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Exploring the Impact of Alcohol Consumption and Smoking on Primary Open Angle Glaucoma: A Mendelian Randomization Study

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Abstract

Objective: Utilizing Mendelian Randomization, this study employs Single Nucleotide Polymorphisms (SNPs) as instrumental variables to explore the causal relationships between bibulosity, smoking, and Primary Open Angle Glaucoma (POAG). **Methods:** GWAS data for bibulosity, smoking, and POAG were obtained from the Social Science Genetic Association Consortium website and the IEU OpenGWAS Project website, respectively. Using a P-value threshold of $<5 \times 10^{-8}$, a linkage disequilibrium coefficient (r^2) of 0.001, and a linkage disequilibrium region width of 10,000 kb, the data were aggregated, resulting in 6 SNPs for bibulosity and 253 SNPs for smoking. Three regression models, MR-Egger, Weighted Median Estimator (WME), and Random-Effects Inverse-Variance Weighted (IVW) were applied to analyze the causal impact of bibulosity and smoking on POAG. **Results:** The GWAS data for alcohol consumption and smoking were derived from European populations, while the GWAS data for Primary Open-Angle Glaucoma (POAG) were sourced from East Asian populations, with no gender restrictions. Analysis using three different regression models revealed that neither excessive alcohol consumption nor smoking significantly increased the risk of developing POAG. Specifically, the odds ratios with 95% confidence intervals for the alcohol consumption group were 0.854 (0.597 - 1.221) in MR-Egger regression, 0.922 (0.691 - 1.231) in WME regression, and 0.944 (0.711 - 1.252) in IVW regression. For the smoking group, the odds ratios were 1.146 (0.546 - 2.406) in MR-Egger regression, 0.850 (0.653 - 1.111) in WME regression, and 0.939 (0.780 - 1.131) in IVW regression. Given the significant hetero-

geneity in the SNPs associated with smoking, the focus was primarily on the results from the IVW regression model. **Conclusion:** Alcohol consumption and smoking are not significant risk factors for the development of POAG.

Keywords

Alcohol Abuse, Smoking, Glaucoma, Causal Relationship, Mendelian Randomization

1. Background

Glaucoma is one of the leading irreversible causes of blindness worldwide [1]. Primary Open Angle Glaucoma (POAG), characterized by its insidious onset and severe optic nerve damage, inflicts significant physical and emotional distress on patients. Although age, familial history, and high myopia are widely acknowledged as major risk factors for glaucoma [2], these factors are largely unmodifiable through personal effort. In contrast, lifestyle habits are adjustable. Previous studies [3]-[7], have shown that lifestyle factors such as Body Mass Index, smoking habits, and alcohol consumption may influence the incidence and severity of glaucoma. Hence, enhancing personal awareness of disease risk and actively improving lifestyle choices may aid in managing and preventing POAG.

Alcohol consumption is one of the major global causes of death and disability, accounting for approximately 3 million deaths and the loss of 132 million disability-adjusted life years in 2016 [8] [9]. Alcohol is associated with over 200 health conditions, posing a significant public health challenge and a key modifiable lifestyle risk factor. Despite the extensive health risks, alcohol consumption remains prevalent in many populations, particularly in China, where reports indicate that 33% of men and 2% of women engage in weekly drinking [10]. This widespread behavior underscores the need for enhanced public health interventions and education. Additionally, China holds the distinction of being the world's largest smoking nation, with about 316 million adult smokers, accounting for 30% of the global smoking population and 40% of the world's tobacco consumption. According to 2015 data, the overall smoking rate in China is 27.7%, with rates as high as 52.1% among men and 2.7% among women [11]. The statistic highlights China's significant role in global smoking and tobacco consumption.

This study aims to investigate the relationship between drinking and smoking behaviors and the onset of POAG, as well as the potential increased risk of disease, using the Mendelian randomization (MR) approach. We hope to reveal the potential impacts of lifestyle factors on the risk of POAG through scientific evidence, thereby providing a basis for preventive strategies.

2. Materials and Methods

2.1. Data Sources

Data for alcohol abuse (PubMed ID: 34140656) and smoking (PubMed ID:

34140656) were obtained from the genome-wide association studies (GWAS) through the Social Science Genetic Association Consortium website (https://www.thessgac.org). The largest sample of GWAS data on primary open-angle glaucoma (PubMed ID: 29452408) was accessed via the IEU OpenGWAS Project website (https://gwas.mrcieu.ac.uk) on April 28, 2024. The study focuses on the potential impact of lifestyle habits of Chinese POAG patients on the condition of glaucoma. However, due to the lack of high-quality GWAS data on lifestyle habits in the Chinese population, the alcohol and smoking GWAS datasets used were from European populations, while the open-angle glaucoma GWAS data originated from East Asia. The alcohol dataset included 6,483,125 single nucleotide polymorphisms (SNPs), the smoking dataset included 1,157,911 SNPs, and the POAG dataset included 5,961,428 SNPs.

