



Full Length Article

Causal associations between smoking and ocular diseases: a Mendelian randomization study

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ABSTRACT

Purpose: To explore the causal associations between smoking and ocular diseases using Mendelian randomization (MR).**Methods:** A two-sample Mendelian randomization (MR) analysis based on publicly

available genome-wide association studies were employed to infer the causal relationship. The effect estimates were calculated using the random-effects inverse-variance-weighted method.

Results: Genetically predicted smoking was positively associated with cataract [Odds ratio (OR) = 1.14, 95% confidence interval (CI): 1.01–1.29; $P = 0.027$], w-AMD [OR = 1.41, 95%CI: 1.06–1.88; $P = 0.019$], diabetic retinopathy [OR = 1.06, 95%CI: 1.04–1.30; $P = 0.01$], disorders of optic nerve and visual pathways [OR = 1.46, 95% CI: 1.00–2.14; $P = 0.049$] in inverse variance weighted analysis. Suggestive evidence of an inverse association between smoking and myopia was also observed [OR=0.75, 95%CI: 0.57–0.97; $P = 0.031$]. No associations were observed for glaucoma, allergic conjunctivitis, pterygium, keratitis, scleritis and episcleritis. After performing weighted median and MR-Egger analysis, consistent results were observed. There was no horizontal pleiotropy in the two-sample MR analysis.**Conclusions:** Smoking may increase the risks of cataract, w-AMD, diabetic retinopathy, disorders of optic nerve and visual pathways. And smoking may decrease the risk of myopia.

1. Introduction

Smoking is a prominent example of unhealthy lifestyle choices. Cigarettes contain numerous hazardous compounds such as tar and nicotine,¹ which can affect various systems in our bodies, either through direct smoking or ambient exposure.² Each year, smoking results in more than 8 million fatalities worldwide and economic losses approaching \$436.7 billion in the US alone.³ Meanwhile, tobacco control remains a critical health concern.⁴ The evidence linking smoking to cancer, respiratory diseases, and cardiovascular diseases is well-established.^{5,6} However, the causal relationship between smoking and ocular diseases is not that clear. Prospective observational studies have previously indicated that smoking may be a risk factor for certain ocular diseases,⁷ yet public still lacks awareness of this.⁸ Many individuals have expressed that

they would refrain from smoking if they understood it could lead to blindness. Furthermore, there is a growing call for ophthalmologists to incorporate smoking cessation interventions as a primary preventive measure when appropriate.^{9,10} However, data regarding other conditions, such as diabetic retinopathy, disorder of the optic nerve and visual pathways, myopia are still inconsistent or restricted.^{11,12} Absence of robust evidence, such as large randomized controlled trials, we aimed to employ Mendelian randomization (MR) to investigate whether smoking is genetically associated with ocular diseases.

MR is a well-established methodology that can also be applied in epidemiology, utilizing genetic variation tools to determine causality. Since genotypes are determined at birth, preceding all exposures in time, MR tends to perform better than non-randomized observational studies in avoiding confounding and causal reversal, gaining increasing appeal

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in recent years.^{13,14} With a greater capacity for making causal inferences than conventional association analyses, MR represents another innovation that allows for a more comprehensive exploitation of genome-wide association study (GWAS).^{15,16}

This study employs two-sample Mendelian randomization to investigate the causality between smoking and multiple ocular disorders, including ten specific diseases. Our findings support smoking is positively correlated with cataracts, w-AMD, diabetic retinopathy, and disorders of optic nerve and visual pathways, while demonstrating a negative association with myopia. Traditional observational studies are prone to confounding factors and reverse causation; therefore, we provide direct evidence to clarify the complex relationship between smoking and ocular diseases.

2. Methods

2.1. Study design

All GWAS data included in this study were from published databases, so no additional approval was required. In this study, we used two-sample MR to assess the causal effect of smoking on the risk of ocular diseases (Fig. 1). The three key hypotheses of this study are as follows: (A) SNPs are strongly associated with smoking; (B) SNPs are independent of known confounders; (C) SNPs affect ocular diseases only through smoking. We extracted SNPs that reached the genome-wide significance

threshold ($P < 5 \times 10^{-8}$) as instrumental variables (IVs). Linkage disequilibrium pruning was performed using an R^2 threshold of < 0.005 and a window size of 2000 kb. All included SNPs were required to have an F-statistic greater than 10. In addition, we conducted a manual search of existing GWAS databases to identify SNPs linked to the exposure factors. And the SNPs were eliminated if containing secondary phenotypes in addition to smoking.

