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Mendelian randomization supports causality between COVID-19 and glaucoma

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Abstract

To determine whether there is a causal relationship between Corona Virus Disease 2019 (COVID-19) and glaucoma, a 2-sample Mendelian Randomization (MR) design was applied with the main analysis method of inverse-variance-weighted. The reliability of the results was checked using the heterogeneity test, pleiotropy test, and leave-one-out method. Four sets of instrumental variables (IVs) were used to investigate the causality between COVID-19 and glaucoma risk according to data from the IEU Genome Wide Association Study (GWAS). The results showed that 2 sets of COVID-19(RELEASE) were significantly associated with the risk of glaucoma [ID: ebi-a-GCST011071, OR (95% CI) = 1.227 (1.076–1.400), $P = .002259$; ID: ebi-a-GCST011073: OR (95% CI) = 1.164 (1.022–1.327), $P = .022450$; 2 sets of COVID-19 hospitalizations were significantly associated with the risk of glaucoma (ID: ebi-a-GCST011081, OR (95% CI) = 1.156 (1.033–1.292), $P = .011342$; ID: ebi-a-GCST011082: OR (95% CI) = 1.097 (1.007–1.196), $P = .034908$)]. The sensitivity of the results was acceptable ($P > .05$) for the 3 test methods. In conclusion, this MR analysis provides preliminary evidence of a potential causal relationship between COVID-19 and glaucoma.

Abbreviations: ACE2 = angiotensin-converting enzyme 2, ADEs = adverse effects, COVID-19 = coronavirus disease 2019, GWAS = genome wide association study, IVs = instrumental variables, MR = Mendelian randomization, PACG = primary angle-closure glaucoma, POAG = primary open-angle glaucoma, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SNPs = single-nucleotide polymorphisms.

Keywords: causality, COVID-19, glaucoma, instrument variables, Mendelian randomization

1. Introduction

Glaucoma is a group of eye diseases traditionally characterized by elevated intraocular pressure. Primary open-angle glaucoma (POAG) manifests as visual field loss, while primary angle-closure glaucoma (PACG) is another form of glaucoma characterized by narrowing or closure of the anterior chamber angle.[1] In those aged 50 years and older in 2020, glaucoma was the second leading cause of blindness in worldwide.[2] It is generally assumed that the major risk factors for developing glaucoma include age, race, and family history,[3] the relation between comorbidity and glaucoma has been investigated in recent years[4–8] as the rapid development of genome-wide association studies (GWAS), ankylosing spondylitis, Iritis or Uveitis, ayopic refractive error, and rheumatic diseases have been reported to possess common single-nucleotide polymorphisms (SNP) with glaucoma. Although the function of the patient organs is widely disturbed, whether coronavirus disease 2019 (COVID-19) increases the risk of glaucoma is unknown.

Initially, reports have supported conjunction as an ocular manifestation of COVID-19,[9,10] and only a few studies have reported the impact of COVID-19 on the incidence and treatment of glaucoma, which in most situation, pandemic of COVID-19 effect the prognosis of glaucoma. A massive reduction in surgical treatment occurred in Germany[11] and patients in proning practice were more susceptible to ocular complications after infection with COVID-19.[12] Moreover, the frequency of trabeculectomy decreased during the pandemic of COVID-19,[13] at the same time, it forced hospitals to provide reliable alternative models for the health care of glaucoma.[14] Most of the suspected physiopathological associations between COVID-19 and glaucoma have been case reports.[15–18] Interestingly, more data are available on the remarkable ocular adverse effects (ADEs) of COVID-19 vaccines. Angle-closure glaucoma is 1 of the 3 most frequent ADEs with AZD-1222,[19] and case reports related to this ADEs[20–23] have arisen, although there is a short interval between the injection and the onset of ADEs.

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The datasets generated during and/or analyzed during the current study are publicly available.

Our analysis used publicly available genome-wide association study (GWAS) summary statistics. No new data were collected and no new ethical approval was required.