2.2. Conditions for SNPs as Instrumental Variables

1) The instrumental variable must be highly correlated with the exposure, with an F-statistic > 10 indicating significant correlation [12].

2) The instrumental variable should not be directly associated with the outcome except through the exposure, indicating no pleiotropy. Pleiotropy tests are carried out where $P \geq 0.05$ suggests no genetic pleiotropy.

3) The instrumental variables should be independent of unmeasured confounders. Given that the Mendelian randomization approach selects SNPs that adhere to the genetic principle of random allocation of alleles from parents to offspring, they are minimally susceptible to environmental influences and postnatal factors. Thus, it is theoretically assumed that the instrumental variables are independent of environmental factors such as socioeconomic and cultural influences.

2.3. SNP Selection

In this Mendelian randomization study, alcohol and smoking were analyzed separately. Initially, SNPs with a significance level of $P < 5 \times 10^{-8}$ were selected from the summary data of alcohol and smoking GWAS to ensure statistical significance. To avoid confounding due to linkage disequilibrium, a linkage disequilibrium coefficient (r^2) threshold of 0.001 was set, with a linkage disequilibrium region width limited to 10,000 kb, ensuring the selected SNPs are independent. Subsequently, loci associated with the selected alcohol and smoking-related SNPs were extracted from the summary data of the POAG GWAS, setting a minimum r^2 of more than 0.8 to ensure high linkage disequilibrium with disease marker loci. SNPs missing in the data were not replaced but directly excluded. Finally, SNPs directly and significantly associated with POAG ($P < 5 \times 10^{-8}$) [13] were excluded from the consolidated dataset to minimize interference from direct genetic effects, thus precisely assessing the potential impact of alcohol abuse and smoking on glaucoma risk. The specific selection process is illustrated in **Figure 1**.

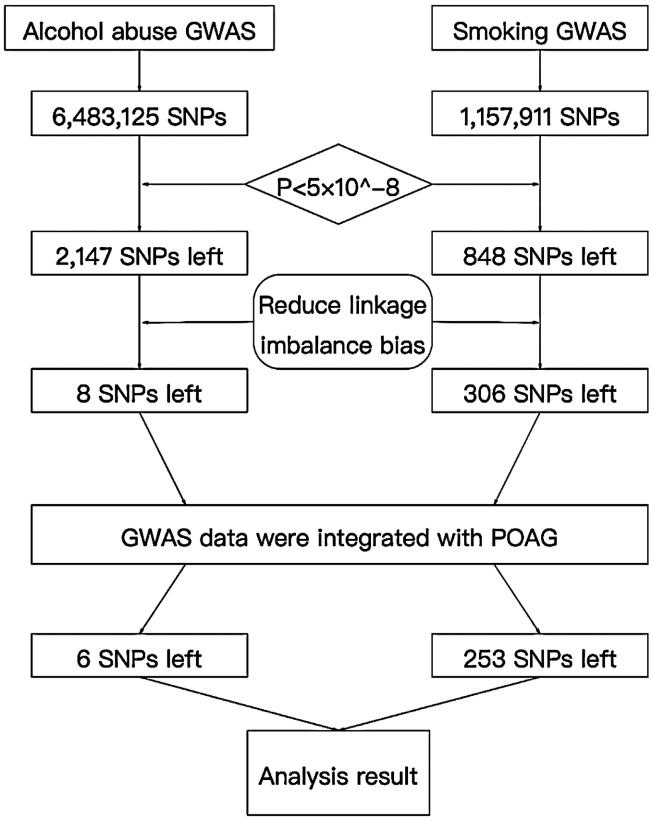

Figure 1. SNP screening process. The diagram illustrates the process of selecting and integrating SNPs for analysis.

2.4. Methods for Causal Inference

To validate the causal relationship between the exposure factors and POAG, this study employs three Mendelian randomization regression models: MR-Egger regression, Weighted Median Estimator (WME), and Inverse-Variance Weighted (IVW) method. These methods use SNPs as instrumental variables. 1) MR-Egger regression analyzes the relationship between each SNP with the exposure and outcome, fitting a linear regression model to estimate a non-zero intercept, thereby detecting potential instrumental variable bias. 2) The WME method calculates the causal effect estimates (β_j) for each SNP and provides a robust optimization of the causal relationship using the median of all valid SNPs. 3) The IVW method relies on summary data to calculate the weighted average of the associations between each SNP and the exposure outcome, estimating the causal effect. This method does not require individual-level data, making it suitable for analysis based on summary statistics.

