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Genetic susceptibility to COVID-19 may increase the risk of erectile dysfunction: A two-sample Mendelian randomization study

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Abstract

Coronavirus disease 19 (COVID-19) and erectile dysfunction (ED) have been linked in some observational research, but the causality of this association in the European population is uncertain. Therefore, the research intended to investigate the causality of susceptibility to COVID-19 on ED. We used Mendelian randomization (MR) analysis for this research. The subjects were from two genome-wide association studies (GWAS) of the European population, including COVID-19 (14,134 cases and 1,284,876 controls) and ED (6175 cases and 217,630 controls). We utilized the inverse variance-weighted (IVW) to evaluate the causality of COVID-19 genetic susceptibility on ED. Heterogeneity and pleiotropy were determined using the Cochran's *Q* test and MR-Egger regression. The robustness of the findings was verified using the Leave-one-out method. We obtained six single nucleotide polymorphisms (SNPs) as COVID-19 genetic instrumental variables (IVs), and there was no significant pleiotropy, heterogeneity or bias in these IVs. MR analysis revealed the causality of genetic susceptibility to COVID-19 on elevated risk of ED ($OR_{IVW} = 1.235$, 95% CI: 1.044–1.462, $p < 0.05$). The present study suggested the causality of genetic susceptibility to COVID-19 on elevated ED risk among the European population. Therefore, in order to decrease the ED risk, the European population ought to positively prevent COVID-19.

KEYWORDS
COVID-19, erectile dysfunction, Mendelian randomization

1 | INTRODUCTION

Coronavirus disease 19 (COVID-19), resulting from SARS-CoV-2, leads to a series of negative consequences globally. In addition to damaging lung tissue, SARS-CoV-2 appears to induce lesions in the digestive, neurological and urinary systems (Gupta et al., 2020; He et al., 2021; Lyoo et al., 2022). Furthermore, men have a greater severity and fatality rate from SARS-CoV-2 infection than women (Mukherjee & Pahan, 2021; Tazerji et al., 2022). Coronavirus disease 19 (COVID-19) and erectile dysfunction (ED) have been linked in observational research (Ates et al., 2021; Katz et al., 2021; Sansone, Mollaioli, Ciocca, Colonnello, et al., 2021; Sansone, Mollaioli, Ciocca, Limoncin, et al., 2021). Such results, however, can be confounded by a few confounders. Therefore, the influence that COVID-19 has on ED may not be clearly reflected. In short, further exploration of the causality of COVID-19 on ED is essential, which may help men be more health-conscious during the COVID-19 epidemic.

Mendelian randomization (MR) utilizes genetic variations for assessing the causality of exposure (COVID-19) on the outcome (ED) (Smith & Ebrahim, 2003). These variations are distributed randomly at pregnancy and are applied as instrumental variables (IVs)

for exposure. As the variants occur ahead of the onset of the disease, MR is not biased by confounders (Emdin et al., 2017). The single nucleotide polymorphisms (SNPs) for exposure and outcome from two independent sample genome-wide association studies (GWAS) in a two-sample MR study, respectively (Yazdanpanah et al., 2022).

In the research, we propose to perform a two-sample MR analysis to explore the causality of COVID-19 on the ED risk.

2 | MATERIALS AND METHODS

2.1 | Design and participants

This study used a two-sample MR. The summary statistics of COVID-19 were downloaded from the MRC IEU OpenGWAS datasets (GWAS ID: ebi-a-GCST010780) to generate the IVs ('The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic', 2020). This GWAS study included 14,134 cases and 1,284,876 controls. Data from 6175 cases and 217,630 controls were collected from the above GWAS database as outcome (ED) variables (GWAS ID: ebi-a-GCST006956) (Bovijn et al., 2019). All data were derived from the European population.

2.2 | IVs for COVID-19

We got the SNPs related to COVID-19 according to $P < 5 \times 10^{-8}$ using RStudio 4.1.1 and the package 'TwoSampleMR'. For linkage disequilibrium, we then pruned the SNPs ($r^2 < 0.3$). Ultimately, as shown in Table 1, we obtained a total of six SNPs serving as IVs.

2.3 | Statistical analysis

In assessing the causality of COVID-19 susceptibility on ED, the inverse variance-weighted (IVW) was mainly applied (Burgess et al., 2013), and other methods including MR Egger (Bowden et al., 2015), weighted-median (Bowden et al., 2016), weighted mode (Hartwig et al., 2017) and simple mode (Zhu et al., 2022). Then, to assess the reliability of the results, we performed sensitivity analyses. Because MR analysis requires that IVs cannot affect outcomes through pathways other than exposure, we tested the pleiotropy of IVs using MR-Egger regression methods (Bowden et al., 2015). We also performed Cochran's Q test to estimate the heterogeneity for individual SNPs. When there was no heterogeneity, a fixed-effects model was utilized ($p > 0.05$). Or else we make use of the random-effects model (Hemani et al., 2018). The robustness of the findings was verified using the Leave-one-out method (Burgess et al., 2017). A statistically significant difference was defined as one with a $p < 0.05$. RStudio (version 4.1.1) was used to carry out all analyses.

