenoids, vitamins C and E) or essential minerals (including selenium and zinc) are less likely to develop AREDs [6, 8, 11, 16]. However, these studies are often confounded by multiple factors, including reverse causality, which complicates the establishment of definitive causal relationships.

Mendelian randomization (MR) provides a robust methodological approach to infer causality by leveraging genetic variants as instrumental variables (IVs) [17]. This approach mitigates confounding and reverse causation, as genetic variants are randomly assigned at conception and remain fixed throughout life [18]. Indeed, recent studies have shown that MR can provide novel and robust evidence for understanding the causal relationship between nutrients and certain diseases, which would be challenging to establish with traditional observational methods [19–21]. Thus, MR can offer more reliable insights into the causal effects of micronutrients on AREDs.

In this study, we aimed to investigate the causal relationship between fifteen circulating micronutrients (CMs) (vitamin A, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E, folate, carotene, copper, calcium, iron, magnesium, potassium, selenium, zinc) and AREDs using a large-scale genome-wide association study (GWAS) and a bidirectional two-sample MR approach. Our findings emphasized the importance of nutrition for eye health and further deepened our understanding of the pathogenesis of AREDS, thereby guiding the development of targeted nutritional recommendations and interventions.

Methods

Study design and data sources

This study utilized the bidirectional two-sample MR to investigate the causal effects of various CM on AREDs, specifically SC, glaucoma, AMD, and DR. Single nucleotide polymorphisms (SNPs) were defined as IVs. The Mendelian randomization study is based on three core assumptions: (1) IVs are strongly associated with the exposure; (2) IVs are independent of confounding factors; and (3) IVs affect the outcome exclusively through the exposure [17, 18]. The study design is illustrated in Fig. 1.

The SNP data associated with CMs levels were obtained from the GWAS database, with the fifteen CMs and their respective identifiers detailed in Supplementary Table S1. The outcome data for AREDs were derived from the FinnGen consortium, comprising 73,410 cases and 3,742,663 controls for SC, 23,483 cases and 430,250 controls for glaucoma, 11,023 cases and 419,198 controls for AMD, and 12,681 cases and 51,410 controls for DR. Additional details are available at https://www.finngen.fi/en/access_results. We ensured the use of independent and statistically powered samples to minimize bias. All data utilized in this study were publicly available summary statistics from previously published GWAS, obviating the need for new ethical approvals.

Selection of IVs

SNPs associated with each CM were selected as IVs from GWAS. Detailed GWAS information is provided in Table 1. The selection criteria included a genome-wide significance threshold of $P < 5 \times 10^{-6}$ for initial IV identification, ensuring sufficient statistical power, as the number of qualified IVs ($P < 5 \times 10^{-8}$) was not enough [22]. Additional criteria for SNP inclusion

