Submitted: 21 March, 2023 Accepted: 18 April, 2023 Published: 30 January, 2024 DOI:10.22514/jomh.2024.009

ORIGINAL RESEARCH

JOMH Journal of Men's Health

Genetic association between COVID-19 and male infertility: a two-sample Mendelian randomization analysis

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Abstract

The impact of COVID-19 on male reproductive function has been widely reported, but the underlying genetic basis of this relationship remains unclear. A new and useful method for exploring causal associations between exposures and outcomes is Mendelian randomization (MR), which utilizes genetic variants, also known as single nucleotide polymorphisms (SNPs), as instrumental variables (IVs) in a retrospective way. In this study, a two-sample MR analysis was conducted to investigate the potential causal effect of COVID-19 on male infertility using summary-level data from large-scale genome-wide association studies (GWAS). SNPs identified in the COVID-19 and male infertility GWAS were used as IVs, and the causal effect was estimated using three methods: inverse-variance weighted (IVW), weighted median, and MR-Egger regression. Additionally, a leave-one-out analysis was performed as a sensitivity analysis to assess the robustness of the findings. The exposures to COVID-19 were obtained from the largest and most recent GWAS, which included 9986 cases versus 1,877,672 controls for hospitalized patients and 5101 cases versus 1,383,241 controls of severe patients of European ancestry. The corresponding outcome for male infertility was also obtained from the largest and most recent GWAS meta-analysis of 680 cases and 72,799 controls of European ancestry. The results based on the three methods showed no significant association between hospitalized or severe COVID-19 and male infertility. Specifically, the odds ratio for IVW was 0.86 (95% confidence interval (CI): 0.65–1.15, $p = 0.308$), 0.96 (95% CI: 0.54–1.69, $p = 0.886$) for MR-Egger, and 0.87 (95% CI: 0.62–1.22, $p = 0.430$) for weighted median. These findings suggest that COVID-19 may have no causal effect on male reproductive function, although further studies are needed to validate these results. The present study provides evidence for a genetic association between COVID-19 (including both hospitalized and severe COVID-19) and male infertility.

Keywords

Male infertility; COVID-19; Mendelian randomization; Genetic variants; Causal associations

1. Introduction

COVID-19 has profoundly impacted global public health, with millions of confirmed cases and deaths reported worldwide [1]. While the virus is primarily known for its effects on the respiratory system, emerging evidence suggests that it may also have implications for other organ systems, including the male reproductive system [2]. Male infertility is a significant public health concern, affecting approximately 7% of the male population [3]. Given the potential impact of COVID-19 on male reproductive function [4], it is critical to investigate the genetic basis and underlying mechanisms of this association and its potential implications for male health, as this may inform clinical management and public health policies related to COVID-19 and its long-term consequences on male health [2, 4].

Observational studies investigating the potential impact of COVID-19 on male reproductive function have yielded conflicting findings [4–6]. While some studies have suggested that COVID-19 may affect male fertility by inducing inflammation and oxidative stress [6], disrupting the hypothalamic-pituitary-gonadal axis, and damaging the testes [2], other studies have reported no significant association between COVID-19 and male infertility [7]. However, these studies were limited by the potential for confounding and reverse causation [8], as well as the small sample size and lack of causal inference [8]. Therefore, further investigations using robust study designs are required to clarify the potential impact of COVID-19 on male

reproductive function.

Mendelian randomization (MR) is a powerful statistical method that utilizes genetic variants, also known as single nucleotide polymorphisms (SNPs), as instrumental variables (IVs) to estimate causal relationships between exposures and outcomes [9]. Compared to traditional observational studies, MR offers several advantages, including a reduced risk of confounding and reverse causation, increased statistical power, and the potential to establish causality [10]. MR can be particularly useful in investigating the potential impact of COVID-19 on male reproductive function, as it enables the assessment of causality while minimizing the risk of bias and confounding [11]. By leveraging genetic variants associated with COVID-19 and male infertility, MR can provide a more robust estimate of the potential causal effect of COVID-19 on male infertility. Therefore, MR analysis has emerged as a valuable tool for investigating potential causal associations and providing critical insights into the long-term impact of exposures on the selected outcomes.

In this study, we conducted an MR analysis to investigate the potential causal association between COVID-19 and male infertility.

2. Methods

2.1 Study design

The current analysis utilized a two-sample MR study design in a retrospective way to investigate the potential causal effect of COVID-19 on male infertility by using genetic variants as IVs to estimate the causal effects between an exposure and an outcome variable [8].