2.2. Data sources

This study was based on published European GWAS data and included both males and females. Summary statistics for smoking ($n = 249752$) were acquired from the results reported by Liu et al.¹⁷ 23 SNPs significantly related to smoking were selected as instrumental variables (Supplementary Table 1) based on results from the original meta-analysis of 249752 individuals with a genome-wide significant level ($P < 5 \times 10^{-8}$). Cataract ($n = 216632$), wet age-related macular degeneration ($n = 208715$), diabetic retinopathy ($n = 216666$), disorders of optic nerve and visual pathways ($n = 218726$), myopia ($n = 212571$), allergic conjunctivitis ($n = 218792$), pterygium ($n = 203880$), keratitis ($n = 214848$), scleritis and episcleritis ($n = 210040$) were obtained from FinnGen biobank. Glaucoma ($n = 462933$) was obtained from UK Biobank.

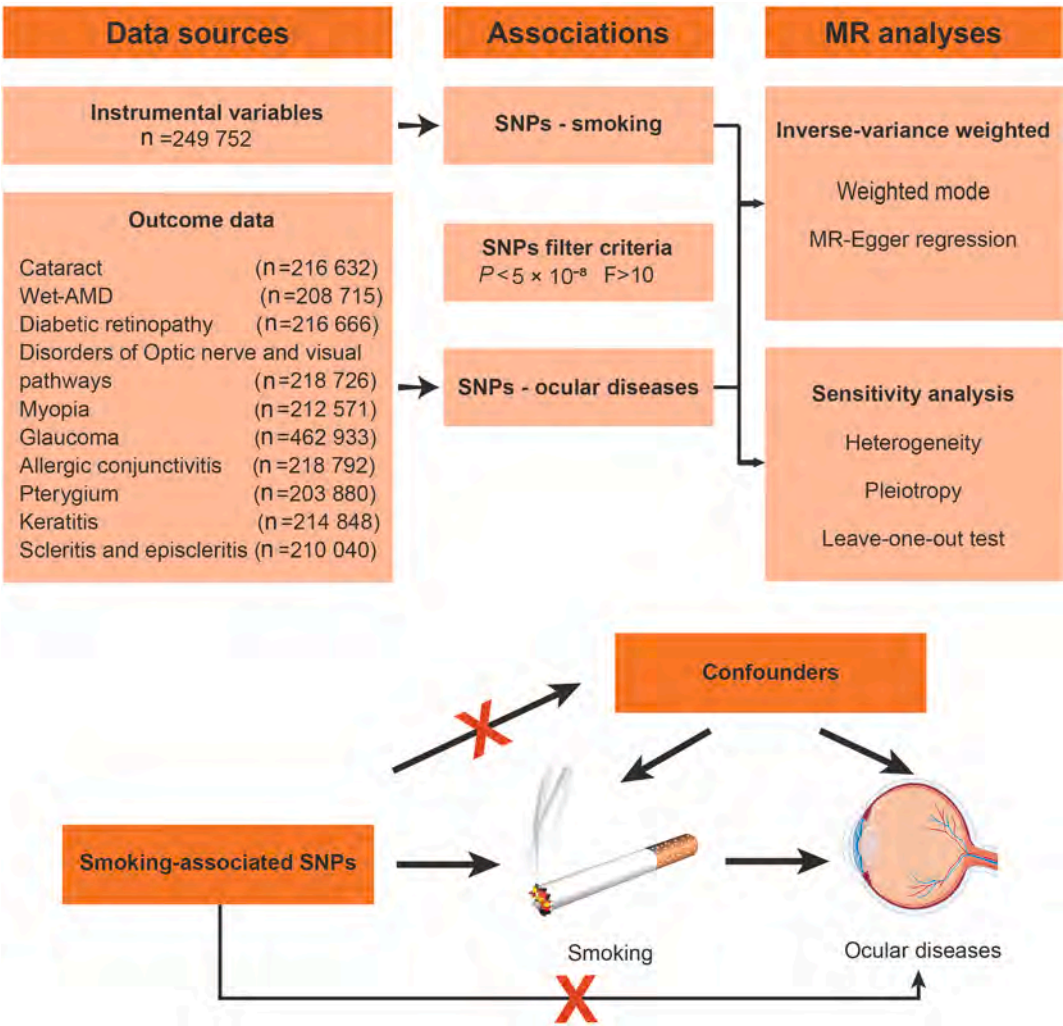


Fig. 1. Study design of the two-sample Mendelian randomization for the effect of genetically predicted smoking on ocular diseases. SNPs, single nucleotide polymorphisms; AMD, age-related macular degeneration.

2.3. MR analysis

We used two-sample MR analysis to assess the causal relationship between smoking and ocular diseases. Because no specific individual level GWAS data is available. To reduce the impact of SNPs heterogeneity on this study, we used inverse variance weighted (IVW) meta-analysis in the primary analysis of smoking and a random effects model to combine instrumental variable rate estimates for 23 smoking-associated SNPs. For sensitivity analysis, weighted median and MR-Egger are adopted. If more than 50% of the information comes from valid IVs,¹⁸ the weighted median method can provide a valid estimate. The MR-Egger method can be used to evaluate the horizontal pleiotropy of selected IVs.¹⁹ IVW, weighted median and MR-Egger methods are based on different models of horizontal pleiotropy to evaluate the effect. The consistency of the three different methods can help us judge the reliability of the results. Bonferroni correction was performed at an adjusted p-value of 0.05 for multiple comparison. The statistical analyses were performed using the "Two-SampleMR" packages²⁰ in R version 4.0.3.

3. Results

3.1. Selected SNPs for smoking

