Causal Associations Between Socioeconomic Status and Corneal Diseases: A Multivariate Mendelian Randomisation Study

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ABSTRACT

Objective: To investigate the causal relationship between socioeconomic status (SES) and corneal diseases.

Study Design: Two-sample Mendelian randomisation (MR) analysis.

Place and Duration of the Study: Department of Pharmacy, Eye Hospital, Wenzhou Medical University, Wenzhou, China, between May and September 2024.

Methodology: The genome-wide significant single-nucleotide polymorphisms (SNPs) ($p < 5 \times 10^{-8}$) associated with educational attainment, household income, and occupational status were selected as instrumental variables (IVs). Linkage disequilibrium (LD) clumping ($r^2 < 0.001$) was applied to ensure independence, and SNPs with F-statistics <10 were excluded. Corneal disease outcomes were analysed using inverse variance weighting (IVW) as the primary method. Sensitivity analyses, including Cochran's Q-test for heterogeneity, the MR-Egger for interception, and MR-PRESSO for pleiotropy, were performed to assess robustness.

Results: A significant negative association was observed between educational attainment and corneal ulcer risk in the univariate MR analysis (IVW OR, 0.77; 95% CI: 0.66-0.92; p = 0.003). In the multivariate MR (MVMR) analysis adjusting for household income and educational attainment, occupational status showed a significant association with corneal ulcer risk (IVW OR, 0.91; 95% CI: 0.82-0.99; p = 0.041). No significant associations were observed with other subtypes of corneal diseases.

Conclusion: These findings indicate that genetic evidence that lower socioeconomic status, particularly lower educational attainment and occupational status, is associated with an increased risk of corneal ulcer. Targeted public health strategies to improve socioeconomic conditions in disadvantaged populations may help reduce the burden of corneal diseases.

Key Words: *Socio-economic status, Corneal diseases, Mendelian randomisation, Corneal ulcers.*

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INTRODUCTION

The cornea, the transparent outer layer of the eye, plays a critical role in vision by refracting light and protecting internal ocular structures. Despite its resilience, the cornea is susceptible to damage. It has limited regenerative capacity, leading to conditions such as corneal ulcers, keratitis, and keratoconus, which are significant causes of global blindness.[1] Notably, socioeconomic factors may influence the incidence and severity of corneal diseases, as evidenced by the higher prevalence of corneal blindness in the developing countries.[2]

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Socioeconomic status (SES), encompassing educational attainment, income, and occupational status, is a well-established determinant of health disparities.[3] However, the causal relationship between SES and corneal diseases remains unclear, as most existing studies are descriptive or cross-sectional.[4]

To minimise confounding mendelian randomisation (MR), a genetic-based approach, offers a robust method for drawing causal inference by using genetic variants as instrumental variables (IVs).[5] The present study employs MR analysis to investigate the potential causal effects of SES on corneal diseases, thereby addressing a critical gap in the literature. By elucidating these relationships, this study aimed to inform targeted interventions and public health strategies to reduce the burden of corneal diseases, particularly among socioeconomically disadvantaged populations.

METHODOLOGY

The present study used pooled data from genome-wide association study (GWAS) to identify exposure-related genetic markers.

The preliminary study explored the genetic correlation between the educational attainment levels and the subtypes of corneal diseases. Genetic data on educational attainment were obtained from the study of Okbay *et al*., which included 71 cohorts from the UK Biobank and 23andMe, comprising 3,037,499 participants from the UK and the US.[6] Educational attainment was quantified as years of schooling, standardised across cohorts by mapping the highest educational level to categories defined by the International Standard Classification of Education (ISCED 1997).