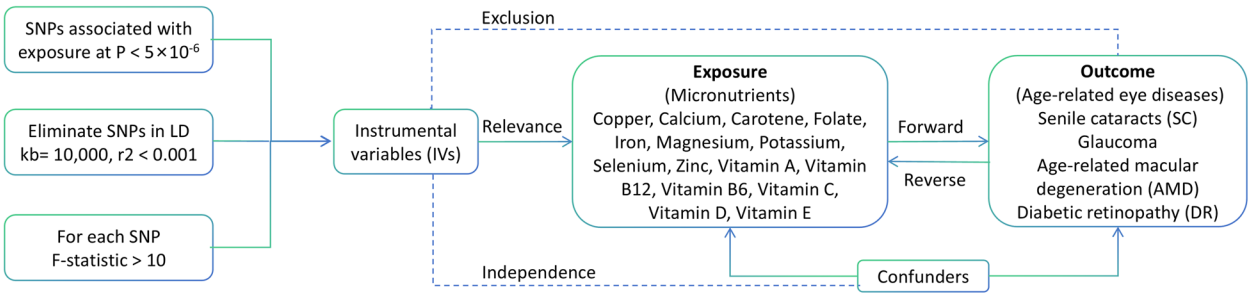

Fig. 1 Schematic diagram of the study design in this bidirectional MR analysis

Table 1 GWAS information for micronutrients

GWAS ID	Year	Micronutrient	Race	Sample size	Number of SNPs
ukb-b-9596	2018	Vitamin A	European	8863	460351
ukb-b-7864	2018	Vitamin B6	European	64979	9851867
ukb-b-19524	2018	Vitamin B12	European	64979	9851867
ukb-b-19390	2018	Vitamin C	European	64979	9851867
ukb-b-18593	2018	Vitamin D	European	64979	9851867
ukb-b-6888	2018	Vitamin E	European	64979	9851867
ukb-b-11349	2018	Folate	European	64979	9851867
ukb-b-16202	2018	Carotene	European	64979	9851867
ieu-a-1073	2013	Copper	European	2603	2543646
ukb-b-8951	2018	Calcium	European	64979	9851867
ukb-b-20447	2018	Iron	European	64979	9851867
ukb-b-7372	2018	Magnesium	European	64979	9851867
ukb-b-17881	2018	Potassium	European	64979	9851867
ieu-a-1077	2013	Selenium	European	2603	2543617
ieu-a-1079	2013	Zinc	European	2603	2543610

were linkage disequilibrium parameters (kb = 10,000, r2 < 0.001) and an F-statistic > 10, which were applied to mitigate weak instrument bias and ensure the robustness of the IVs [18, 23, 24]. Additionally, in the reverse MR analysis, SNPs in the SC, AMD, and DR summary data were selected with a threshold of $P < 5 \times 10^{-8}$ [17, 25]. The same method was employed to eliminate linkage disequilibrium and remove weak IVs (kb = 10,000, r2 < 0.001, F-statistic > 10) [17, 23].

Statistical analysis

The inverse-variance weighted (IVW) method provides a comprehensive estimate of causal effects by weighting the inverse variance of the effect size of each SNP [26]. It has the highest statistical power among all MR methods. Five primary MR analysis methods were employed in this study, with the IVW method as the primary approach, supplemented by MR-Egger, weighted median, simple mode, and weighted mode methods [17]. If heterogeneity

was present, the random-effect IVW model was applied; otherwise, the fixed-effect IVW model was used [27]. This approach was supplemented by visual tools, including scatter plots, forest plots, and funnel plots, to illustrate the relationship between micronutrients and AREDS outcomes [17, 22]. The effect of exposure factors on the outcomes was conveyed by odds ratios (OR) and corresponding 95% confidence intervals (CI) [17].

Sensitivity analysis

To assess the robustness of the findings, a sensitivity analysis was performed, which included the use of MR-Egger regression to detect pleiotropy and a weighted median approach to provide reliable causal estimates if some IVs were ineffective [28]. MR-PRESSO analysis was utilized to identify horizontal pleiotropy and to detect and correct outlier SNPs [29, 30]. Additionally, a leave-one-out approach was implemented to exclude outlier SNPs, preventing a single SNP from unduly influencing the causal relationship between exposure and outcome [18]. Heterogeneity among SNPs was assessed using the Cochrane Q test [25]. Sensitivity analyses confirmed the absence of significant horizontal pleiotropy and heterogeneity, supporting the causal inferences drawn from the primary IVW analysis [17]. For all analyses, results were considered significant at the traditional $P < 0.05$ level [18].

The findings were visually depicted using forest plots, funnel plots, scatter plots, and leave-one-out plots. All statistical analyses were conducted using the TwoSampleMR (version 0.6.6) and MRPRESSO (version 1.0) packages within R software (version 4.3.2).

Results

Detailed information on the included SNPs

To ensure an adequate number of SNPs for subsequent MR analysis, a significance threshold of $P < 5 \times 10^{-6}$ was employed when screening SNPs associated with each CM and AREDs. Following the remaining IVs selection criteria (kb = 10,000, r2 < 0.001, F-statistic > 10), a total of 188 SNPs were identified as IVs for 15 micronutrients (Supplementary Table S1). In the reverse MR analysis of CM and AREDs, a more stringent significance threshold of $P < 5 \times 10^{-8}$ was applied, resulting in the selection of 44 SNPs as IVs for SC (Supplementary Table S2), 34 SNPs for AMD (Supplementary Table S3), and 11 SNPs for DR (Supplementary Table S4).