As shown in Table 1, the 11 studies included in the analysis were all published between 2019 and 2021 (Table 1). The population they based on were all European. 23 SNPs used as genetic instrumental variables all attain the level of genome-wide significance, with their F statistics completely above 10 (Supplementary Table 1).

3.2. Results from causal inference

The IVW analysis showed that the genetically predicted cigarette consumption per standard-deviation increase was positively correlated with four diseases, including cataract [Odds ratio (OR) = 1.14, 95% confidence interval (CI): 1.01–1.29; $P = 0.027$], w-AMD [OR = 1.41, 95%CI: 1.06–1.88; $P = 0.019$], diabetic retinopathy [OR = 1.06, 95% CI: 1.04–1.30; $P = 0.01$], disorders of optic nerve and visual pathways [OR = 1.46, 95%CI: 1.01–2.14; $P = 0.049$]. On the contrary, suggestive evidence of an inverse association between smoking and myopia was also noticed [OR = 0.75, 95%CI: 0.57–0.97; $P = 0.031$]. In parallel, no associations were observed for glaucoma, allergic conjunctivitis, pterygium, keratitis, scleritis and episcleritis (Fig. 2). When sensitivity analysis was performed by MR-Egger and weighted median regression (Table 2), the results bear a resemblance to the IVW method (SFIGs. 1 and 2). Moreover, we refined the assessment of sensitivity through Leave-one-out analysis, observing whether our overall causal estimate could be influenced by individual SNPs. When the individual SNPs were sequentially eliminated in turn, there was no major deviation in the estimated causal effect (SFIG. 3). Hence, we draw a conclusion that any single SNPs can not be completely attribute to the estimated effect.

Table 1
Baseline characteristics of smoking and ocular diseases.

Trait	Year	Author	Population	Sample Size	n case	n control	n SNP
Cigarettes smoked per day	2019	Liu M	European	249752	–	–	12003613
Cataract	2021	–	European	216632	26,758	189604	16380461
Wet age-related macular degeneration	2021	–	European	208715	2,114	206601	16380422
Diabetic retinopathy	2021	–	European	216666	14,584	202082	16380459
Disorders of optic nerve and visual pathways	2021	–	European	218726	785	217491	16380465
Myopia	2021	–	European	212571	1,640	210931	16380455
Glaucoma	2018	Ben Elsworth	European	462933	4,737	458196	9851867
Allergic conjunctivitis	2021	–	European	218792	9,833	208959	16380466
Pterygium	2021	–	European	203880	363	203517	16380437
Keratitis	2021	–	European	214848	5,561	209287	16380449
Scleritis and episcleritis	2021	–	European	210040	753	209287	16380407

SNP: single nucleotide polymorphism.