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Mendelian randomization (MR) analysis represents a novel epidemiological study design that incorporates genetic information into traditional epidemiologic methods.[24,25] It provides an approach to address questions of causality without many of the typical biases that impact the validity of traditional epidemiologic approaches. When a single exposure-outcome association was estimated, 3 separate associations were ascertained in an MR study. The first is the association between the risk allele (instrumental variable) and risk factor (intermediate variable). The second is the association between the risk allele and outcome of interest. The third is the association between the intermediate variable (risk factor) and outcome. Using the estimates of the first and second associations, the investigator can determine the causal effect of the intermediate risk factor on the outcome. Wang et al[26] revealed that PD was significantly linked to COVID-19 severity based on a 2-sample MR study that used SNPs as the intermediate.

SNPs are one of the most commonly studied genetic variables that occur less frequently than mutations and generally have ADEs on protein function. As mechanisms of glaucoma have not been clearly elucidated, and whether COVID-19 represents a risk marker for glaucoma needs further study, we employed a 2-sample MR analysis to examine common SNPs of COVID-19 and COVID-19 hospitalized with glaucoma in this study by using the data from the IEU GWAS study.

2. Method

2.1. Data source

Our data all come from the MRC Integrative Epidemiology Unit (IEU) GWAS summary date (https://www.ebi.ac.uk/gwas/). SNPs related to COVID-19 for genetic instruments were based on a study of the COVID-19 host genetics initiative of GWAS from COVID-19 and COVID-19 hospitalized,[27] the majority of studies on the exposure are conducted in Europe (55%) and the US (28%), with the United Kingdom (10%) and Italy (9%). The outcome glaucoma[28] genes cohorts are from Australia, the United Kingdom, and the United States. In total, 4 sets of instrument variables were enrolled to investigate the causal role of COVID-19 in glaucoma, including SNPs related to glaucoma (multi-trait analysis), which were extracted from a multi-trait analysis of GWAS.

2.2. Gene instruments

To obtain eligible genetic variants as instrumental variables (IVs), a set of quality control analyses was performed. Based on the 3 core assumptions of the MR analysis, we selected SNPs that were independently associated with genome-wide exposure ($P < 5 \times 10^{-8}$) as instrumental SNPs. Meanwhile, we set parameters (R^2 <0.001 and kb = 1000) to exclude linkage disequilibrium, and discarded variants that had a stronger association with other IVs. The confounders were selected using GWAS Catalog (https://www.ebi.ac.uk/gwas/). R^2 was calculate according to the formula as below:

$$R^2 = \beta^2 (1 - EAF) * 2EAF$$

R^2 was variation each SNP can explain, effect allele frequency, was the gene frequency of the mutation, β was the beta coefficient associated with the exposure.

To minimize weak instrumental bias, we set an F-statistic < 10 as the exclusion criterion and we used the F-statistic through the formula as below:

$$F = \beta^2/SE^2$$

where β was the effect size of IV on the exposure and "SE" was the corresponding standard error of β.

2.3. Statistical analysis

Statistical analysis was performed using the R software (version 4.3.0, The R Development Core Team, Vienna, Austria), TwoSampleMR (version 0.5.7), and MRPRESSO (version 1.0). We used 2-sample MR analysis and inverse variance weight to evaluate the relationship between COVID-19 and glaucoma. A P value < 5×10^{-8} after Bonferroni correction was considered statistically significant. In addition, other methods were used to complement the MR results, including the MR–Egger regression, weighted median, simple mode, and weighted mode methods.

The sensitivity was checked using the heterogeneity test, pleiotropy test, and leave-one-out method. If the pleiotropy test by MR–Egger regression analysis showed horizontal pleiotropy, the MR-PRESSO outlier correction was applied.