MR results

The causal relationships between CMs and AREDs were elucidated through a comprehensive series of analyses. The circular heatmap in Fig. 2 presents the MR analysis results, with CMs as exposures and AREDs as outcomes, using IVW as the primary analytical method. The results, including scatter plots, forest plots, funnel plots, and leave-one-out plots, are visualized in Fig. 3. Specifically, selenium was suggested to be a protective factor against SC and DR, while magnesium was indicated as a protective factor against AMD. However, no associations were found between the fifteen CMs and the risk of glaucoma (Supplementary Table S5). Further detailed results are provided in the supplementary materials (Supplementary Tables S6-8).

Causality between CMs and SC

The causal relationship between CMs and SC was primarily assessed using the IVW method. It was observed that genetically predicted circulating selenium levels were negatively correlated with SC risk (OR = 0.961, 95% CI = 0.932–0.991, $P = 0.012$) (Fig. 4). Comprehensive insights into individual SNPs were provided by the scatter plot, funnel plot, leave-one-out plot, and forest plot (Fig. 3A-D). Additionally, MR-PRESSO analysis did not identify any outlier SNPs for selenium ($P = 0.887$). Sensitivity analyses, including MR-Egger regression and the weighted median method, confirmed the robustness of the results, indicating no significant horizontal pleiotropy (MR Egger intercept = 0.0054, $P = 0.484$) or heterogeneity ($P = 0.869$) (Supplementary Table S9). The reverse MR analysis did not yield significant results ($P = 0.757$) (Fig. 5).

Causality between CMs and AMD

The IVW analysis indicated that higher circulating magnesium levels were negatively associated with AMD risk, suggesting a protective effect (OR = 0.679, 95% CI = 0.515–0.895, $P = 0.006$) (Fig. 4). The scatter plot, funnel plot, leave-one-out plot, and forest plot provided detailed insights into individual SNPs (Fig. 3E-H). MR-PRESSO analysis revealed no outlier SNPs for magnesium ($P = 0.983$). Sensitivity analyses demonstrated no significant heterogeneity ($P = 0.977$) or horizontal pleiotropy (MR Egger intercept = −0.0167, $P = 0.165$) (Supplementary Table S9). No significant results were detected in the reverse MR analysis ($P = 0.099$) (Fig. 5).

Causality between CMs and DR

MR analysis showed a negative correlation between genetically predicted circulating selenium levels and DR risk (OR = 0.927, 95% CI = 0.870–0.987, $P = 0.019$) (Fig. 4). Detailed insights into individual SNPs were provided by the scatter plot, funnel plot, leave-one-out plot, and forest plot (F ig. 3I-L). MR-PRESSO analysis did not identify any outlier SNPs for selenium ($P = 0.798$). Sensitivity analyses indicated no significant heterogeneity ($P = 0.643$) or horizontal pleiotropy (MR Egger intercept = −0.0053, $P = 0.734$) (Supplementary Table S9). No