To assess heterogeneity among SNPs in the model, this study conducts heterogeneity tests [14]. If significant heterogeneity is detected, it is advisable to focus more on the results of the IVW model [15]. Additionally, sensitivity analyses were conducted using the Leave-one-out method to examine the impact of individual SNPs on the model's estimates.

All analyses are conducted using the TwoSampleMR package in R software

(version 4.3.3). The significance level is set at $\alpha = 0.05$ to ensure the reliability of the statistical results.

3. Results

3.1. Alcohol Abuse and POAG

As shown in Figure 1, the GWAS data for the alcohol consumption group yielded 6,483,125 SNPs. After screening with $P < 5 \times 10^{-8}$, 2147 SNPs remained. After reducing bias due to linkage disequilibrium, 8 SNPs remained. The POAG GWAS data revealed 5,961,428 SNPs. After integrating the data from both studies, 6 SNP datasets remained, as detailed in Table 1.

Heterogeneity analysis was performed on these results, with a P-value of 0.44 (>0.05), indicating no significant heterogeneity and thus high reliability. Analysis and causal inference using these 6 SNP data through the three regression formulas showed that an increase of one standard deviation in alcohol abuse was associated with less than 1 increase in POAG risk, which was not statistically significant, as detailed in Table 2. The pleiotropy analysis showed a P-value of 0.42, indicating no other unknown interfering factors. Scatter plots clearly show that both IVW and WME regression lines pass through the origin, also indicating no other unknown interfering factors. Scatter plot situations and stability tests are detailed in Figure 2 and Figure 3, showing good stability and high reliability of the results.

The outcome heatmap situation is detailed in Figure 4, where, except for rs1229984 which shows lower reliability, the remaining SNP sites are filled in blue, representing lower standard errors, meaning the corresponding outcome estimates are more precise and reliable. These points are all close to zero, indicating that alcohol abuse does not significantly increase the risk of developing POAG.

Table 1. Final integrated SNP data results for alcohol abuse and POAG.

No.	SNP	CHR	Location	Equivalent base	Case frequency	Control frequency	β	SE
1	rs11039216	11	47406592	C	0.175	0.179	−0.02266	0.00383
2	rs11666792	19	49227043	G	0.054	0.052	−0.02119	0.00382
3	rs1229984	4	100239319	T	0.222	0.222	−0.23091	0.01241
4	rs1260326	2	27730940	T	0.44	0.442	−0.02689	0.0039
5	rs28712821	4	39413780	G	0.418	0.413	−0.03701	0.00394
6	rs4844948	1	210306844	A	0.476	0.466	0.02157	0.00388

Table 2. MR Regression results of three methods of alcohol abuse and POAG.

Method	β	SE	OR (95% CI)	P
MR-Egger	−0.158	0.183	0.854 (0.597 - 1.221)	0.435
WME	−0.081	0.147	0.922 (0.691 - 1.231)	0.582
IVW	−0.058	0.144	0.944 (0.711 - 1.252)	0.688