3. Results

3.1. Results of SNPs and the weak IV test

Finally, we extracted data from the IEU and analyzed 2 cohorts of COVID-19 (RELEASE 5)-related SNPs (GWAS ID ebi-a-GCST011071 and ebi-a-GCST011073), 2 cohorts of COVID-19 hospitalization-related SNPs (GWAS ID ebi-a-GCST011081 and ebi-a-GCST011082), and 1 cohort of glaucoma (GWAS ID ebi-a-GCST009722) (Table 1). A total of 24 SNPs from the 2 COVID-19 cohorts were used as genetic instruments, and 2 COVID-19 hospitalized cohorts were associated with glaucoma risk (Tables 2 and 3). All SNPs set as IVs possessed $P < 5 \times 10^{-8}$ and F > 10.

3.2. Results of the 2-sample MR analyses

Overall, there were significant causal associations between COVID-19 and COVID-19 hospitalized with glaucoma after MR estimates using different methods (Table 4 and Fig. 1). The results showed COVID-19 (ebi-a-GCST011071): OR (95% CI) = 1.227 (1.076~1.400), P = .002259; COVID-19 (ebi-a-GCST011073): OR (95% CI) = 1.164 (1.022~1.327), P = .022450; COVID-19 hospitalized (ebi-a-GCST011081): OR (95% CI) = 1.156 (1.033~1.292), P = .011342; COVID-19 hospitalized (ebi- a-GCST011082): OR (95% CI) = 1.097 (1.007~1.196), P = .034908. In addition, the MR–Egger regression, weighted median, simple mode, and weighted mode methods yielded similar results.

Table 1

Detailed information about the aggregated GWAS results.

GWAS ID	Trait	Sample size	Cases (n)	Controls (n)	SNPs (n)	Population
ebi-a-GCST011071	COVID-19	1588,783	29,071	1559,712	8103,014	European
ebi-a-GCST011073	COVID-19	1683,768	38,984	1644,784	8660,177	European
ebi-a-GCST011081	COVID-19 (hospitalized vs population)	1887,658	9986	1877,672	8107,040	European
ebi-a-GCST011082	COVID-19 (hospitalized vs population)	1557,411	8316	1549,095	6814,406	European
ebi-a-GCST009722	Glaucoma (multi-trait analysis)	224,431	133,492	90,939	7981,170	European

COVID-19 = coronavirus disease 2019, GWAS = genome-wide association study, SNPs = single nucleotide polymorphisms.

Table 2

Summary genetic instruments between COVID-19 and glaucoma.

			Exposure				Outcome					
Exposure	SNP	Chr	beta	eaf	se	*P*	beta	eaf	se	*P*	R^2	F
ebi-a-GCST011071	rs10774671	12	0.0602	0.6719	0.0110	.2322	0.0131	NA	0.0090	2.0898E-11	0.0016	30.0380
	rs11923452	3	−0.0568	0.3517	0.0110	.2841	−0.0117	NA	0.0091	3.6380E-10	0.0015	26.8030
	rs12482060	21	0.0555	0.3417	0.0114	.0223	0.0260	NA	0.0094	3.6570E-09	0.0014	23.8772
	rs17078346	3	0.0825	0.1055	0.0187	.5866	0.0102	NA	0.0140	4.1120E-09	0.0013	19.4978
	rs2109069	19	0.0544	0.3161	0.0112	.6244	0.0055	NA	0.0098	2.7590E-08	0.0013	23.5390
	rs2271616	3	0.1421	0.1171	0.0156	.5457	0.0094	NA	0.0141	9.6316E-24	0.0042	83.4529
	rs612169	9	0.0906	0.3529	0.0113	.0004	0.0399	NA	0.0091	1.5431E-23	0.0037	64.2637
ebi-a-GCST011073	rs10936744	3	−0.0626	0.3588	0.0110	.2853	-0.0117	NA	0.0100	3.5110E-10	0.0018	32.6220
	rs12482060	21	0.0620	0.3375	0.0114	.0223	0.0260	NA	0.0105	3.9580E-09	0.0017	29.7227
	rs17078348	3	0.0921	0.0997	0.0187	.7945	0.0049	NA	0.0162	1.1960E-08	0.0015	24.2356
	rs2271616	3	0.1563	0.1181	0.0156	.5457	0.0094	NA	0.0151	3.6083E-25	0.0051	100.9742
	rs4971066	1	−0.0768	0.1777	0.0142	.9365	0.0011	NA	0.0134	1.0150E-08	0.0017	29.0540
	rs643434	9	0.1013	0.371	0.0111	.0021	0.0342	NA	0.0101	1.2921E-23	0.0048	83.2277
	rs757405	12	0.0689	0.7092	0.0112	.0603	0.0211	NA	0.0108	1.6390E-10	0.0020	37.6669