2.2 Data sources of exposure

The exposure variable in this study is COVID-19, and the genetic variants associated with COVID-19 were obtained from recent genome-wide association studies (GWASs) of COVID-19. Specifically, the genetic variants were obtained from the GWAS of hospitalized patients, which included 9986 cases versus 1,877,672 controls, and the GWAS of severe patients, which included 5101 cases versus 1,383,241 controls (Table 1) [12]. The specific definition of severity was referred from the original study [12], and both studies were conducted on individuals of European ancestry.

2.3 Database sources of the outcomes

The outcome variable in this study is male infertility, and the genetic variants associated with male infertility were obtained from a GWAS meta-analysis comprising 680 cases and 72,799 controls of European ancestry (Table 1) retrieved from several large-scale studies investigating the genetic basis of male infertility.

2.4 Selection criteria of IVs

Genetic variants associated with COVID-19 and male infertility at genome-wide significance (p-value $< 5 \times 10^{-8}$) were selected as IVs, with the conditions that these selected variants should be robustly associated with the exposure or outcome variable and should not be associated with potential confounders or mediators that may affect the relationship between the exposure and outcome variables, such as smoking, drinking, or certain inflammatory factors. To ensure the validity of the selected instrumental variables and identify potential pleiotropic effects, we conducted a range of sensitivity analyses, including MR-Egger regression, the weighted median method, and leave-one-out analysis.

2.5 MR analysis

After harmonizing all SNPs and removing palindromic SNPs, we utilized summary-level data to estimate the causal effect of COVID-19 on male infertility using the inverse-variance weighted (IVW) method, MR-Egger regression, and weighted median method. These methods provide different approaches to estimating causal effects and have different assumptions about the underlying causal model. The IVW method combines the estimates from individual genetic variants using inverse-variance weights, where larger weights are assigned to variants with smaller standard errors [8, 11]. MR-Egger regression accounts for potential pleiotropy, or the presence of genetic variants that affect both the exposure and outcome through other pathways, by allowing for an intercept term in the regression model [8, 11]. The weighted median method estimates the causal effect by taking the median of the estimates from individual genetic variants, providing robustness against potential bias from pleiotropy [8, 11]. To assess the robustness of our findings, we performed sensitivity analyses, including the leave-one-out analysis to detect potential pleiotropy. We also performed an MR pleiotropy test to evaluate the impact of potential horizontal pleiotropy and heterogeneity on our results. Finally, we considered a p-value < 0.05 as statistically significant and reported the effect estimate and its 95% confidence interval (CI).

3. Results

3.1 The characteristics of included IVs

When analyzing the potential role of hospitalized COVID-19 on the risk of male infertility, 5 SNPs with an F statistic of 30–267 were included (Table 2). Similarly, when exploring the causal role of severe respiratory COVID-19 on the risk of male infertility, 7 SNPs with an F statistic of 36–248 were included (Table 3).

3.2 MR analysis

Our MR analysis did not find any evidence of a causal association between hospitalized COVID-19 and male infertility, with an odds ratio of 0.86 (95% CI: 0.65–1.15, $p = 0.308$). The MR-Egger method yielded similar results with an odds ratio of 0.96 (95% CI: 0.54–1.69, $p = 0.886$), and the weighted median method also showed no significant causal association with an odds ratio of 0.87 (95% CI: 0.62–1.22, $p = 0.430$). The sensitivity analyses did not alter the main findings. Similarly, the MR analysis between severe COVID-19 and male infertility revealed no causal associations. The potential effect of each SNP on COVID-19 and the risk of male infertility is illustrated

TABLE 1. Characteristics of the included trials.

Variable	GWAS ID	Population	No. of SNPs	No. cases	No. controls	Year
Hospitalized COVID-19	ebi-a-GCST011081	European	8,107,040	9986	1,877,672	2020
Severe COVID-19	ebi-a-GCST011075	European	9,739,225	5101	1,383,241	2020
Male infertility	finn-b-N14_MALEINFERT	European	16,377,329	680	72,799	2021

GWAS, genome-wide association studies; SNPs, single nucleotide polymorphisms.

TABLE 2. Characteristics of included IVs in hospitalized COVID-19 patients.

