· Mendelian Randomization ·

Causal relationships between 41 inflammatory cytokines and myopia: a Mendelian randomization study

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Abstract

● **AIM:** To investigate the potential causal associations between 41 inflammatory cytokines and myopia using a two-sample Mendelian randomization (MR) approach.

● **METHODS:** Publicly available genome-wide association study (GWAS) datasets were utilized for this two-sample MR analysis. Inflammatory cytokine-related GWAS data were extracted from The University of Bristol's Research Data Repository, and myopia-related GWAS data were obtained from the FinnGen project. Single nucleotide polymorphisms (SNPs) associated with inflammatory cytokines were systematically selected as instrumental variables (IVs) based on three rigorous criteria: relevance, independence, and exclusion of pleiotropy. Five MR methods were employed for causal inference: the inverse-variance weighted (IVW) method as the primary analysis, supplemented by MR-Egger regression, weighted median estimator, simple mode, and weighted mode approaches. Sensitivity analyses were performed to evaluate the robustness of the causal estimates.

● **RESULTS:** A total of 773 myopia-associated SNPs were identified. MR analysis revealed that higher levels of macrophage inflammatory protein 1-α (MIP-1α) were associated with a 17% reduced risk of myopia [odds ratio (OR)=0.83; 95% confidence interval (CI): 0.69-0.99; P<0.05]. In contrast, elevated levels of eotaxin (OR=1.26; 95%CI: 1.07-1.47; P<0.01), stromal cell-derived factor-1α (SDF-1α; OR=1.68; 95% CI: 1.08-2.62; P<0.05), and interleukin-2 receptor subunit alpha (IL-2Rα; OR=1.25; 95%CI: 1.01-1.53; P<0.05) were significantly associated with an increased risk of myopia. Sensitivity analyses confirmed the reliability of these results.

● **CONCLUSION:** This study provides evidence supporting a causal relationship between specific inflammatory cytokines and myopia. MIP-1α may act as a protective factor against myopia, while eotaxin, SDF-1α, and IL-2Rα are potential risk factors for myopia. These findings emphasize the critical role of inflammatory pathways in the pathogenesis of myopia, offering novel insights for the development of preventive and therapeutic strategies for myopia.

● **KEYWORDS:** myopia; inflammatory cytokines; Mendelian randomization; causal association; single nucleotide polymorphism; genome-wide association study

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INTRODUCTION

Myopia, or nearsightedness, refers to a condition where distant objects are focused anterior to the retina, when the eyes are in a relaxed state of accommodation, resulting in blurred vision. It is increasingly recognized as an urgent public health problem worldwide[1]. Predictions suggest that by 2050, nearly half of the global population may be affected by myopia, with 9.8% experiencing high myopia. This heightens the risk of severe visual impairments and blindness-related complications, such as retinal detachment, myopic maculopathy and glaucoma[2]. The prevalence of myopia among East Asian populations is particularly remarkable, with over 80% of young adults possibly affected[3-4]. This worrisome trend highlights the urgent need for effective strategies to prevent and control myopia. It is widely accepted that both genetic predispositions and environmental influences contribute to the development of myopia[5]. Factors such as poor visual habits, lack of outdoor activities, micronutrient deficiencies, imbalanced nutritional intake, inflammation, and environmental pollutants are all considered possible contributors to the development of myopia[6-7].

Inflammation is an important immune response that helps our body maintain homeostasis. However, excessive activation of the inflammatory response is a common basis for many

Table 1 Characteristics of inflammatory cytokines and myopia

Exposure	Sample	SNP	Population	Database	Sex	Year
Inflammatory cytokines	8293	NA	European	The data.bris Research Data Repository	Male and female	2017, 2000
Myopia	212571	16380455	European	FinnGen	Male and female	2021

diseases. Investigations have indicated that individuals suffering from specific inflammatory disorders, including Vogt-Koyanagi-Harada disease and juvenile idiopathic arthritis, exhibit a heightened risk of developing myopia[8-9]. A clinical observational study revealed that individuals with pathological myopia have higher levels of serum high-sensitivity C-reactive protein as well as increased levels of complement component 3[10]. Yu *et al*[11] investigated the inflammatory cytokines and oxidative stress within the aqueous humor of individuals diagnosed with high myopia, discovering elevated concentrations of interleukin-6, matrix metalloproteinase-2, and interleukin-1 beta in the high myopic cohort. Similar studies have also reported elevated levels of monocyte chemoattractant protein-1, interleukin-8, interleukin-6, and tumor necrosis factor-alpha[12-13].