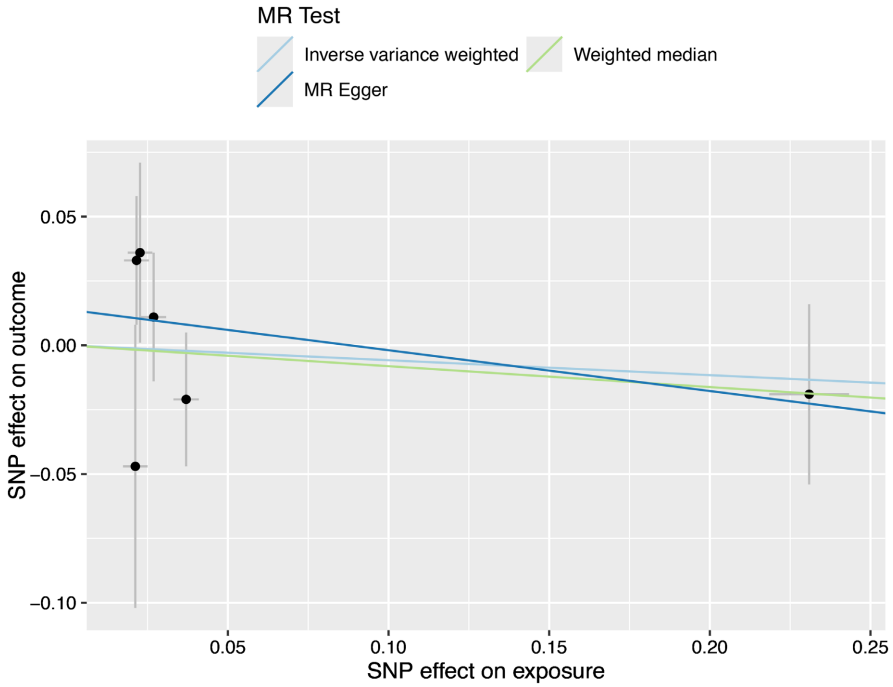

Figure 2. Scatter plot and regression line display of alcohol abuse SNP to POAG. The regression line's intersection with the y-axis is close to zero, indicating no significant confounders. The near-horizontal curvature of the regression line, with a slope approaching zero, suggests that the exposure factor does not significantly impact the outcome.

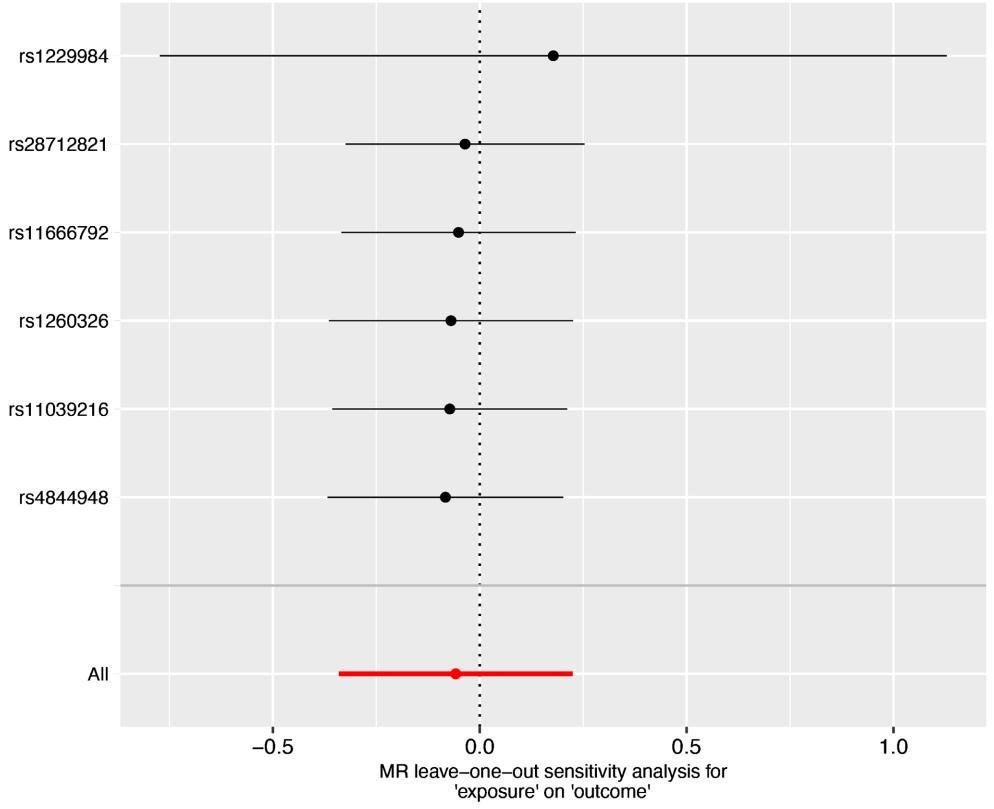

Figure 3. Stability of MR Analysis between alcohol abuse and POAG. Results remain unchanged regardless of the SNP removed, indicating the reliability of the conclusions.