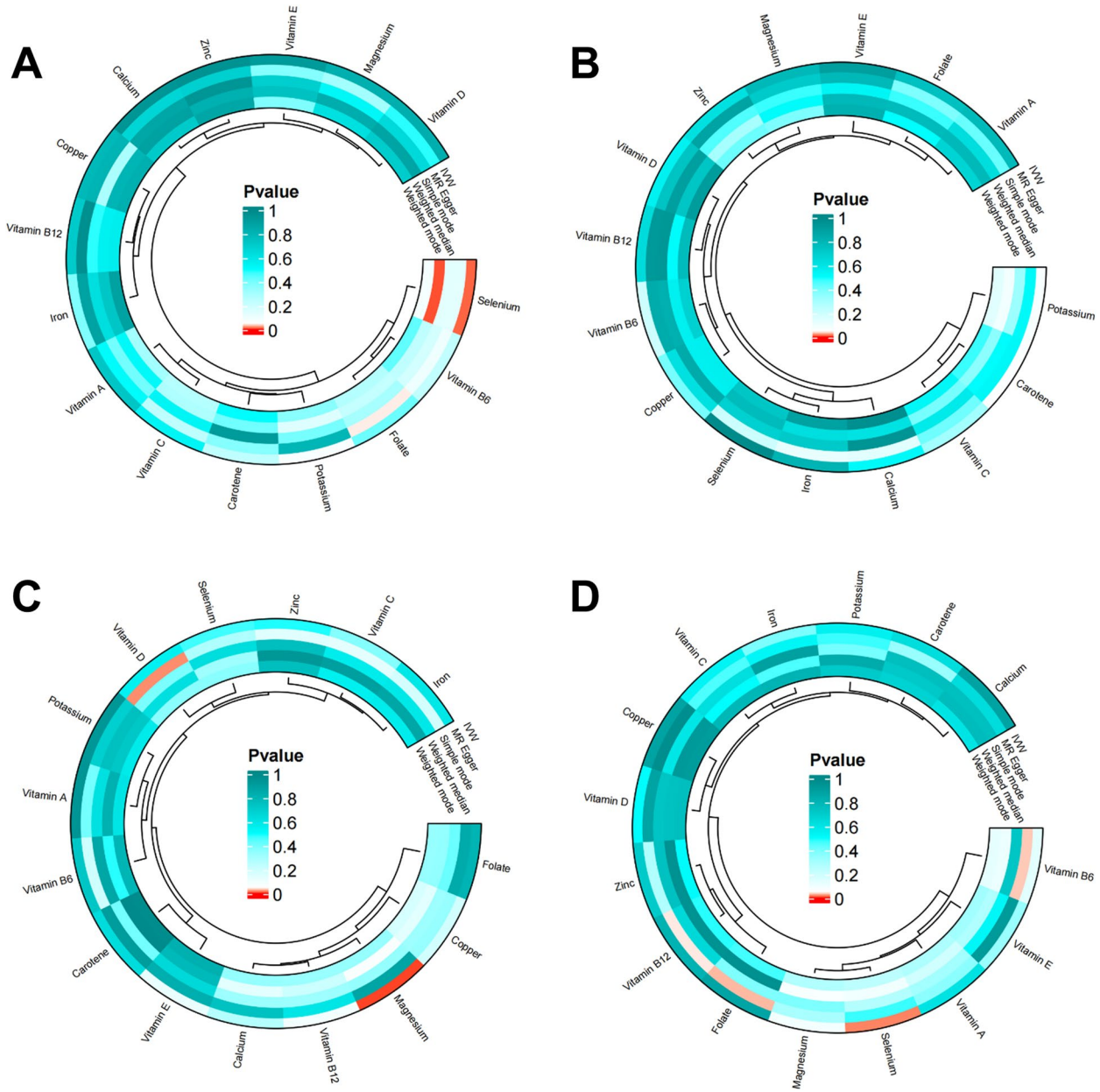

Fig. 2 Circular heatmap of the MR analysis. **A** The circular heatmap of *p*-value with micronutrients as the exposure and senile cataract as the outcome. **B** The circular heatmap of *p*-value with micronutrients as the exposure and glaucoma as the outcome. **C** The circular heatmap of *p*-value with micronutrients as the exposure and age-related macular degeneration as the outcome. **D** The circular heatmap of *p*-value with micronutrients as the exposure and diabetic retinopathy as the outcome

significant results were obtained in the reverse MR analysis for selenium and DR ($P=0.100$) (Fig. 5).

Discussion

With an aging global population, AREDs are significant public health concerns due to their impact on vision and quality of life [1–3]. Recent studies have suggested that certain CMs may play a role in the prevention or progression of these conditions [8, 31, 32]. In this study, the potential causal relationships between fifteen CMs and AREDs, including SC, glaucoma, AMD, and DR were investigated. Significant causal relationships were identified for selenium and magnesium, with circulating selenium demonstrating a protective effect on SC and DR, and circulating magnesium on AMD. Moreover, reverse MR analysis showed no reverse causation.