beta = allele effect value, Chr = chromosome, eaf = effector allele frequency, NA = not available, se = standard error, SNP = single nucleotide polymorphism.

Table 3

Summary genetic instruments between COVID-19 hospitalized and glaucoma.

			Exposure				Outcome					
Exposure	SNP	Chr	beta	eaf	se	*P*	beta	eaf	se	*P*	R^2	F
ebi-a-GCST011081	rs13050728	21	−0.1683	0.6528	0.0114	.0226	−0.0259	NA	0.0202	7.4370E-17	0.0128	219.4710
	rs2109069	19	0.1513	0.3227	0.0112	.6244	0.0055	NA	0.0199	2.9370E-14	0.0100	181.9462
	rs2660	12	0.1164	0.6902	0.0110	.1686	0.0151	NA	0.0194	2.0050E-09	0.0058	112.0147
	rs35081325	3	0.4883	0.0812	0.0208	.8103	−0.0050	NA	0.0315	3.6838E-54	0.0356	552.3721
	rs505922	9	0.1118	0.3501	0.0113	.0007	0.0382	NA	0.0191	4.4160E-09	0.0057	97.8514
ebi-a-GCST011082	rs10774679	12	0.1202	0.6913	0.0109	.0575	0.0207	NA	0.0189	1.8030E-10	0.0062	121.6577
	rs111837807	6	0.1894	0.0996	0.0215	.8932	−0.0029	NA	0.0299	2.2630E-10	0.0064	77.6813
	rs13050728	21	−0.1536	0.6289	0.0114	.0226	−0.0259	NA	0.0192	1.4608E-15	0.0110	182.6440
	rs2109069	19	0.1754	0.3151	0.0112	.6244	0.0055	NA	0.0205	1.2151E-17	0.0133	244.4655
	rs35081325	3	0.5507	0.0896	0.0208	.8103	−0.0050	NA	0.0331	4.8328E-62	0.0495	702.7375

beta = allele effect value, Chr = chromosome, eaf = effector allele frequency, NA = not available, se = standard error, SNP = single nucleotide polymorphism.

3.3. Evaluation of sensitivity

As shown in Table 5, the results of the MR-Egger intercept and MR-PRESSO global tests were statistically non-significant, indicating that the MR analysis results were reliable. The results of the leave-one-out method showed that after gradually removing each SNP, the results with the remaining SNPs were similar to the original results ($P > .05$; Fig. 2A, C, E, and G), and the funnel plots appeared generally symmetrical (Fig. 2B, D, F, and H), indicating that no SNPs with a strong influence on the results were found in the IVs.

4. Discussion

In our study, we explored IEU GWAS summary statistics and carried out a 2-sample MR analysis to minimize the impact of confounders and obtained a strong causal relationship between COVID-19 and COVID-19 hospitalized and glaucoma in Europe. To the best of our knowledge, this is the first study to explore causality between COVID-19 and glaucoma. In summary, COVID-19 and hospitalization increased the risk of glaucoma according to the SNPs as IVs.