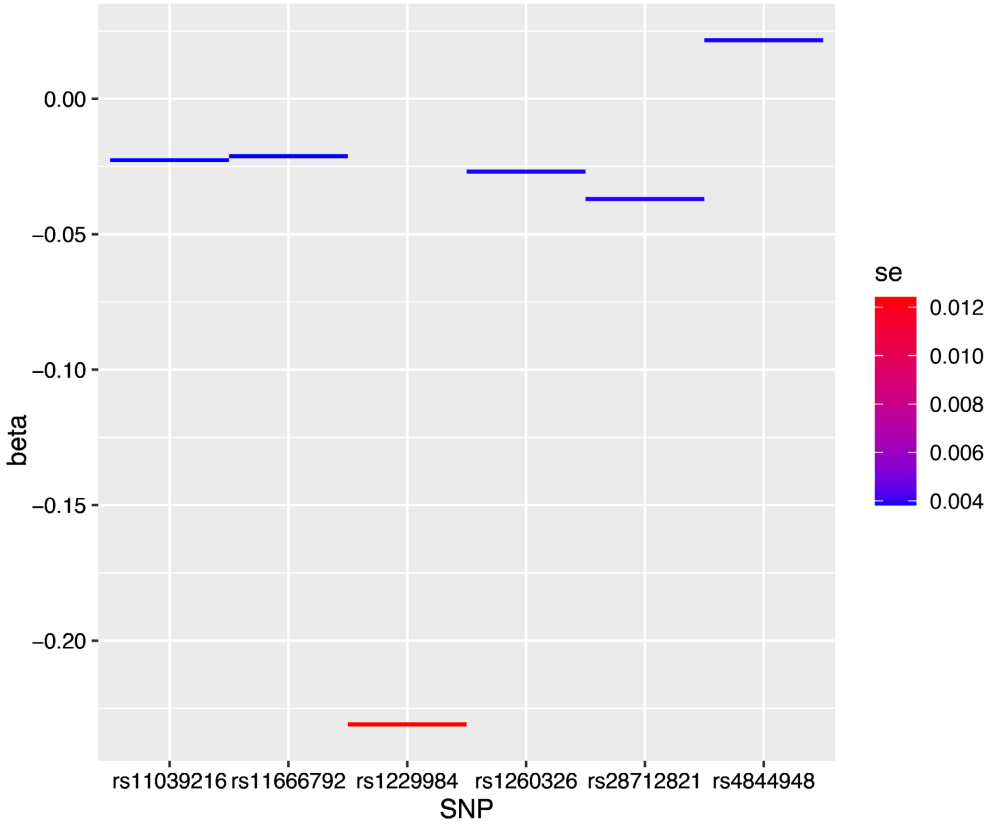

Figure 4. Heatmap of MR analysis results for alcohol abuse and POAG. The heatmap predominantly shows blue, representing high-reliability SNPs, all nearing zero, suggesting that the exposure factor does not significantly affect the outcome.

3.2. Smoking and POAG

As shown in **Figure 1**, the GWAS data for the smoking group comprised 1,157,911 SNPs. Following selection based on $P < 5 \times 10^{-8}$, 848 SNPs remained, with 306 SNPs left after reducing bias due to linkage disequilibrium. Reading POAG GWAS data retrieved 5,961,428 SNPs. After integrating both datasets, 253 SNPs remained, detailed in **Table 3**.

Heterogeneity analysis of these results showed a P-value < 0.05, indicating significant heterogeneity; therefore, the focus was primarily on the results of the IVW regression model. Analysis and causal inference using these 253 SNP data through various regression formulas showed P-values all greater than 0.05, detailed in **Table 4**. Given the considerable heterogeneity in this part of the results, consideration should be given to the results of the IVW regression model. An increase of one standard deviation in smoking was associated with an increased POAG risk of 0.94, but this was still not statistically significant. Bias conditions and stability tests are detailed in **Figure 5** and **Figure 6**, showing good stability and high reliability of the results. The heatmap of the analysis results, detailed in **Figure 7**, shows that most SNP effect values are roughly symmetrically distributed around 0.02 and −0.02. Although the large presence of SNP outcome sites inevitably leads to high heterogeneity in this part, the heatmap reveals that

Table 3. Partial display of the final integrated SNP data results for smoking and POAG.