3 | RESULTS

According to $P < 5 \times 10^{-8}$ and linkage disequilibrium, we obtained a total of six SNPs serving as IVs. Then, we used these IVs to assess the causality of susceptibility to COVID-19 on ED using different

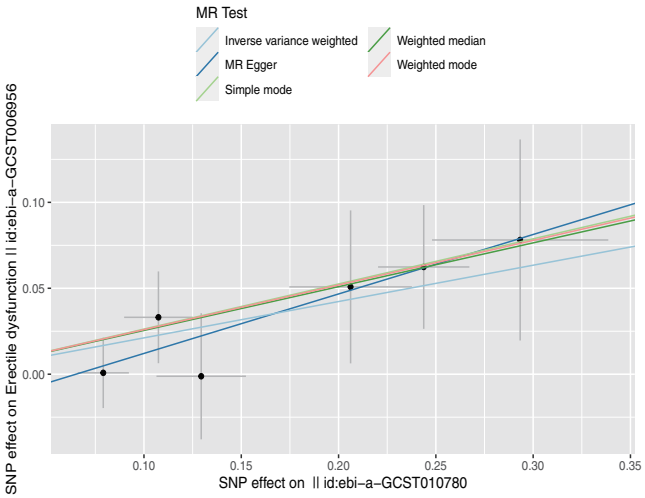

FIGURE 1 The causality of COVID-19 on ED risk. The slope represents the magnitude of the causal effect. MR, Mendelian randomization; ED, erectile dysfunction

TABLE 1 IVs for COVID-19

SNP	Chr	Pos	EA	NEA	EAF	Beta	SE	P
rs67959919	3	45,871,908	A	G	0.087	0.244	0.023	2.81E−25
rs35951367	3	46,118,439	C	T	0.168	0.107	0.018	1.09E−09
rs73062394	3	45,839,176	T	A	0.052	0.206	0.032	5.94E−11
rs75826707	3	45,908,859	A	G	0.037	0.293	0.045	9.47E−11
rs111837807	6	31,121,232	C	T	0.092	0.129	0.023	1.81E−08
rs505922	9	1.36E+08	C	T	0.345	0.079	0.013	1.88E−09

Abbreviations: IVs, instrumental variables; COVID-19, coronavirus disease 19; Chr, chromosome; EA, effect allele; NEA, non-effect allele; EAF, effect allele frequency; Pos, position; SNP, single nucleotide polymorphism.

TABLE 2 Causal effect of COVID-19 with ED

Exposure	Outcome	*N* (SNP)	Method	OR (95% CI)	*p*
COVID-19	ED	6	MR Egger	1.413 (0.973–2.054)	0.144
COVID-19	ED	6	Weighted median	1.290 (1.053–1.581)	0.014
COVID-19	ED	6	Inverse variance weighted	1.235 (1.044–1.462)	0.014
COVID-19	ED	6	Simple mode	1.300 (0.974–1.736)	0.135
COVID-19	ED	6	Weighted mode	1.296 (1.004–1.675)	0.104

Abbreviations: COVID-19, coronavirus disease 19; ED, erectile dysfunction; SNP, single-nucleotide polymorphism; OR: odds ratio; CI, confidence interval.

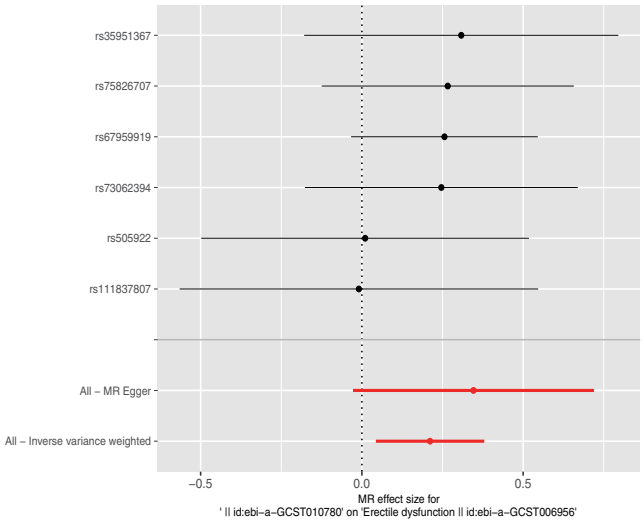

FIGURE 2 The causality of each SNP on ED risk. MR, Mendelian randomization; ED, erectile dysfunction

methods. The IVW result showed that genetic susceptibility to COVID-19 was related to an increased ED risk ($OR_{IVW} = 1.235$, 95% CI: 1.044–1.462, $p < 0.05$) (Figure 1, Table 2). In addition, the effect of each SNP in the IVs on ED was also shown in Figures 1 and 2. Then, we performed sensitivity analyses. The results of Cochran's *Q* test suggested that there was no heterogeneity among SNPs (*Q_P* value >0.05) (Table 3). No indication of horizontal pleiotropy was found in our investigation, according to the findings of the MR-Egger regression (*p* value >0.05) (Table 3). We conducted a leave-one-out test to examine the influence of every SNP on the findings. The results showed no significant differences while we deleted a single SNP and duplicated the MR analysis except for rs67959919 (Figure 3), demonstrating our results' robustness.