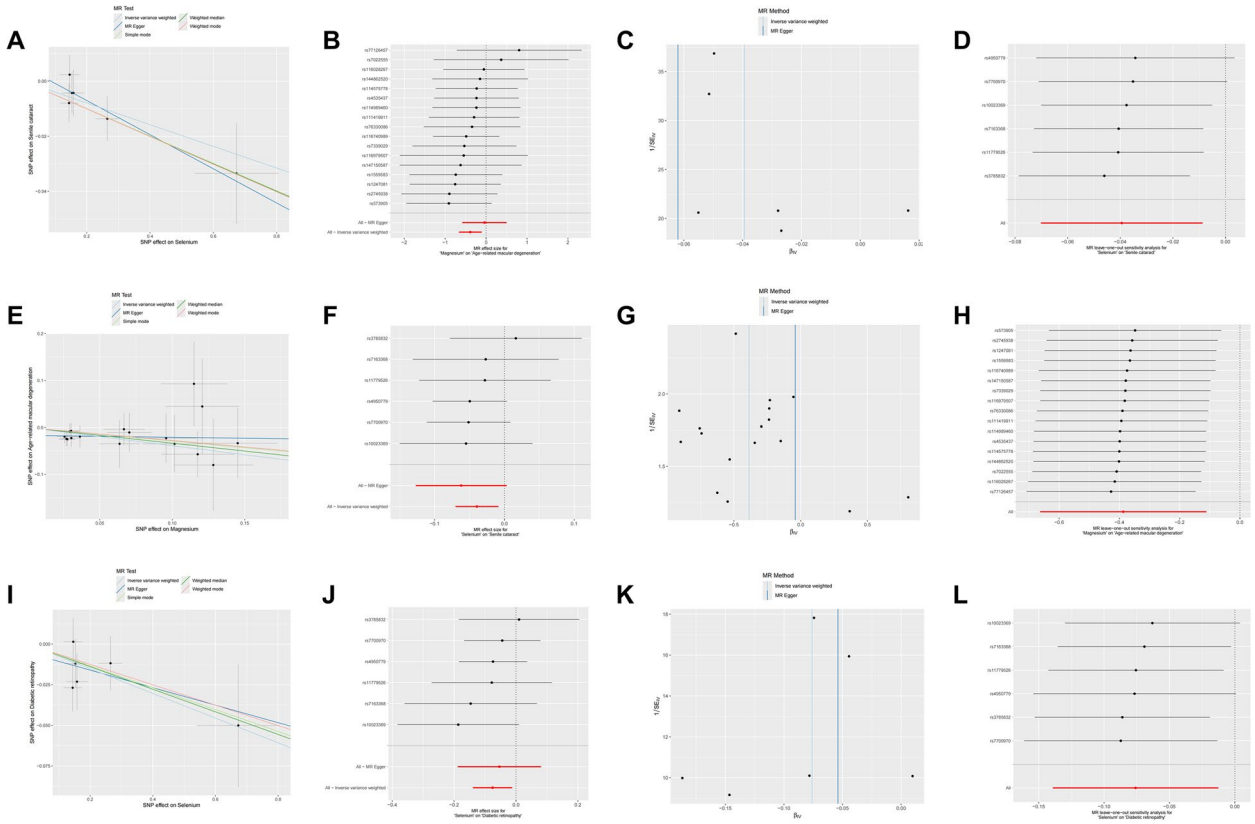

Fig. 3 Visualization of the MR analysis. **A**-**D** Visualization of the causal effects of selenium on senile cataract. **E**-**H** Visualization of the causal effects of magnesium on age-related macular degeneration. **I**-**L** Visualization of the causal effects of selenium on diabetic retinopathy. **A**, **E**, **I**, scatter plots; **B**, **F**, **J**, forest plots; **C**, **G**, **K**, funnel plots; **D**, **H**, **L**, leave-one-out plot

Exposure	Outcome	nsnp	Method	P-value	OR(95% CI)
Magnesium	Age−related macular degeneration	17	MR Egger	0.884	0.960 (0.559 to 1.648)
		17	Weighted median	0.067	0.715 (0.500 to 1.024)
		17	Inverse variance weighted	**0.006**	0.679 (0.515 to 0.895)
		17	Simple mode	0.339	0.751 (0.424 to 1.328)
		17	Weighted mode	0.337	0.758 (0.439 to 1.311)
Selenium	Senile cataract	6	MR Egger	0.135	0.940 (0.881 to 1.003)
		6	Weighted median	**0.008**	0.951 (0.917 to 0.987)
		6	Inverse variance weighted	**0.012**	0.961 (0.932 to 0.991)
		6	Simple mode	0.138	0.952 (0.900 to 1.005)
		6	Weighted mode	0.083	0.951 (0.909 to 0.995)
Selenium	Diabetic retinopathy	6	MR Egger	0.476	0.948 (0.828 to 1.084)
		6	Weighted median	0.095	0.933 (0.860 to 1.012)
		6	Inverse variance weighted	**0.019**	0.927 (0.870 to 0.987)
		6	Simple mode	0.270	0.935 (0.841 to 1.040)
		6	Weighted mode	0.247	0.939 (0.855 to 1.032)