No.	SNP	CHR	Location	Equivalent gene	Case frequency	Control frequency	β	SE
1	rs1059490	6	26171250	T	0.125	0.13	0.02381	0.0029
2	rs10745324	1	112708722	A	0.823	0.822	0.01837	0.00302
3	rs10774030	12	2292690	G	0.36	0.354	-0.01599	0.00291
4	rs10789369	1	73824909	A	0.771	0.777	0.02983	0.00289
5	rs10882723	10	97897752	A	0.015	0.017	-0.01543	0.00281
6	rs10885480	10	115378364	T	0.449	0.455	0.02431	0.00313
7	rs10891481	11	112830562	A	0.611	0.616	-0.0462	0.00289
8	rs10905649	10	10042641	C	0.36	0.363	0.01926	0.00282
9	rs10914684	1	33795572	G	0.145	0.146	0.01985	0.00302
10	rs10945141	6	69470709	G	0.69	0.685	-0.02245	0.00318
11	rs10953957	7	121954709	G	0.416	0.417	-0.01791	0.00292
12	rs1095578	12	39179392	C	0.328	0.328	-0.03221	0.00535
13	rs10956675	8	133702102	G	0.675	0.672	0.01716	0.00283
14	rs10966092	9	23831658	T	0.126	0.12	0.02665	0.00318
15	rs11036413	11	41501879	C	0.746	0.745	0.0209	0.00297
16	rs11057005	12	16748721	A	0.352	0.346	0.0192	0.00283
17	rs1106363	11	131966264	C	0.077	0.077	-0.02007	0.00297
18	rs1109480	12	121083279	G	0.237	0.233	0.02106	0.0029
19	rs11162019	1	87913176	C	0.441	0.445	0.01893	0.00293
20	rs11186625	10	93365911	T	0.052	0.049	-0.0162	0.00294
21	rs11231963	11	79873627	A	0.345	0.338	0.0174	0.00282
22	rs1126757	19	55879872	C	0.751	0.737	-0.01732	0.00281
23	rs113230003	19	18460956	G	0.404	0.414	0.02418	0.00327
24	rs11594623	10	103960351	T	0.094	0.097	-0.03155	0.00333
25	rs11611651	12	133380790	G	0.156	0.149	-0.03307	0.00491
26	rs11616731	13	101212300	A	0.203	0.21	0.02053	0.00282
27	rs11642231	16	89608702	G	0.211	0.207	0.02037	0.00295
28	rs11707697	3	2363069	C	0.054	0.054	-0.02348	0.00373
29	rs11712680	3	75009019	A	0.185	0.172	0.02692	0.00358
30	rs1173461	5	157707571	C	0.181	0.186	-0.0212	0.00301
31	rs11786924	8	12686438	T	0.125	0.122	-0.02099	0.00365
32	rs11791671	9	3398679	C	0.044	0.046	-0.03225	0.00552
33	rs1187820	3	173072584	C	0.287	0.29	0.01676	0.00289
34	rs1190234	14	103398706	G	0.37	0.368	-0.02561	0.00413
35	rs11924735	3	181380708	C	0.159	0.163	-0.02387	0.00382
36	rs12038362	1	154102171	T	0.397	0.407	0.03044	0.00452

Table 4. MR Regression results of three methods of smoking and POAG.

Method	β	SE	OR (95% CI)	P
MR-Egger	0.136	0.378	1.146 (0.546 - 2.406)	0.719
WME	−0.162	0.134	0.850 (0.653 - 1.111)	0.214
IVW	−0.062	0.095	0.939 (0.780 - 1.131)	0.508