Subsequently, multivariate MR (MVMR) analysis was performed to evaluate the combined effects of educational attainment, household income, and occupational status on the risk of corneal diseases. Genetic data for household income and occupational status were obtained from the UK Biobank, comprising 286,301 and 248,847 participants, respectively.[7,8] Household income was assessed through self-reported data collected on a 5-point scale, representing total pre-tax household income: 1 (<£18,000), 2 (£18,000–£29,999), 3 (£30,000–£51,999), 4 (£52,000–£100,000), and 5 (>£100,000). These categories were treated as continuous variables in the analysis. Participants who responded did not know or prefer not to answer were excluded, yielding a final sample of 286,301 individuals with both genotype and income data. Occupational status was defined according to job classifications from the UK Standard Occupational Classification (SOC) system, developed by the Office for National Statistics.[9] The phenotype was derived from the nine major SOC groups, which rank occupations hierarchically from elementary jobs to senior managerial roles. Occupational codes were treated as ordinal variables from 1 to 9, with higher values reflecting greater occupational complexity and cognitive demands. Outcome data for corneal diseases were obtained from the latest release (R10) of the FinnGen consortium, a large-scale biomedical database in Finland.[10] All phenotypes classified under corneal diseases in the FinnGen R10 dataset were included in this study without any additional filtering. These phenotypes were defined according to ICD-10 codes and standardised phenotype mappings provided by FinnGen. All original studies included in this analysis had received prior ethical approval from the corresponding review boards; therefore, no additional ethical approval or informed consent was required.

To explore the potential causal association between educational attainment and corneal diseases, single-nucleotide polymorphisms (SNPs) significantly associated with years of schooling ($p < 5 \times 10^{-8}$) were selected from the large-scale GWAS by Okbay *et al*., in which educational attainment was harmonised across cohorts using the ISCED 1997. IVs were retained if they satisfied the three core assumptions of MR: the relevance assumption, the independence assumption, and the exclusion restriction.[11] The genome-wide significance threshold ($p < 5 \times 10^{-8}$) was used to ensure the correlation of IVs. Based on the 1000 Genomes Project of the European reference panel, a strict linkage disequilibrium (LD) clustering ($r^2 = 0.001$) was adopted within the 1Mb genetic window to ensure the independence of IVs.[12] SNPs with missing data, minor allele frequency (MAF) below 0.01, or palindromic structure were excluded. In addition, the statistical power of IVs was evaluated using the F-statistics ($F = (N-2) \times R^2 / (1-R^2)$), in which SNPs with F-statistical values <10 were considered weak IVs and excluded from the study. To ensure the exclusivity of the hypothesis, the included SNPs were screened by PhenoScanner (https://www.phenoscanner.medschl.cam.ac.uk) to exclude SNPs and potential confounders associated with the outcome at the genome-wide significance level. A random-effect inverse variance weighting (IVW) was used as the primary method of MR analysis, while MR-Egger, weighted median, and weighted mode were used to comprehensively evaluate the potential causal effect of education level on corneal disease risk. Statistical significance ($p < 0.05$) was taken as a potential causal relationship between exposure and outcome.

Results were tested using heterogeneity test and pleiotropic test. The heterogeneity test assessed whether a significant difference existed between causal estimates provided by different IVs, thereby determining the presence of heterogeneity among IVs. The test was mainly performed using Cochran's Q-test within the IVW method; if $p < 0.05$, significant heterogeneity among different IVs was indicated.[13] The pleiotropic test was used to determine whether multiple IVs affect the outcome of the study through different biological pathways, thereby violating the exclusion restriction assumption of MR analysis and affecting the effectiveness of MR estimation. The pleiotropic test first used the MR-PRESSO method to identify outliers that may introduce directional pleiotropy at the overall level. These outliers were excluded prior to each MR analysis to reduce potential bias. In addition, MR-Egger regression was used to evaluate pleiotropic effects of the IVs; If MR-Egger interception was significantly different from zero ($p < 0.05$), the presence of pleiotropic effects were indicated.[14]

Initially, univariate MR analysis was performed to assess the potential causal effect of educational attainment on corneal disease subtypes. Subsequently, MVMR analysis was conducted, incorporating educational attainment, household income, and occupational status, to evaluate the independent effects of each exposure after mutual adjustment. The IVW method was applied in both univariate and multivariate analyses. In the MVMR analysis, a p-value of <0.05 indicated a statistically significant causal relationship between a specific socioeconomic factor and the risk of corneal diseases, after adjusting for the potential confounding effects of the other socioeconomic variables.