3.3. Examination of horizontal pleiotropy

Funnel plots can identify the individual Wald ratios of each SNPs in proportion to their accuracy. The presence of asymmetry means directed horizontal pleiotropy can be detected.

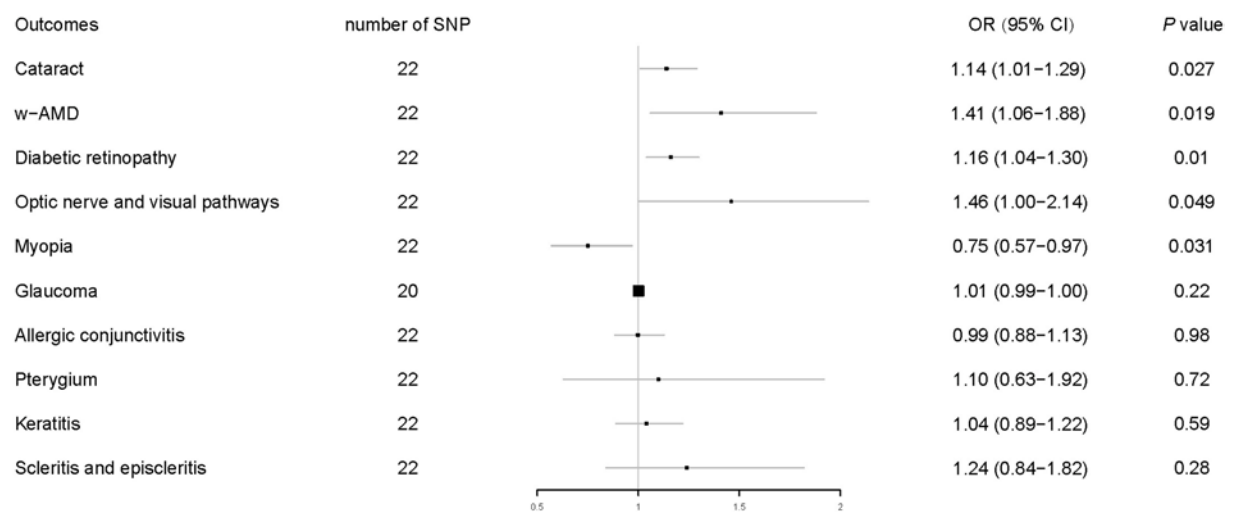
Funnel plots of this investigation indicate horizontal pleiotropy doesn't exist, as they were symmetrical (SFIG. 4).

4. Discussion

Smoking, a health risk remaining prevalent in modern society, insidiously causes severe health damage to both the smoker and those around them. It has also been identified as one of the most critical and modifiable risk factors preceding the onset of major diseases. Through previous observational research and systematic reviews, smoking has been established as a risk factor for two common age-related ocular diseases: cataracts^{21–23} and age-related macular degeneration.^{24–26}

Petri et al. conducted a comparison of two nationwide cross-sectional surveys spanning 11 years within the Finnish population and observed a higher incidence of cataracts among smokers. The results remained consistent even after adjusting for age and stratifying by gender.²⁷ Lack of quantitative evidence to substantiate this association, Ye et al.²⁸ reviewed 21 observational studies up to 2014 for a meta-analysis and discovered that smoking is a significant risk factor for cataract development, particularly for nuclear cataract. Currently, this can usually be explained by the accumulation of lead and cadmium in the lens during the formation of cataracts, while smoking causes oxidative stress and depletes antioxidants. These damages further lead to inflammation, with the involvement of immune cells and enzymes, ultimately resulting in various types of cataracts.^{10,23,29} Furthermore, our research also indicates that smoking contributes to the onset of wet-AMD. Chelsea et al.,³⁰ who reported findings from a 20-year period in the Beaver Study, validated that current smoking may increase an individual's risk of developing both early and late types of AMD. Similar conclusion can be drawn from the combined results of 16 studies that reported smoking status.³¹ Oxidative stress, choroidal vasoconstriction, vascular endothelial growth factor overexpression, and abnormal complement factor may be the main reason why smoking brings AMD.^{24,32,33} Smoking may also participate in inducing choroidal neovascularization by upregulating the Sema4D-PlexinB1 signaling pathway, activating pericytes, and ultimately causing the onset and progression of w-AMD, according to a recent study based on clinical samples and animal models.^{24,34}