However, these conclusions were inconsistent. They mainly come from clinical observational studies that were easily affected by confounding variables, reverse causality, and measurement inaccuracies. The limitations make it difficult to draw a clear conclusion about the causal connection between inflammatory cytokines and myopia.

Mendelian randomization (MR) represents an innovative statistical approach that establishes causal relationships by utilizing genetic variation as instrumental variables (IVs). The concept relies on the foundations of genetic inheritance, where alleles are assigned randomly at conception, thereby reducing the influence of confounding variables and enhancing the accuracy of causal relationship assessments[14]. Recently, with the ongoing accumulation of vast quantities of data from genome-wide association studies (GWAS), the utilization of MR analysis in ocular diseases have become increasingly prevalent[15-18]. To date, no specific MR studies have been identified that examine the causal relationships between multiple inflammatory cytokines (totaling 41 types) and the susceptibility to myopia.

Therefore, we applied the MR design to investigate the genetic relationship between multiple inflammatory cytokines and myopia at the genetic level through GWAS data. This provides novel perspectives on the mechanisms underlying myopia and will guide future management and prevention strategies.

MATERIALS AND METHODS

Data Resources The relevant datasets were obtained from two publicly accessible GWAS database. Summary statistics regarding inflammatory cytokines were obtained from the Research Data Repository of the University of Bristol (https://data.bris.ac.uk/data/dataset/3g3i5smgghp0s2uvm1doflkx9x), which aimed to analyze associations between these cytokines and single nucleotide polymorphisms (SNPs)[19]. Based on published large-scale GWAS meta-analyses of 41 inflammatory cytokines[20], we analyzed 8293 Finns from three separate cohorts (the Cardiovascular Risk in Young Finns Study (YFS), FINRISK1997, and FINRISK2002). GWAS data on myopia (finn-b-H7_MYOPIA) were retrieved from the official FinnGen project website (https://www.finngen.fi/fi) in the publicly available fifth version (R5) of the FinnGen database. The final dataset used in this study primarily consists of the European population, with no specific gender excluded, as detailed in Table 1. We accessed the study data on June 23, 2024. Ethical approval was not needed for this analysis, because all GWAS data utilized in the research were accessible to the public and had previously received approval from the appropriate ethical review committees.

SNPs Screening In MR analysis, SNPs from GWAS were used as IVs. Each IV's validity must comply with three essential assumptions[21], as shown in Figure 1.

We established the threshold for genome-wide significance at $P<5\times10^{-8}$. The independence of the identified SNPs was assessed through linkage disequilibrium analysis, and those with $r^2>0.001$ within a 10 000-kb clumping window were filtered out. Subsequently, the strength of the IVs was assessed through the application of the F-statistic. SNPs with an F-value exceeding 10 were considered sufficiently robust to be associated with exposure factors. Further, we checked whether these screened candidate SNPs had a significant genetic association ($P<5\times10^{-8}$) with both the confounding factors (such as education and time outdoors)[22] and the study outcome *via* PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/), and no significant association was found between them. Finally we extracted SNPs related to inflammatory cytokines from the summary data of the GWAS on myopia, setting a minimum threshold of $r^2>0.8$, while excluding any SNPs directly associated with myopia ($P<5\times10^{-8}$)[23-24].

Causal Relationship Verification Our primary analytical approach was the Inverse-Variance Weighted (IVW) method, due to its efficiency and robustness. In order to strengthen the reliability of our results, we incorporated four supplementary approaches: MR-Egger, weighted median, simple mode, and weighted mode.