MR analysis was performed using the Two-SampleMR, MVMR, and MRPRESSO packages in R version 4.3. Forest plot was drawn by GraphPad Prism 9.0. Statistical significance of the causal effect was set at $p < 0.05$.

RESULTS

The mean (SD) educational level was 15.4 (3.4) years. The genetic information for education attainment level as an exposure factor was obtained from the UK Biobank and 23andMe.

Table I: Heterogeneity and pleiotropy assessments of univariate MR analysis.

Outcomes	Cochran's Q test statistic	p-values (Q-test)	MR-Egger intercept	p-values (Egger intercept)
Corneal ulcers	614.33	0.046	0.0053	0.068
Corneal scars and opacities	568.28	0.361	-0.0016	0.846
Corneal degeneration	490.81	0.978	0.0258	0.025
Corneal pigmentations and deposits	505.12	0.944	-0.0034	0.868
Changes in corneal membranes	549.13	0.586	-0.0251	0.383
Other corneal oedema	555.83	0.494	0.0120	0.443
Other and unspecified corneal deformities and disorders	665.69	0.001	-0.0063	0.413
Other disorders of the cornea	722.77	2.50E-06	-0.0057	0.216
Keratoconus	536.85	0.723	-0.0109	0.177
Bullous keratopathy	581.77	0.226	-0.0082	0.583
Herpes viral keratitis and keratoconjunctivitis	576.95	0.261	-0.0020	0.747

Cochran's Q-test p-values were used to assess heterogeneity across IVs, while MR-Egger intercept p-values evaluated directional pleiotropy. A p-value <0.05 was considered statistically significant.

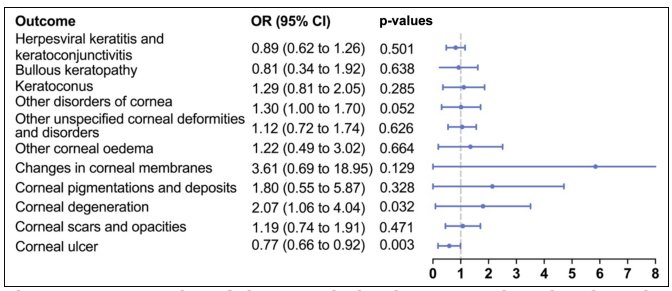

Figure 1: Forest plot of the association between educational attainment and corneal diseases.

OR: Odd ratio; CI: Confidence interval. The p-values were derived from the IVW method. Statistical significance was set at p <0.05.

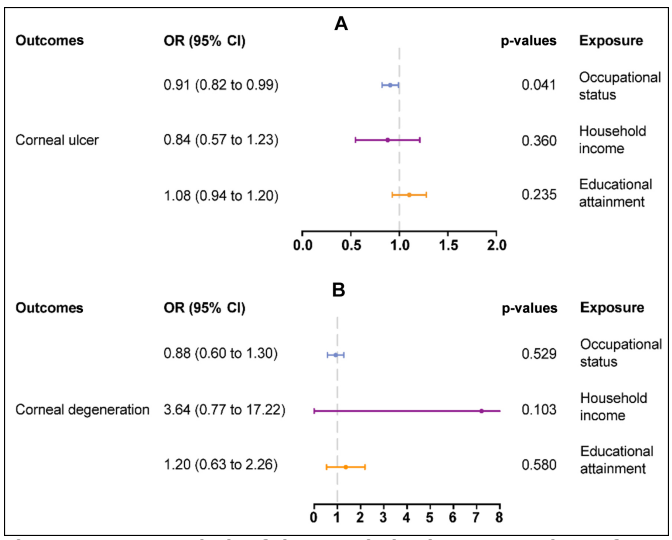

Figure 2: MVMR analysis of the association between each SES factor and corneal disease after adjusting for the other two factors. (A) Direct causal effect of SES on corneal ulcer; (B) Direct causal effect of SES on corneal degeneration. The p-values were derived from the multivariable IVW method, with statistical significance set at p <0.05.