4 | DISCUSSION

Our study assessed the causality of the susceptibility to COVID-19 on ED by a two-sample MR. The results suggested that COVID-19 genetic susceptibility might elevate the ED risk. And the sensitivity analysis indicated that the results are generally robust.

Our discovery was agreed with previous studies. Several observational research found COVID-19 can lead to an increased risk of ED. For example, Kevin Y Chu et al. used the TrinetX research network to assess ED risk in men with COVID-19. They found an elevated likelihood of new-onset ED after contracting SARS-CoV-2 (Chu et al., 2022). And another study, after adjusting for known risk factors and demographics such as obesity, circulatory disease, and diabetes, also showed a strong relationship between COVID-19 and ED (Katz et al., 2021). Researchers discovered that sales of ED drugs increased significantly over the COVID-19 epidemic, suggesting a possible correlation between COVID-19 and ED (Hernandez et al., 2021). However, due to several unknown confounding variables, these investigations are prone to bias. A pilot study has also directly confirmed the invasion and damage to the penis due to SARS-CoV-2. The authors demonstrated that once infected with the virus, the SARS-CoV-2 remained in the penis for 7 months and that the virus caused extensive endothelial cell dysfunction that could lead to ED (Kresch et al., 2021). In the present research, we further demonstrated the causality of COVID-19 on ED using MR analysis.

ED and COVID-19 have some common risk factors, including cardiovascular disease, obesity, diabetes and vitamin D deficiency (Guo et al., 2020; Katz et al., 2021; Wei et al., 2019). And endothelial dysfunction is considered a potential pathophysiological cause of COVID-19 and ED (Pons et al., 2020). Angiotensin-converting enzyme 2 (ACE2) is widely present in endothelial cells of the male genital tract, contributing to SARS-CoV-2 invasion, making this organ more susceptible to SARS-CoV-2 invasion (Hoffmann et al., 2020; Zipeto et al., 2020). Although ED and COVID-19 share a pathophysiological basis, further basic studies are warranted to investigate the causality of the susceptibility to COVID-19 on ED.

There are several advantages of this study. First, MR analysis is a genetic epidemiological method (Lawlor et al., 2008) that utilizes IVs for examining the causality of the exposure (COVID-19) on the outcome (ED). Second, the MR principle ensured no bias caused by confounders and no reverse causality in the MR analysis. Therefore, the results of this study suggested a long-term risk of ED due to COVID-19. Third, our study populations were of the European population, reducing population structure bias.

Our study also has limitations. First, data resource limitations made it impossible to conduct the analyses stratified or adjusted for

TABLE 3 Pleiotropy tests and heterogeneity of MR

Pleiotropy test			Heterogeneity test					
			MR egger			IVW		
Egger_intercept	SE	*p* Value	*Q*	*df*	Q_*P* Value	Q	*df*	Q_*P* Value
−0.023	0.028	0.473	0.927	4.000	0.921	1.553	5.000	0.907

Abbreviations: IVW, inverse variance weighted; MR, Mendelian randomization.

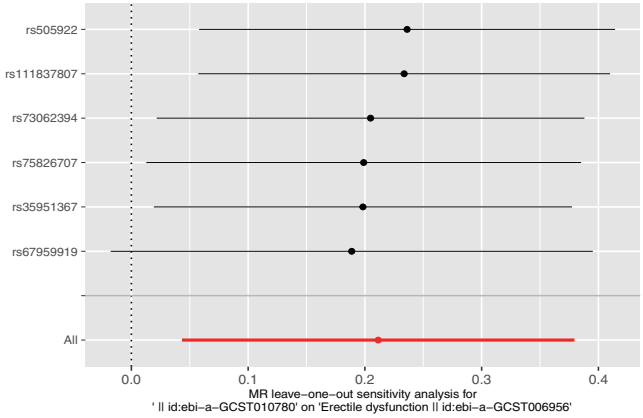

FIGURE 3 Leave-one-out analysis of the effect of COVID-19 on ED. MR, Mendelian randomization; ED, erectile dysfunction

other covariates. Second, because the study was limited to the European population, our findings might not apply to extrapolation to populations outside Europe.

5 | CONCLUSION

In conclusion, our study found that the COVID-19 genetic susceptibility could increase the ED risk in the European population, and this causal effect warrants further investigation.

AUTHOR CONTRIBUTIONS

Kun Zhang and Mingwei Chen developed this study and drafted the main manuscript. Mingwei Chen and Hengxing Gao conducted the data collation and analysis. The manuscript was reviewed by all authors.

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We thank this network for providing the main data (https://gwas.mrcieu.ac.uk/).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The raw data are available in the figshare repository, https://doi.org/10.6084/m9.figshare.19692307.v1.

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