Sensitivity Analysis The Cochrane's Q statistic, utilizing the IVW approach, was employed to measure the heterogeneity

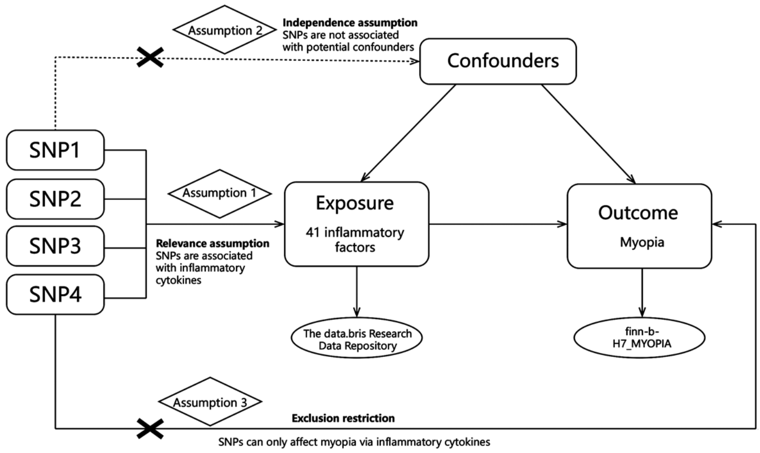

Figure 1 Diagram illustrating the design of a two-sample MR study Forty-one inflammatory cytokines were set as exposure variables, with myopia identified as the outcome variable, in order to investigate the associations between them. The loop diagram shows the three essential principles of MR: relevance, independence, and exclusion. MR: Mendelian randomization; SNP: Single nucleotide polymorphism.

of estimates associated with each SNP. Additionally, we examined the intercept term in the MR-Egger approach to establish whether horizontal pleiotropy was present. If the intercept term deviated significantly from 0, it suggested that pleiotropy might exist. In such a situation, the inference of causal relationships would be founded on the MR-Egger regression. Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) was also used to evaluate pleiotropy. The number of distributions was established at 10 000, with a threshold set at 0.05. In addition, we performed a leave-one-out analysis to further validate the dependability and robustness of the analytical outcomes.

Statistical Analysis All analyses were carried out with the TwoSample MR package in R (version 4.2.2). To account for multiple comparisons, the false discovery rate (FDR) correction was employed. Results yielding a *P*-value of less than 0.05 prior to FDR adjustment were classified as suggestive causal associations.

RESULTS

SNP Screening and Preliminary Analysis of Myopia Dataset After thorough screening, our myopia dataset finally encompassed 773 SNPs. The F-statistics of the SNPs spanned from 19.45 to 782.45, with an average value of 32.97. This suggests a minimal likelihood of weak instrument bias on causal associations. Although FDR correction did not indicate significant confirmative associations, the *P* values before FDR correction suggested the presence of potentially associated factors. A total of 4 suggestive causal associations were identified, involving macrophage inflammatory protein 1-α (MIP-1α), eotaxin, stromal cell-derived factor-1α (SDF-1α), and interleukin-2 receptor subunit alpha (IL-2Rα).

Causal Association between MIP-1α and Myopia The IVW method demonstrated that a genetically determined one-standard-deviation increase in MIP-1α levels corresponded to a 17% decrease in the likelihood of developing myopia [odds ratio (OR): 0.83, 95% confidence intervals (CI): 0.69-0.99, $P<0.05$; Table 2]. The Cochrane Q test for MIP-1α revealed an absence of significant heterogeneity in the SNPs analyzed ($Q=8.03$, $P>0.05$). And the intercept term of the MR-Egger regression did not demonstrate any statistical significance compared to zero ($P>0.05$), indicating no SNP pleiotropy (Table 3). The MR-PRESSO results ($P>0.05$) also confirmed the absence of horizontal pleiotropy in MIP-1α (Table 3).

Causal Association Analysis between Eotaxin and Myopia Conversely, a one-standard-deviation increase in eotaxin levels was associated with a 26% increase in the odds of myopia (OR: 1.26, 95%CI: 1.07-1.47, $P<0.01$; Table 2). The Cochrane Q test for eotaxin demonstrated no SNP heterogeneity ($Q=30.95$, $P>0.05$). Further, the MR-Egger intercept test ($P>0.05$) and MR-PRESSO ($P>0.05$) did not reveal any indications of horizontal pleiotropy (Table 3).