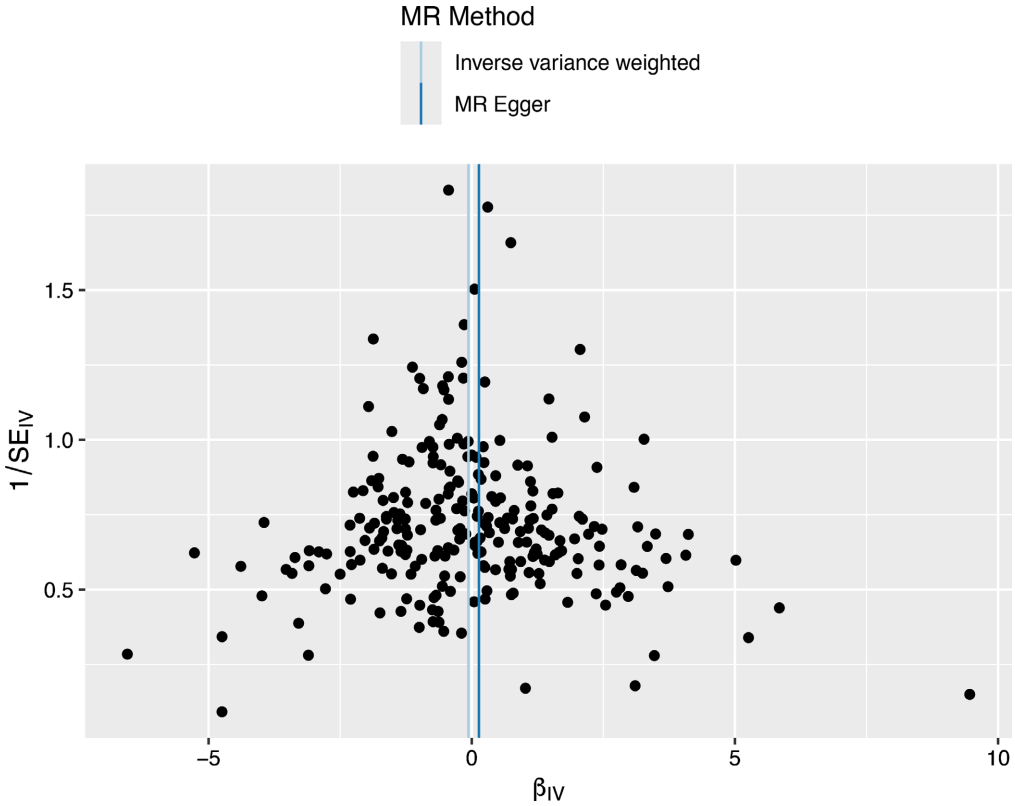

Figure 5. Scatter plot and regression line display of smoking SNP to POAG and stability analysis of results. The symmetry of SNP data is well-maintained across the analysis.

smoking is not a factor causing an increased risk of POAG.

4. Discussion

Glaucoma is a group of diseases characterized by progressive optic nerve damage and is one of the leading causes of irreversible blindness worldwide [16]. It is estimated that by 2040, the number of people with glaucoma will increase from the current 76 million to 112 million [17]. Although numerous genetic and environmental factors are known to be associated with the development and progression of glaucoma, the only confirmed modifiable risk factor to date is intraocular pressure [18]. However, as medical research methods deepen, it becomes increasingly important to enhance public awareness about the positive impact of lifestyle changes on the prognosis of glaucoma. This comprehensive approach aids in optimizing the management and prevention of glaucoma, potentially reducing the disease burden.

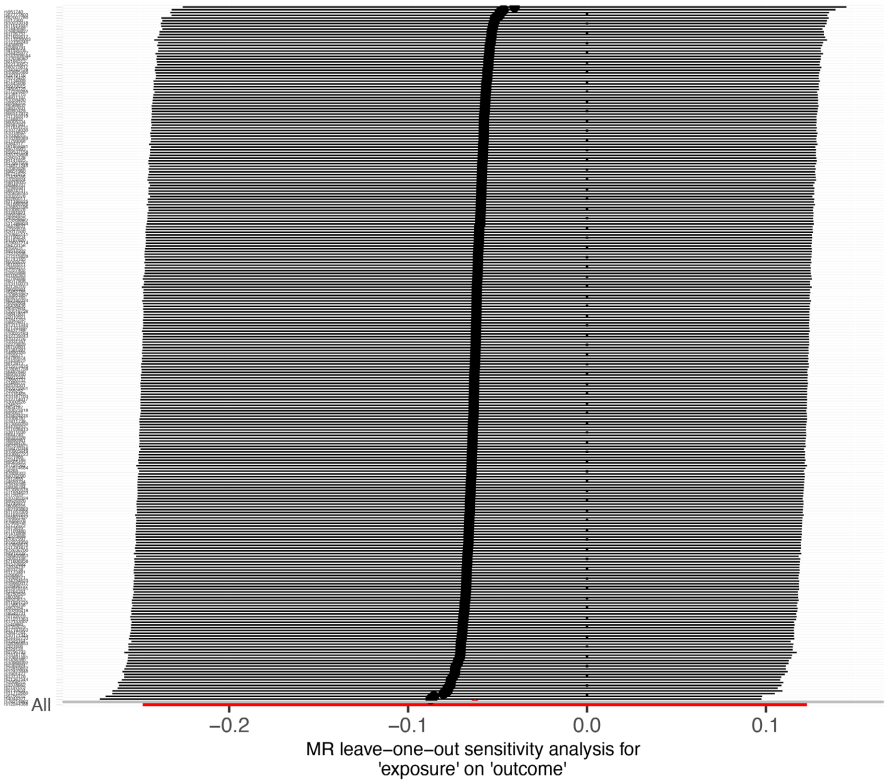

Figure 6. Stability of MR Analysis between Smoking and POAG. The outcome remains stable regardless of the SNP removed from the analysis.