So far, there is no consensus on whether a causal relationship exists between smoking and the development of diabetic retinopathy, as well as disorders of the optic nerve and pathway disease. Smoking is not expected to contribute to the development of diabetic retinopathy, according to major observational studies that have been conducted.^{35,36} However, Cai et al.³⁷ concluded that individuals with type I diabetes have a significantly higher likelihood of developing retinopathy, based on a comprehensive analysis involving 19 studies. After controlling for



F2. The association between genetically determined smoking and the risk of ocular diseases in the primary results. OR, odds ratios; CI, confidence interval. SNPs, single nucleotide polymorphisms; AMD, age-related macular degeneration.

Table 2
Associations between genetically predicted smoking and ocular diseases in sensitivity analyses.

Outcomes	Weighted Median		MR-Egger		Pleiotropy		Heterogeneity	
	OR (95%CI)	P	OR (95% CI)	P	Intercept	P	Q	P
Cataract	1.11 (0.99–1.25)	0.070	1.09 (0.88–1.34)	0.450	0.004	0.570	40	0.008
wet age-related macular degeneration	1.43 (1.02–2.00)	0.036	1.41 (0.84–2.37)	0.204	–0.00004	0.998	30	0.102
Diabetic retinopathy	1.23 (1.07–1.41)	0.003	1.15 (0.94–1.41)	0.190	0.0008	0.914	29	0.120
Optic nerve and visual pathways	1.46 (0.88–2.43)	0.140	1.11 (0.57–2.15)	0.770	0.02	0.330	18	0.630
Myopia	0.61 (0.42–0.90)	0.013	0.68 (0.43–1.08)	0.120	0.007	0.650	16	0.750
Glaucoma	1.00 (0.99–1.00)	0.430	1.00 (0.99–1.00)	0.830	6*e–05	0.560	29	0.060
Allergic conjunctivitis	1.08 (0.93–1.25)	0.310	1.18 (0.97–1.44)	0.120	–0.01	0.060	24	0.300
Pterygium	0.88 (0.42–1.84)	0.730	1.11 (0.42–2.94)	0.840	–0.0002	0.990	17	0.730
Keratitis	0.98 (0.80–1.19)	0.810	0.96 (0.72–1.27)	0.770	0.0069	0.480	25	0.240
Scleritis and episcleritis	0.99 (0.57–1.72)	0.980	0.97 (0.49–1.89)	0.920	0.02	0.390	14	0.870

OR, odds ratios; CI, confidence interval.

confounding factors and minimizing reverse causation, we also believe that diabetic retinopathy is more likely to occur in smokers. Smoking may promote the development of diabetic retinopathy by reducing retinal blood flow and disrupting oxygen regulation in diabetic patients, as well as through nicotine-induced neoangiogenesis.³⁸ Among optic neuropathy diseases, the following three conditions will be discussed: non-arteritic anterior ischemic optic neuropathy (NA-AION), tobacco optic neuropathy (TON), and Leber's hereditary optic neuropathy (LHON). In a recent study involving the Korean population, Dae et al.³⁹ conducted a retrospective review of comprehensive specialist imaging data from 45 NA-AION patients. After comparing these findings with data from the normal population, the study demonstrated a significant association between smoking and the development of NA-AION. Currently, there is insufficient evidence to draw firm conclusions regarding NA-AION due to the limited number of studies and small sample sizes. TON) is a rare and controversial disease that was once more prevalent but is now uncommon. After excluding nutritional optic neuropathy, smoking contributes to the toxic damage of the optic nerve.⁴⁰ Although prevailing studies suggest that smoking is a risk factor for Leber's hereditary optic neuropathy,⁴¹ reverse causation cannot be dismissed.⁴² Our research provides significant evidence that smoking causes diseases affecting the optic nerve system. It could be connected that smoking causes endothelial injury and oxidative stress harms nerves.⁴³ This mechanism further contributes to increased blood-brain barrier permeability, triggers inflammatory cell infiltration, and thereby exacerbates tissue damage.⁴⁴