Causal Association between SDF-1α, IL-2Rα and Myopia For SDF-1α and IL-2Rα, the intercept term test of the MR-Egger method suggested the presence of horizontal pleiotropy ($P<0.05$). Consequently, we primarily employed the MR-Egger regression to analyze the causal associations. The MR-Egger regression analysis revealed that a one standard deviation increases in SDF-1α levels corresponded to a 68% increase in myopia odds (OR: 1.68, 95%CI: 1.08-2.62, $P<0.05$). Similar causal associations were established for IL-2Rα (OR: 1.25, 95%CI: 1.01-1.53, $P<0.05$; Table 2). The MR-PRESSO results provided evidence for the lack of horizontal pleiotropy in SDF-1α ($P>0.05$) and IL-2Rα ($P>0.05$; Table 3). The Cochrane Q test showed no SNP heterogeneity in either SDF-1α ($Q=14.42$, $P>0.05$) or IL-2Rα ($Q=18.59$, $P>0.05$; Table 3).

Visualization of Cytokine-Myopia Association The results of the IVW analyses for MR involving the 41 inflammatory

Table 2 Result of MR estimates for the 4 inflammatory cytokines

Exposures	SNP	Method	OR (95%CI)	*P*	FDR
MIP-1α	12	MR Egger	0.6721 (0.4509-1.0019)	0.0797	0.7188
		Weighted median	0.9231 (0.7152-1.1914)	0.5388	0.9547
		Inverse variance weighted	0.834 (0.6959-0.9995)	0.0494	0.7810
		Simple mode	1.0003 (0.6598-1.5165)	0.9988	0.9988
		Weighted mode	0.997 (0.6692-1.4854)	0.9885	0.9945
SDF-1α	16	MR Egger	1.6848 (1.0832-2.6207)	0.0363	0.6670
		Weighted median	0.9158 (0.6702-1.2516)	0.5811	0.9547
		Inverse variance weighted	1.0975 (0.8782-1.3715)	0.4135	0.9183
		Simple mode	0.8214 (0.4721-1.4292)	0.4969	0.9988
		Weighted mode	0.8449 (0.5077-1.4061)	0.5265	0.9945
Eotaxin	27	MR Egger	1.5177 (1.072-2.1487)	0.0268	0.6670
		Weighted median	1.2629 (1.0002-1.5945)	0.0498	0.9547
		Inverse variance weighted	1.2591 (1.0761-1.4732)	0.0040	0.1655
		Simple mode	1.1258 (0.7358-1.7227)	0.5896	0.9988
		Weighted mode	1.2967 (0.9758-1.7231)	0.0849	0.9945
IL-2Rα	19	MR Egger	1.2482 (1.0171-1.5318)	0.0488	0.6670
		Weighted median	1.0913 (0.9186-1.2964)	0.3202	0.9547
		Inverse variance weighted	1.0052 (0.8891-1.1363)	0.9343	0.9789
		Simple mode	0.9069 (0.6528-1.2601)	0.5676	0.9988
		Weighted mode	1.1093 (0.9145-1.3455)	0.3062	0.9945

MR: Mendelian Randomization; SNP: Single nucleotide polymorphism; OR: Odds ratio; CI: Confidence interval; FDR: False discovery rate; MIP-1α: Macrophage inflammatory protein 1-α; SDF-1α: Stromal cell-derived factor-1α; IL-2Rα: Interleukin-2 receptor subunit alpha.

Table 3 Analysis of heterogeneity and horizontal pleiotropy of the 4 inflammatory cytokines

Exposures	Heterogenity		Horizontal pleintropy			MR-PRESSO	
	Cochran's Q	*P*	Egger intercept	SE	*P*	RSSobs	*P*
MIP-1α	8.0302	0.7106	0.0433	0.0365	0.2621	9.5180	0.718
SDF-1α	14.4163	0.4942	-0.0556	0.0253	0.0449	16.3925	0.504
Eotaxin	30.9455	0.2303	-0.0265	0.0225	0.2497	33.3871	0.240
IL-2Rα	18.5902	0.4175	-0.0566	0.0220	0.0200	21.2517	0.429

SE: Standard error; RSSobs: Observed residual sum of squares; MIP-1α: macrophage inflammatory protein 1-α; SDF-1α: Stromal cell-derived factor-1α; IL-2Rα: Interleukin-2 receptor subunit alpha.

cytokines were presented in Figure 2. The leave-one-out sensitivity analysis indicated that the outcomes remained stable even after the sequential removal of individual SNPs (Figure 3). No SNP was found to have a significant impact on the causal estimates, thus demonstrating the robustness of the research findings.