Coronaviruses are known pathogens that can invade the central nervous system and cause neurological pathologies[29,30] with the mechanism of direct viral invasion of neurons, systemic response to, or immune dysfunction.[31,32] Many neurological complications of COVID-19 have been reported, including central nervous system manifestations (headache, dizziness, stroke, encephalitis, and seizure), as well as peripheral nervous system manifestations, such as taste and smell impairment, nerve pain and vision impairment.[33–35]

Glaucoma is a neurodegenerative disease characterized by progressive degeneration of retinal ganglion cells and the optic nerve.[36,37] Although seldom reported, the relationship between glaucoma and COVID-19 should attract more attention because disease progression requires a chronic period of observation. Based on existing evidence, the common pathophysiological mechanisms and explanations of the association between COVID-19 and glaucoma are as follows. On the one hand, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) invades the human body by binding to angiotensin-converting enzyme 2 (ACE2) receptors on cells,[38] and the expression of these receptors have been detected in different ocular cell types and visual processing centers of the brain.[39] Increasing evidence supports the hypothesis that SARS-CoV-2 may invade the human body through the eyes[40] although there are inconsistent conclusions on whether the SARS-CoV-2 receptor ACE2 is more expressed in the conjunctiva or optic nerve.[41–43] Furthermore, it is verified that the activation of intrinsic ACE2 is a potential therapeutic strategy to treat glaucoma,[44] at the same time, drugs targeting ACE2 receptors can be considered as therapeutic candidates for COVID-19 treatment.[45,46] However, COVID-19

Table 4

Results of the 2-sample MR analyses.

Exposure	Outcome	Method	*P*	OR (95% CI)
COVID-19 (RELEASE 5)	Glaucoma (multi-trait analysis)	MR Egger	.58557	1.137 (0.743–1.739)
		Weighted median	.13378	1.143 (0.96–1.362)
		Inverse variance weighted	.00226	1.227 (1.076–1.4)
		Simple mode	.44790	1.124 (0.851–1.484)
		Weighted mode	.52831	1.087 (0.853–1.386)
COVID-19 (RELEASE 5)	Glaucoma (multi-trait analysis)	MR Egger	.77633	1.079 (0.669–1.738)
		Weighted median	.16568	1.119 (0.955–1.312)
		Inverse variance weighted	.02245	1.164 (1.022–1.327)
		Simple mode	.75783	1.046 (0.8–1.368)
		Weighted mode	.66694	1.058 (0.835–1.34)
COVID-19 (hospitalized)	Glaucoma (multi-trait analysis)	MR Egger	.67471	0.846 (0.43–1.662)
		Weighted median	.01127	1.147 (1.032–1.276)
		Inverse variance weighted	.01134	1.156 (1.033–1.292)
		Simple mode	.19429	1.135 (0.978–1.316)
		Weighted mode	.14349	1.136 (1.001–1.29)
COVID-19 (hospitalized)	Glaucoma (multi-trait analysis)	MR Egger	.36644	0.748 (0.457–1.223)
		Weighted median	.03770	1.104 (1.006–1.212)
		Inverse variance weighted	.03491	1.097 (1.007–1.196)
		Simple mode	.14765	1.17 (0.998–1.372)
		Weighted mode	.61147	1.04 (0.907–1.192)

COVID-19 = coronavirus disease 2019, MR = Mendelian randomization.

Table 5

Reliability test of MR analysis results.

Exposure	Id.exposure	Outcome	Method	Q_pval	MR-Egger intercept test p	MR-PRESSO global test p
COVID-19	ebi-a-GCST011071	Glaucoma (multi-trait analysis)	MR Egger	0.25065		
			Inverse variance weighted	0.35066	0.72689	0.301
COVID-19	ebi-a-GCST011073	Glaucoma (multi-trait analysis)	MR Egger	0.20022		
			Inverse variance weighted	0.30750	0.76225	0.332
COVID-19 (hospitalized)	ebi-a-GCST011081	Glaucoma (multi-trait analysis)	MR Egger	0.12213		
			Inverse variance weighted	0.11245	0.45492	0.097
COVID-19 (hospitalized)	ebi-a-GCST011082	Glaucoma (multi-trait analysis)	MR Egger	0.53454		
			Inverse variance weighted	0.30178	0.26161	0.229

COVID-19 = coronavirus disease 2019, MR = Mendelian randomization.