The F-statistic values of all SNPs were greater than 10 (44.17 to 939.89), indicating a strong correlation between these IVs and the exposure. PhenoScanner was used to perform further screening, and the instrumental variable rs77882218, which is directly related to corneal disease, was excluded from the study. In addition, since diabetes is a key risk factor for diabetic retinopathy, the IVs rs4766975, rs3869097, and rs9388490, which are also directly related to diabetes, were not included in the study. Finally, the 597 SNPs were included in this study for subsequent genetic analysis.

The IVW results showed that genetically predicted education attainment was not significantly associated with herpes viral keratitis and keratoconjunctivitis (IVW OR, 0.89; 95% CI: 0.62-1.26; p = 0.501), bullous keratopathy (IVW OR, 0.81; 95% CI: 0.34-1.92; p = 0.638), keratoconus (IVW OR, 1.29; 95 % CI: 0.81-2.05; p = 0.285), other disorders of the cornea (IVW OR, 1.30; 95% CI: 1.00-1.70; p = 0.052), other unspecified corneal imperfections and disorders (IVW OR, 1.12; 95% CI: 0.72-1.74; p = 0.626), corneal oedema (IVW OR, 1.22; 95% CI: 0.49-3.02; p = 0.664), changes in corneal membranes (IVW OR, 3.61; 95% CI: 0.69-18.95; p = 0.129), corneal pigmentations and deposits (IVW OR, 1.80; 95% CI: 0.55-5.87; p = 0.328) and corneal scars and opacities (IVW OR, 1.19; 95% CI: 0.74-1.91; p = 0.471). However, a notably significant positive correlation between education attainment and corneal degeneration existed (IVW OR, 2.07; 95% CI: 1.06-4.04; p = 0.032). Simultaneously, there was a significant negative correlation between education attainment and the risk of corneal ulcer (IVW OR, 0.77; 95% CI: 0.66-0.92; p = 0.003). These results suggest that education attainment may be a potential factor affecting the occurrence of corneal ulcers and corneal degenerative diseases. The MR results are shown in Figure 1.

The heterogeneity test results showed no significant heterogeneity between the education attainment level and corneal diseases. However, significant heterogeneity was observed in the associations between educational attainment and corneal ulcer (p = 0.046), as well as with other and unspecified corneal disorders (p = 0.001). To reduce the impact of heterogeneity, the present study used the random effect IVW model as the primary method of estimation in the univariate MR analysis. Additionally, although MR-PRESSO did not identify any outlier SNPs, the MR-Egger intercept suggested evidence of directional pleiotropy in the association between educational attainment and corneal degeneration (p = 0.025). Table I presents the results of heterogeneity and pleiotropy tests from the univariate MR analysis using educational attainment as the exposure.

Educational attainment, household income, and occupational status are widely recognised as the core components of SES, each reflecting distinct but interrelated aspects of an individual's social and economic position. To further investigate the independent contributions of these socioeconomic factors and to strengthen causal inference, the present study conducted an MVMR analysis incorporating all the three method as simultaneous exposures. The MVMR analysis results based on SES factors and corneal diseases showed that after adjusting for household income and occupational status, the correlation between educational attainment and corneal degeneration disappeared, and none of the SES factors showed significant correlation with corneal degeneration (Figure 2A). Notably, even after adjusting for educational attainment and household income, occupational status remained significantly negatively correlated with corneal ulcer (IVW OR, 0.91; 95% CI: 0.82-0.99; p = 0.041), indicating a potential impact of SES on corneal ulcer (Figure 2B).