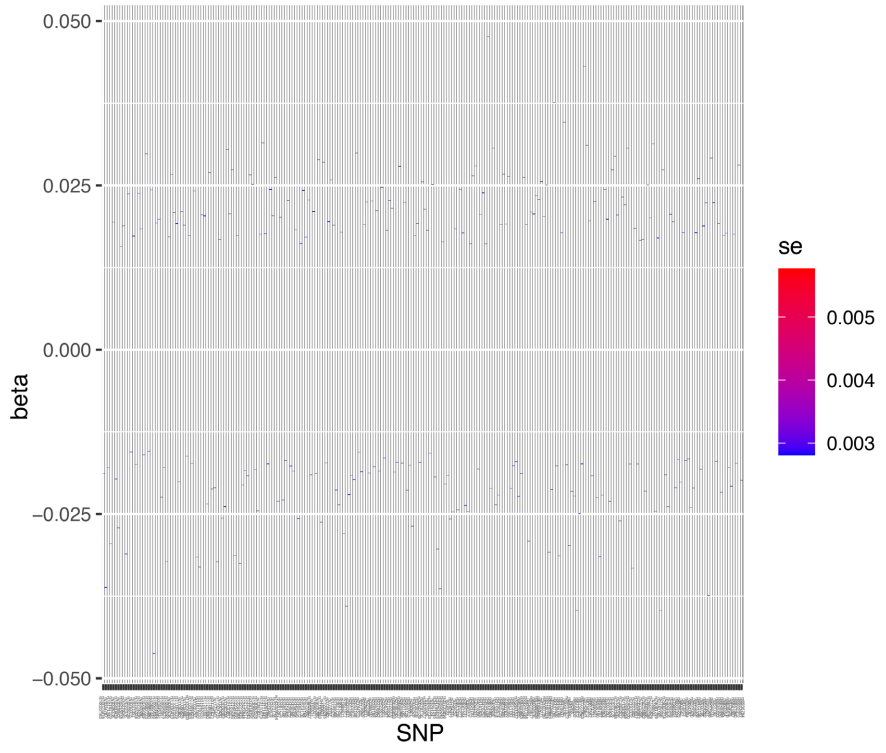

Figure 7. Heat map of MR Analysis results of smoking to POAG. The heatmap displays a uniform distribution of SNP locations within the range of y = +0.025 and y = −0.025, with symmetry indicating that smoking does not significantly influence the incidence of POAG.

Many studies indicate [19]-[23] that alcohol consumption is a high-risk factor for POAG. Although alcohol can temporarily lower intraocular pressure [24], long-term drinking may have a sustained negative impact on intraocular pressure, which is biologically plausible. Alcohol consumption leads to increased urine secretion which can cause dehydration, increasing blood viscosity and flow resistance, thereby potentially affecting intraocular pressure [25]. Furthermore, long-term alcohol consumption can trigger the release of cortisol, further increasing the risk of elevated intraocular pressure [26]. Additionally, the oxidative stress and DNA damage associated with long-term alcohol use may exacerbate age-related changes in the trabecular meshwork, a key structure in regulating intraocular pressure [27] [28].

Although studies suggest that alcohol is only associated with high intraocular pressure and seems to have a weaker direct link to glaucoma [29], this view may stem from the limitations of using cross-sectional data. Reverse causation may occur in such studies, for example, glaucoma patients might have consumed more alcohol when younger but reduced their drinking after diagnosis, thus diminishing the potential link between alcohol consumption and glaucoma.

A similar situation also appears in studies exploring the relationship between smoking and POAG, where some researchers find no apparent association [3] [30] [31], while others have found that smoking increases the risk of POAG [5]. In these cases, the Mendelian randomization study method shows its advantages, as it can use genetic variants as instrumental variables to help identify causal relationships between drinking and the development of glaucoma [32], avoiding common biases in traditional observational studies.

Through Mendelian randomization studies, we find no significant causal relationship between alcohol misuse and smoking with POAG. Although the SNP data volumes for alcohol misuse and smoking differ, leading to differences in data heterogeneity, the conclusions remain stable after analysis using regression formulas based on heterogeneity results, indicating that neither alcohol misuse nor smoking significantly increases the risk of POAG. It is important to note that the study uses the GWAS dataset described in English as "Alcohol Misuse," and the definition of what constitutes alcohol misuse seems not reflected. The smoking GWAS dataset is described as "Ever Smoker", including "beginners", "former smokers who have quit" and "consistent smokers". This might lead to a weakening of the conclusion's association.

Of course, this study has certain limitations, as mentioned at the outset. The study aimed to align results more closely with Chinese patients, using a GWAS dataset from East Asian POAG. However, the quality of East Asian GWAS datasets for alcohol misuse and smoking was insufficient for this study, ultimately necessitating the use of European GWAS data, which may impact the conclusions. Therefore, the results of this study still need to be verified in the Chinese population through clinical trials and randomized controlled trials.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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