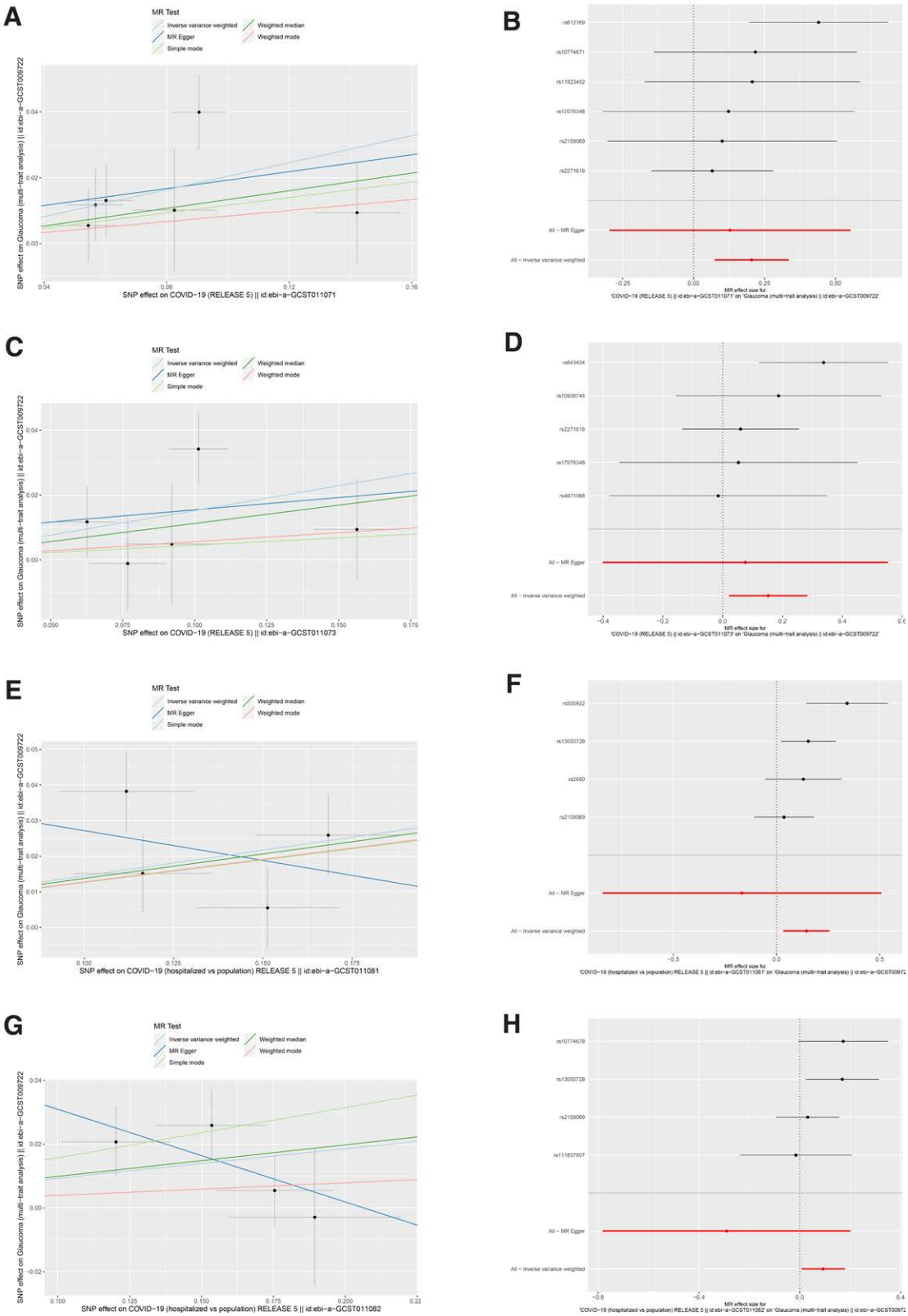

Figure 1. Scatter plot and forest plot of the causal relationships between COVID-19 and glaucoma using different MR methods. (A) Scatter plot of the causal relationships between COVID-19 (ebi-a-GCST011071) and Glaucoma; (B) Forest plot of the causal relationships between COVID-19 (ebi-a-GCST011071) and Glaucoma; (C) Scatter plot of the causal relationships between COVID-19 (ebi-a-GCST011073) and Glaucoma; (D) Forest plot of the causal relationships between COVID-19 (ebi-a-GCST011073) and Glaucoma; (E) Scatter plot of the causal relationships between COVID-19 hospitalized (ebi-a-GCST011081) and Glaucoma; (F) Forest plot of the causal relationships between COVID-19 hospitalized (ebi-a-GCST011081) and Glaucoma; (G) Scatter plot of the causal relationships between COVID-19 hospitalized (ebi-a-GCST011082) and Glaucoma; (H) Forest plot of the causal relationships between COVID-19 hospitalized (ebi-a-GCST011082) and Glaucoma. The slope of each line corresponds to the causal estimates for each method. The individual SNP effect on the outcome (point and vertical line) against its effect on the exposure (point and horizontal line) was delineated in the background. COVID-19 = coronavirus disease 2019, MR = Mendelian randomization, SNP = single nucleotide polymorphism.