It is noteworthy that the effects of smoking on the eyes are not solely detrimental. Our research supports the findings of previous observational

studies, indicating that smoking may act as a protective factor against myopia. Utilizing data on children's cycloplegic refraction and parental smoking status from the STARS study, Iyer et al.⁴⁵ found that both paternal and maternal histories of smoking—whether during the child's life or pregnancy—were associated with a reduced risk of childhood myopia. Additionally, another study analyzing ALSPAC data reported that a grandmother's smoking during pregnancy was linked to a lower prevalence of myopia in children up to the age of seven.⁴⁶ This phenomenon may be attributed to the pharmacological potential of nicotinic acetylcholine receptors, suggesting a protective role in the development of the eye.⁴⁷ Recent animal studies have confirmed the precise physiological mechanism, which shows that nicotine can slow the progression of myopia by preventing vitreous chamber elongation and, in turn, axial length growth.⁴⁸

Consistent with previous findings, we were unable to establish a causal relationship between smoking and glaucoma, conjunctivitis, pterygium, keratitis, and scleritis. The current study cannot infer a strong causal relationship for glaucoma,⁴⁹ although some previous cross-sectional studies have suggested that smoking may be a potential risk factor.^{50,51} At present, most studies on pterygium are cross-sectional, and smoking is often considered a protective factor, but a definitive causal relationship cannot be established at this stage.^{52,53} Research on keratitis, conjunctivitis, and scleritis is currently insufficient. We look forward to more research in the future.

This study has several limitations that should be considered. Initially, the potential for horizontal pleiotropy is an inherent concern with Mendelian randomization methods, as traits unrelated to genetic instruments may also influence outcomes and can often be observed.

Horizontal pleiotropy is typically assessed using methods such as MR-PRESSO and MR-Egger. In this study, we adopted MR-Egger and the results showed minimal presence of horizontal pleiotropy, which was further confirmed through sensitivity analysis. Additionally, our results may not be generalizable to global populations, as we used GWSA data from European populations, which are characterized by higher levels of genetic homogeneity. Furthermore, the data we used lacked important details, including the age of smoking initiation, the quantity of cigarettes smoked, family smoking history, and so on. Also, cigarette additives and production processes vary by region. These have hindered further analysis.

5. Conclusions

Overall, our findings from this two-sample Mendelian randomization drew the conclusion that cigarette consumption had a positive causal effect on cataract, w-AMD, diabetic retinopathy, disorders of optic nerve and visual pathways, as well as a causal negative association with myopia. No significant associations could be identified between glaucoma, allergic conjunctivitis, pterygium, keratitis, scleritis, and episcleritis. Encouraging people to stay away from cigarettes may be helpful in preventing ocular diseases that cause blindness.

Author contributions

The authors confirm contribution to the paper as follows: ZH: Data curation, Formal analysis, Investigation, Software, Methodology, Visualization, Writing - original draft; JC: Formal analysis, Investigation, Writing - review and editing; LS and JH: Conceptualization, Funding acquisition, Project administration, Supervision. Writing - review and editing, All authors reviewed the results and approved the final version of the manuscript.

Study approval

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

MR	Mendelian randomization
OR	odds ratio
CI	confidence interval
IVs	instrumental variables
SNPs	single nucleotide polymorphism
GWAS	genome-wide association study
IVW	inverse variance weighting
NA-AION	Non-arteritic anterior ischemic optic neuropathy
TON	Tobacco optic neuropathy
LHON	Leber's hereditary optic neuropathy
w-AMD	wet age-related macular degeneration
DR	Diabetic retinopathy

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.aopr.2025.06.002>.

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