DISCUSSION

Using MR examination, we explored the potential associations between inflammatory cytokines and the risk of myopia. Our results showed that MIP-1α may act as a protective factor against myopia, whereas eotaxin, SDF-1α, and IL-2Rα were identified as suggestive risk factors. This highlights the important role that inflammatory processes play in the pathogenesis of myopia.

Previous studies have also demonstrated a correlation between inflammatory cytokines and myopia risk. In a study involving 147 patients who underwent implantable collamer lens implantation, researchers detected elevated levels of inflammatory cytokines such as chitinase 3-like protein 1, interleukin-6 receptor subunit alpha, interleukin-8, a proliferation-inducing ligand, B cell activating factor, and interleukin-34 in the aqueous humor[25]. In a form-deprivation myopia model, resveratrol, an anti-inflammatory drug, inhibited the progression of myopia[26]. This further supported the idea that inflammation was key to myopia development.

MIP-1α, also known as chemokine ligand 3 (CCL3), primarily functions as a chemotactic agent, attracting immune cells such as monocytes, T lymphocytes, and eosinophils to the site of inflammation. It is important for immune regulation and the maintenance of immune homeostasis[27]. The findings from this research indicated that MIP-1α (OR: 0.83, 95%CI: 0.69-0.99, P<0.05) was a protective factor that helped prevent the development of myopia. Existing research has shown that lipopolysaccharide can activate the expression of MIP-1α[28]. In addition, pre-stimulation with lipopolysaccharide has been proven to enhance the body's tolerance to long-term inflammation[29]. Therefore, the high expression of MIP-1α prior to the onset of myopia may, to some extent, reduce

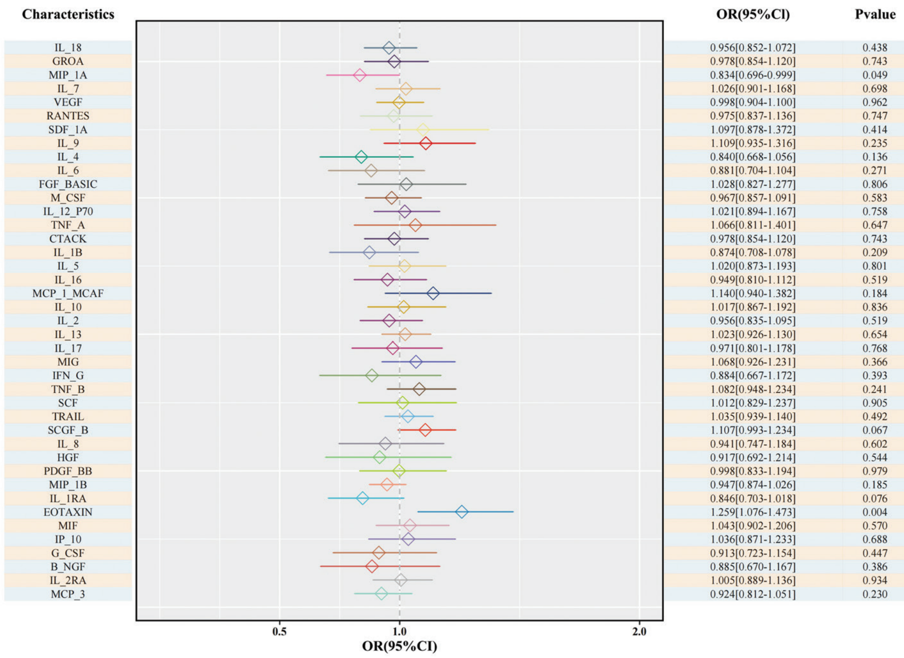

Figure 2 A forest plot illustrating the relationship between 41 inflammatory cytokines and myopia by IVW method IVW: Inverse-variance weighted; OR: Odds ratio; CI: Confidence interval.