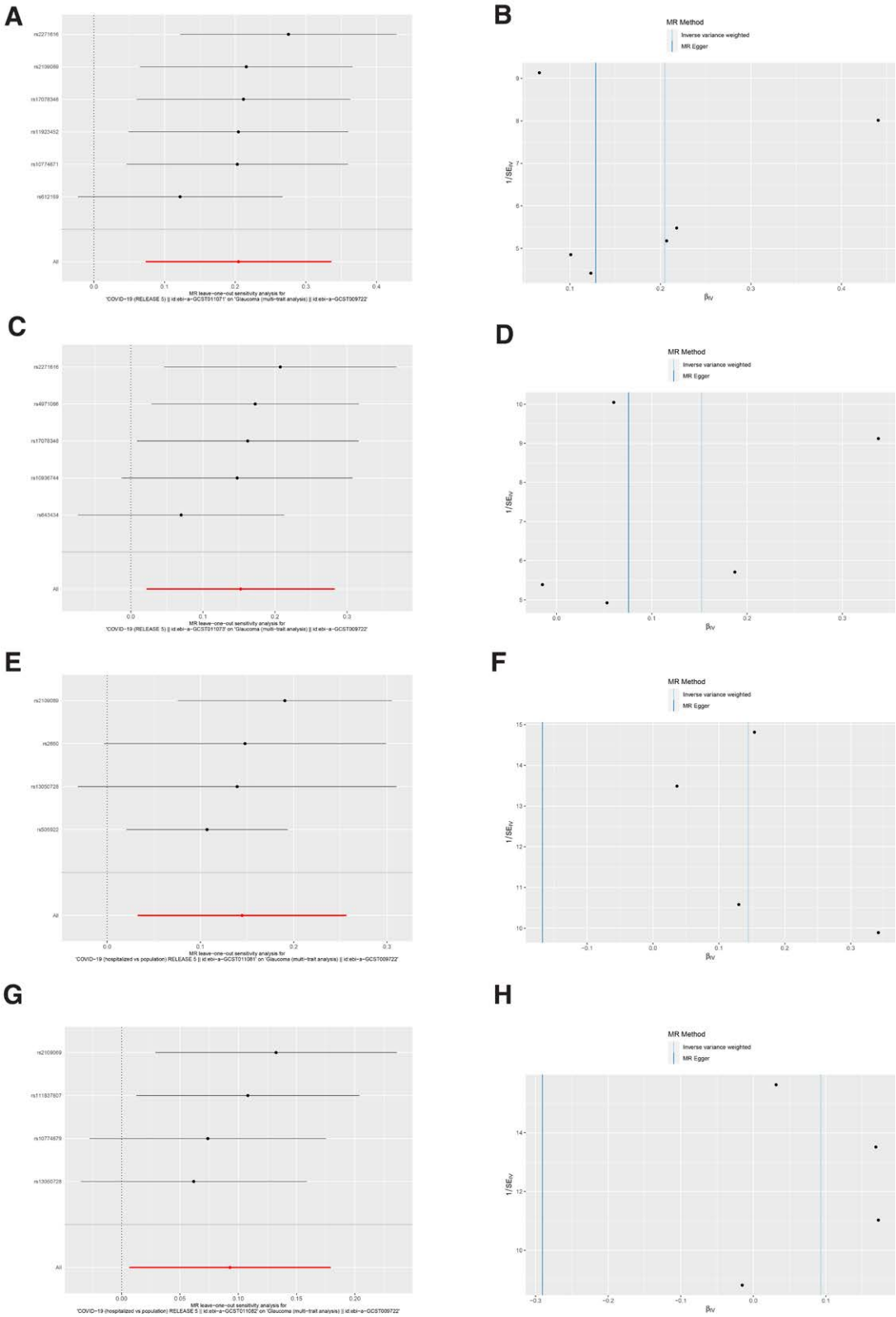

Figure 2. Results of leave-one-out method sensitivity analysis and funnel plots. (A) Leave-one-out sensitivity analysis for the effect of COVID-19 (ebi-a-GCST011071) and Glaucoma; (B) Funnel plot for the effect of COVID-19 (ebi-a-GCST011071) and Glaucoma; (C) Leave-one-out sensitivity analysis for the effect of COVID-19 (ebi-a-GCST011073) and Glaucoma; (D) Funnel plot for the effect of COVID-19 (ebi-a-GCST011073) and Glaucoma; (E) Leave-one-out sensitivity analysis for the effect of COVID-19 hospitalized (ebi-a-GCST011081) and Glaucoma; (F) Funnel plot for the effect of COVID-19 hospitalized (ebi-a-GCST011081) and Glaucoma; (G) Leave-one-out sensitivity analysis for the effect of COVID-19 hospitalized (ebi-a-GCST011082) and Glaucoma; (H) Funnel plot for the effect of COVID-19 hospitalized (ebi-a-GCST011082) and Glaucoma.COVID-19 = coronavirus disease 2019.

is thought to be a cause of vascular complications.[47] These findings suggest that endothelial dysfunction, inflammation, cytokine release, hypercoagulability, and hypoxia contribute to the development of thrombosis. Based on these studies, a causal association between COVID-19 and ischemic neuroophthalmic events is plausible.

Although the study designs are hypothesis-generating, most of the literature on neuro-ophthalmic complications associated with COVID-19 and COVID-19 vaccination consists of case series or case reports. Therefore, it is worth noting that establishing a causal relationship between COVID-19 and neuro-ophthalmic consequences is essential. In the present 2-sample MR study, we used 3 sets of IVs to verify the causal association among COVID-19, COVID-19 hospitalization, and glaucoma risk. The consistent results of these analyses indicated that the conclusions were reliable. A weighted median check showed no indication of pleiotropy and the MR-PRESSO outlier test did not find any outlier SNPs.

MR-designed surveys have many advantages and can complement traditional epidemiologic studies; however, there are still some limitations. First, it was limited to individuals of European ancestry, indicating that our findings cannot be directly inferred from other populations. Second, although no evidence of multiplicity of causal associations was found through different MR methods, it is still plausible that variants used in MR may confer glaucoma risk through multiplicity of effect pathways. Third, the database did not distinguish POAG from PACG; although the former is optic neuropathy, PACG is characterized by narrowing or closure of the anterior chamber angle. Therefore, further, MR analysis with individual-level data should be conducted to evaluate the causal relationship between COVID-19 and the risk of glaucoma in different subtypes and populations.

As the biological basis of glaucoma is not yet fully understood, our MR analysis provides preliminary evidence of a potential causal relationship between COVID-19 and glaucoma.

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Yilan Huang and Longyang Jiang are the co-corresponding authors.

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Writing – original draft: Maolin Chen.
Writing – review & editing: Yinhui Zhang.

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