0.4 0.6 0.8 1 1.2

Fig. 4 Forest plot for the causal effects of micronutrients on age-related eye diseases

Selenium, an essential micronutrient, is naturally found in antioxidant-rich foods and plays a critical role in maintaining cellular redox balance, mitigating oxidative stress, and protecting against DNA damage [33, 34]. After absorption in the small intestine, selenium is distributed to various tissues throughout the body, where it is incorporated into selenoproteins, particularly glutathione peroxidase [34, 35]. This enzyme is crucial for neutralizing

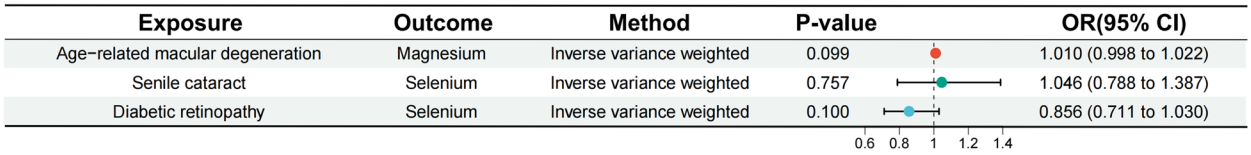

Fig. 5 Forest plot for the causal effects of age-related eye diseases on micronutrients

reactive oxygen species (ROS) and preventing oxidative damage in tissues, including those in the eye [34, 36].

In the context of ocular health, selenium's antioxidant effects are especially vital in the lens and retina, which are highly susceptible to oxidative damage due to both intrinsic and extrinsic factors, including aging and environmental stressors [36]. Oxidative stress is a key player in the pathogenesis of AREDs like SC and DR [9, 36], and selenium's ability to reduce ROS may mitigate these conditions. Furthermore, recent evidence suggests that selenium's role extends beyond its general antioxidative properties, possibly slowing the progression of chronic ocular conditions through its modulation of oxidative stress pathways [36]. This reinforces the notion that selenium plays a protective role not only in systemic conditions but also in eye health. Although meta-analyses indicate that selenium, as part of antioxidant mixtures, reduces cardiovascular risk, studies focused solely on selenium have not demonstrated consistent cardiovascular benefits [37, 38]. This highlights that the effects of selenium may differ across various health conditions, underscoring the complexity of its biological actions. In contrast, our genetic evidence provides stronger causal inferences regarding selenium's protective effect against SC and DR, offering more robust conclusions than those from traditional observational studies.

Magnesium is a mineral that is widely distributed throughout the human body, playing a vital role in numerous physiological processes [39]. It functions as an essential cofactor for γ-glutamyltransferase, an enzyme that is crucial for the synthesis of glutathione, a potent antioxidant [39]. A cross-sectional study has indicated that magnesium intake is associated with lower levels of IL-6 [40], which suggests that maintaining magnesium homeostasis is crucial for mitigating oxidative stress and inflammation. AMD, characterized by degeneration of the retinal pigment epithelium and photoreceptor cells, is primarily driven by oxidative damage and chronic inflammation [4, 6, 31]. Existing evidence suggests that adequate magnesium intake may lower the risk of developing AMD and potentially slow its progression, particularly from early to late stages [31]. This protective effect is likely attributable to magnesium's role in maintaining the balance of ROS within retinal tissues, thereby preventing the accumulation of oxidative damage that contributes to the pathogenesis of AMD [31, 39]. Moreover, dietary magnesium intake, especially when combined with other beneficial nutrients such as lutein, zeaxanthin, and omega-3 fatty acids, has been shown to be inversely associated with the risk of AMD [31]. The synergistic effects of magnesium with these nutrients imply that a balanced diet enriched with magnesium may play a significant role in AMD prevention. Our findings, which demonstrate a negative correlation between genetically predicted circulating magnesium levels and AMD risk, further support the hypothesis that magnesium may contribute to the prevention of AMD by attenuating oxidative stress and inflammation.