DISCUSSION

In the present study, both univariate and multivariate MR analyses were utilised to investigate the potential relationship between SES and corneal diseases. The results revealed a significant negative causal association between one of the SES factors and the risk of developing corneal ulcers.

Previous observational studies had demonstrated that SES was highly correlated with the occurrence and progression of eye diseases. For instance, in China, the prevalence of visual impairment was significantly higher in rural regions than in urban areas, with lower education and income levels associated with increased visual impairment.[15] Similarly, in the United States, Latino populations with poorer economic conditions, lower education levels, and lower acculturation were found to have a higher prevalence of eye diseases compared to non-Latino white populations.[16] Based on these findings, the present study aimed to explore the potential causal relationship between socioeconomic factors and corneal diseases. In the univariate MR analysis, a significant negative correlation was observed between educational attainment and corneal ulcers, indicating that individuals with lower education levels were more likely to suffer from corneal ulcers. This finding aligned with the previous inferences. Furthermore, the MVMR analysis confirmed a negative association between occupational status and the risk of corneal ulcers. These results directly supported the impact of SES on the risk of corneal ulcers, suggesting that lower SES is associated with a higher risk of developing these conditions.

Numerous factors, including environmental and indivisual factors, influence the formation of corneal ulcers. Ultra-violet light and pollutants can damage the cornea and disrupt corneal epithelial cell homeostasis.[17,18] Personal behaviours, such as prolonged contact lens use, can increase the risk of corneal microbial infection.[19] Additionally, prolonged hyperglycaemia alters corneal structure, leading to diabetic keratopathy.[20] Occupational hazards also play a significant role in the formation of conrneal ulcers. Individuals engaged in outdoor occupations, such as construction work, chemical factory work, or farming, are more susceptible to physical damage from dust, wood chips, metal debris, and chemical exposure.[21] Excessive ultraviolet radiation from prolonged outdoor exposure further exacerbates corneal damage.[22] Environmental pathogens can infect the cornea through various means, worsening the condition.[23] These occupational risks are compounded in settings lacking proper safety measures or health education, particularly in the developing countries.[24] Conversely, higher levels of education and socioeconomic status are associated with a better understanding and management of eye health risks, demonstrating an inverse relationship between SES and the prevalence of corneal diseases.[25] In general, different socioeconomic levels determine both disease risks and the capacity of risk aversion within populations, representing one of the specific social mechanisms underlying the relationship between SES and corneal ulcers.

Compared with previous studies, the present study has several significant advantages. By utilising two-sample MR analysis, it provides direct evidence of a causal relationship between SES and corneal diseases, while minimising susceptibility to confounding factors. Additionally, the robustness of the results is enhanced by considering household income and occupational status as confounding factors in the multivariate MR analysis. However, this study has certain limitations. First, the research samples were mainly limited to European populations, with insufficient representation from Asian or other regions, which may limit the global applicability of the findings. Secondly, due to the absence of GWAS data on corneal ulcer severity classification, the specific association between SES and disease severity could not be assessed in detail.

CONCLUSION

The present study provided direct genetic evidence supporting a causal relationship between SES and corneal diseases. The findings highlight the need for enhanced eye protection among lower SES groups and improved preventive measures, clinical management, and public health education in economically underdeveloped regions. Broader socioeconomic reforms, including improved education, expanded job opportunities, and equitable income distribution, are essential to address the root causes of health disparities and reduce the burden of corneal diseases.

ETHICAL APPROVAL:
Ethical approval was not required as the data were publicly available.

PATIENTS' CONSENT:
Informed consent was not required as the data were publicly available.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
JY: Methodology, visualisation, and writing of the original draft.
RJ: Formal analysis and investigation.
LW: Supervision, writing, review, and editing.
All authors approved the final version of the manuscript to be published.

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