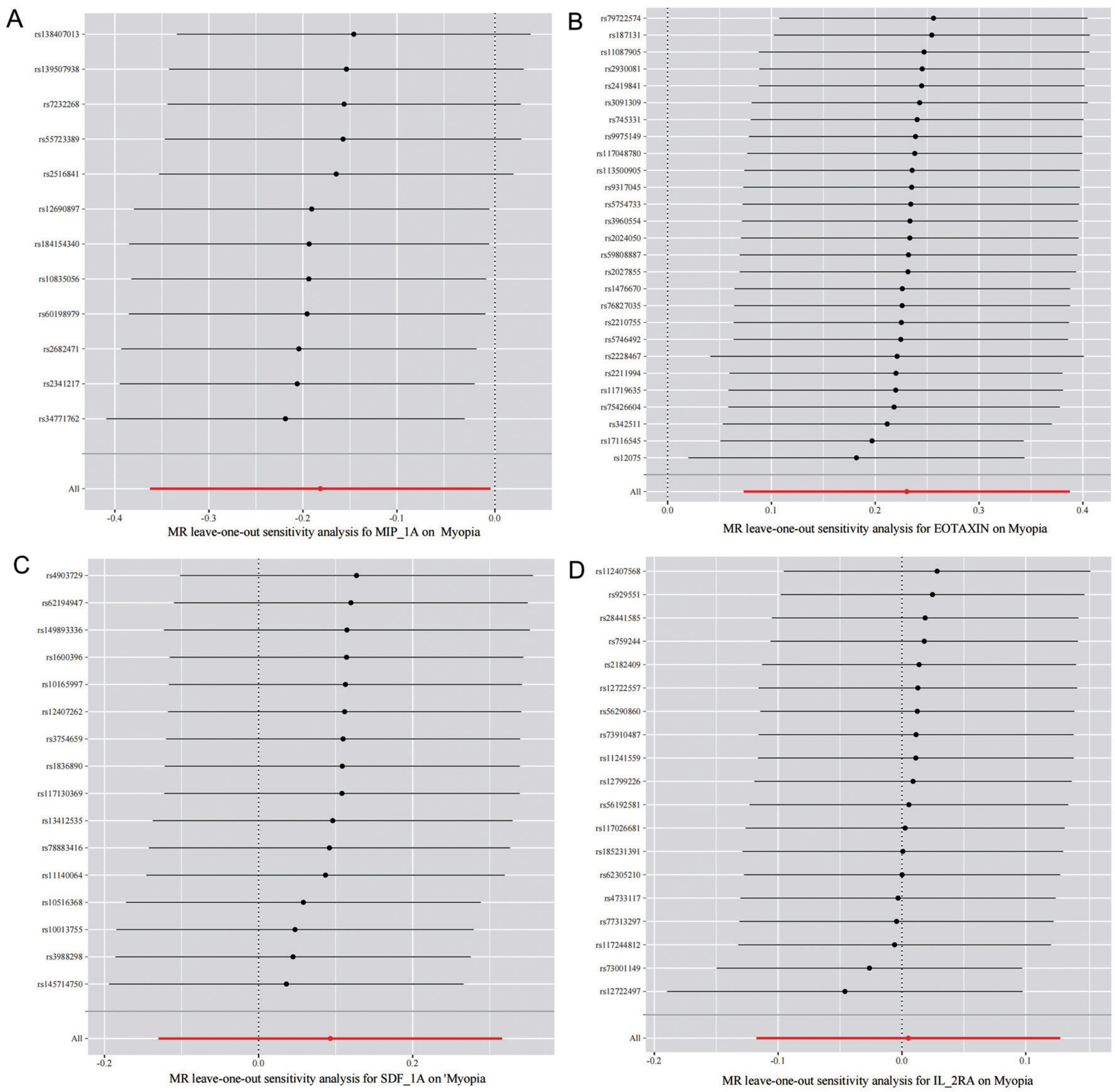

Figure 3 Leave-one-out sensitivity analysis of the association between inflammatory cytokines and myopia A: MIP-1α; B: Eotaxin; C: SDF-1α; D: IL-2Rα. MIP-1α: Macrophage inflammatory protein 1-α; SDF-1α: Stromal cell-derived factor-1α; IL-2Rα: Interleukin-2 receptor subunit alpha.

the risk of myopia by inducing adaptive immune regulation or maintaining tissue homeostasis. However, Wei *et al*[30] reported elevated levels of MIP-1α in the vitreous humor of individuals suffering from high myopia, which seemingly contradict the findings of our study. The discrepancy might reflect a secondary inflammatory response following the onset of myopia rather than MIP-1α's role in the pre-myopia stage. In addition, it has been reported that systemic inflammatory diseases increase the risk of myopia[31-32]. At the same time, MIP-1α shows a negative correlation in various systemic inflammatory diseases, such as knee osteoarthritis[31], which may provide evidence for the protective effect of MIP-1α against myopia.