Interestingly, no significant associations were found between the fifteen investigated CMs and glaucoma risk. This result contrasts with some epidemiological studies that have suggested the protective effects of nutrients like selenium, zinc, and vitamin B6 against glaucoma [11, 32, 41]. Several factors may explain these discrepancies. First, differences in study designs may play a pivotal role. Our study employed a two-sample Mendelian randomization approach, which reduces confounding, whereas many of the studies reporting significant associations were observational. Observational studies are more susceptible to biases, including confounding by lifestyle factors, which may distort the observed relationships between micronutrients and glaucoma risk [42]. Second, heterogeneity among glaucoma subtypes may account for the varying findings. Glaucoma encompasses multiple subtypes with distinct pathophysiological mechanisms [11], and as our study did not differentiate between these subtypes, potential associations with specific micronutrients may have been diluted. Future studies that distinguish between different glaucoma subtypes could provide more precise insights into how various nutrients influence distinct forms of glaucoma. Another possible explanation for the discrepancies lies in genetic diversity across study populations. Our research primarily focused on individuals of European descent, while other studies may have included more genetically diverse cohorts. Genetic differences in nutrient metabolism could lead to variations in how micronutrients affect glaucoma risk. Finally, environmental factors, including diet, socioeconomic status, and access to healthcare, may also contribute to the observed differences in study outcomes [11,

41, 42]. These factors could interact with micronutrient intake and influence glaucoma risk, further complicating the interpretation of results.

Although our results did not show significant causal relationships between the remaining micronutrients and AREDs, their roles in health remain noteworthy. For instance, the concentrations of zinc and copper, which decrease with age, have been implicated in AMD progression [43]. Iron deposition in the retina, if increased, can lead to photoreceptor cell loss, while its deficiency does not cause adverse effects [44]. A meta-analysis suggested that dietary vitamins A, C, E, and carotenoids may reduce the risk of SC [8, 45]. However, a randomized controlled trial found no significant protective effect of vitamin E supplementation compared to placebo [45]. Moreover, antioxidant vitamin and mineral supplements may slow the progression of late-stage AMD [31]. Several cross-sectional studies have shown that vitamin D may have a protective effect against AMD in specific populations [32]. Nevertheless, most of the existing evidence comes from small-scale studies with varying methods and assessment criteria, which may compromise accuracy [20].

While our study benefited from the robust methodological framework of MR, which mitigated biases such as confounding and reverse causation, several limitations must be acknowledged [17, 26]. The generalizability of our findings was constrained by the genetic ancestry of the study population, which was predominantly of European descent. Future research should aim to include diverse populations to validate these findings across different genetic backgrounds. Additionally, while we accounted for horizontal pleiotropy, the possibility of residual pleiotropy cannot be entirely ruled out [30]. Potential false-positive results due to multiple hypothesis testing were not corrected by the false discovery rate. Further research is required to confirm the protective roles of selenium and magnesium in AREDs. Expanding MR studies to include a broader range of micronutrients and diverse genetic backgrounds will be crucial for advancing our understanding of the pathogenesis of micronutrient-related AREDs.

In conclusion, this study advances our understanding of the complex relationships between CMs and AREDSs, offering promising avenues for preventative strategies and public health interventions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12263-025-00767-8.

Supplementary Material 1.

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Acknowledgements
The authors thank the investigators of the original studies for sharing the GWAS summary statistics.

Authors' contributions
XC and XY were responsible for the conception and design of the study. XC, ZX, and BZ were responsible for the acquisition and analysis of data. XC and ZX wrote the paper. ZJ and XY reviewed the paper. All authors read and approved the final manuscript for submission. XC and ZX contributed equally to this work.

Funding
This work was funded by the National Natural Science Foundation of China (82371033, 32200684), the Tianjin Health Research Project (TJWJ2022QN078), the Tianjin Key Medical Discipline (Specialty) Construction Project (TJYXZDXK-016A).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study used publicly available GWAS summary statistics and conducted secondary analyses of these data. Each GWAS was approved by its respective ethics committee.

Competing interests
The authors declare no competing interests.

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Received: 3 December 2024 Accepted: 12 March 2025
Published online: 28 March 2025

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