Eotaxin, an eosinophil chemotactic factor, plays a key role in immune and inflammatory responses. Individuals with chronic inflammatory conditions, particularly allergic asthma, chronic obstructive pulmonary disease, and rheumatoid arthritis, had elevated levels of eotaxin amounts[32-34]. Researchers found that patients with high myopia exhibited elevated concentrations of eotaxin in their vitreous fluid[26]. In our study, an increase of one standard deviation in eotaxin levels correlated with 26% higher odds of developing myopia, highlighting its potential as a risk factor.

IL-2Rα, also referred to as cluster of differentiation 25 or p55, is primarily expressed on activated T lymphocytes and regulatory T cells. It plays an important role in immune cell activation and immune regulation[35]. In our study, high IL-2Rα levels were associated with an elevated myopia risk (OR: 1.25, 95%CI: 1.01-1.53, $P<0.05$). Liang *et al*[36] found in a comprehensive genome-wide association study that elevated IL-2 and IL-2Rα levels were associated with a higher myopia risk. They also found that, IL-2 was significantly upregulated in the vitreous of form-deprivation myopia guinea pigs, validating the importance of IL-2 and its receptors in myopia pathogenesis.

SDF-1α, also known as C-X-C motif chemokine ligand 12, a member of the Cysteine-X-Cysteine (CXC) chemokine family is ubiquitously expressed across diverse cell types. It is mainly involved in chemotaxis, angiogenesis and immune regulation[37]. Our study revealed that elevated levels of SDF-1α were correlated with an increased risk of myopia (OR: 1.68, 95%CI: 1.08-2.62, $P<0.05$). However, researches on the relationship between SDF-1α and myopia, including its underlying mechanisms, is limited. Thus, further research is needed to clarify the causal relationships between them and the specific signaling pathways involved.

Our study was the first to apply MR to investigate the causal links between 41 common inflammatory cytokines and myopia. We used a large sample size composed of 212 571 European individuals and a diverse set of genetic variants as IVs to reduce confounding factors. However, the study has certain limitations. First, our samples were mainly sourced from the European population, which led to sampling bias. Given the high prevalence of myopia in East Asia and potential ethnic differences in the genetic and environmental factors related to myopia, the generalizability of our results to non-European populations, especially those in East Asia, is limited. Second, the study depended on potentially biased publicly - available GWAS data and lacks clinical sample verification, which may affect result accuracy and clinical translation. Third, the MR method assumes that genetic associations are linear. However, genetic pleiotropy can still occur in reality. Although we have made efforts to control for these factors, unidentified pathways may still introduce biases in causal inference.

Our research conclusions support existing evidence that inflammatory cytokines significantly contribute to the progression of myopia. The findings clarified that MIP-1α might function as a protective factor against myopia, while eotaxin, SDF-1α, and IL-2Rα were recognized as suggestive factors that increased the risk of developing myopia. Future studies should prioritize trans-ethnic validation, especially in East Asian populations where myopia is highly prevalent. The inconsistencies found in other researches underscore the need for further investigation of the complex interplay between myopia pathogenesis and genetic and environmental factors.

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Data Availability: We obtained relevant datasets from two publicly accessible GWAS databases: inflammatory cytokine data from The University of Bristol's Research Data Repository (https://data.bris.ac.uk/data/dataset/3g3i5smgghp0s2uvm1doflkx9x) and myopia data from the FinnGen project (https://r5.finngen.fi/pheno/H7_ MYOPIA).

Conflicts of Interest: Wu XF, None; **Yu L,** None; **Zhang Y,** None; **Li S,** None; **Li R,** None; **Sun LY,** None.

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