SNP	EA	OA	beta.E	beta.O	eaf.E	eaf.O	chr	pos	se.O	pval.O	se.E	pval.E	No.E	*F*
rs13050728	C	T	−0.17	0.03	0.65	0.62	21	34615210	0.06	0.55	0.02	7.44×10^{-17}	1887658	72.25
rs2109069	A	G	0.15	−0.06	0.32	0.35	19	4719443	0.06	0.28	0.02	2.94×10^{-14}	1887658	56.25
rs2660	A	G	0.12	0.01	0.69	0.73	12	113357442	0.06	0.92	0.02	2.00×10^{-9}	1887658	36.00
rs35081325	T	A	0.49	−0.03	0.08	0.08	3	45889921	0.10	0.74	0.03	3.68×10^{-54}	1887658	266.78
rs505922	C	T	0.11	−0.02	0.35	0.43	9	136149229	0.06	0.65	0.02	4.42×10^{-9}	1887658	30.25

Abbreviations: EA, effect alleles; OA, other alleles; E, exposures; O, outcomes; EAF, the effect allele frequency; No, sample size; chr, chromosome; pos, position; beta.E, beta value of exposure; beta.O, beta value of the outcome; eaf.O, EAF (the effect allele frequency) of the outcome; eaf.E, the EAF in our exposure; SNP, single nucleotide polymorphism; se.O, the standard error in the outcome; pval.O, the p-value in an outcome; se.E, the standard error in the exposure; pval.E, the p-value in the exposure; F, the values of F statistics; rs, the references SNPs.

in Fig. 1.

3.3 Forest plot and leave-one-out analysis for individual IV and overall causal estimate

The forest plot is a widely used graphical representation in MR studies to display effect estimates and confidence intervals for each individual instrumental variable and the overall causal estimate [3]. In this study, we utilized a forest plot to illustrate the causal estimates and 95% confidence intervals for each genetic variant included in the analysis, as well as the overall causal estimate (see Figs. 2,3).

A leave-one-out analysis was then conducted, which involved removing each genetic variant from the analysis one at a time, to assess the influence of each variant on the overall causal estimate [3]. It is an important sensitivity analysis in MR studies, as it helps identify any particularly influential variants that could be driving the overall estimation [8]. In this present study, the leave-one-out analysis aimed to evaluate the stability of the findings when excluding any single variant. As demonstrated in Fig. 4, our results remained consistent and did not show significant alterations when conducting the leave-one-out analysis.

3.4 Heterogeneity and pleiotropy analysis

As part of the MR analysis, we conducted MR heterogeneity and pleiotropy tests. The MR heterogeneity test was conducted to determine if there was any heterogeneity among the genetic instruments used in our study. The results indicated no significant heterogeneity among the instruments (Fig. 5), suggesting that they were suitable for use in MR analysis. The MR pleiotropy test was also performed to examine the possibility of pleiotropy, where a genetic variant influences multiple traits [3]. Similarly, the results did not reveal any significant pleiotropy in our genetic instruments (both $p > 0.05$), implying that any observed effects were likely due to the exposure of interest rather than other confounding factors. These tests play a crucial role in ensuring the validity of our MR analysis and reducing the possibility of biased estimates.

4. Discussion

The MR analysis conducted in this study did not provide evidence of a causal association between male infertility and COVID-19, suggesting that any potential associations observed in observational studies may be attributable to confounding or reverse causation. Nonetheless, it is essential to acknowledge some of the limitations of this study and conduct further research to confirm our findings and uncover

TABLE 3. Characteristics of included IVs in severe respiratory COVID-19 patients.

SNP	EA	OA	beta.E	beta.O	eaf.E	eaf.O	chr	pos	se.O	pval.O	se.E	pval.E	No.E	*F*
rs10860891	A	C	−0.24	−0.05	0.89	0.91	12	103024899	0.10	0.58	0.04	1.64×10^{-9}	1388342	36
rs111837807	C	T	0.29	−0.03	0.10	0.15	6	31121232	0.12	0.80	0.04	5.66×10^{-12}	1388342	53
rs13050728	C	T	−0.20	0.03	0.66	0.62	21	34615210	0.06	0.55	0.03	2.44×10^{-12}	1388342	44
rs2109069	A	G	0.26	−0.06	0.33	0.35	19	4719443	0.06	0.28	0.03	6.12×10^{-20}	1388342	75
rs2237698	T	C	0.24	−0.02	0.09	0.09	7	107607902	0.10	0.86	0.04	2.41×10^{-9}	1388342	36
rs2384074	T	C	0.20	0.00	0.68	0.73	12	113382977	0.06	0.98	0.03	2.10×10^{-12}	1388342	44
rs35081325	T	A	0.63	−0.03	0.08	0.08	3	45889921	0.10	0.74	0.04	5.75×10^{-45}	1388342	248
rs77534576	T	C	0.46	0.01	0.03	0.05	17	47940666	0.13	0.91	0.07	8.52×10^{-10}	1388342	43

Abbreviations: EA, effect alleles; OA, other alleles; E, exposures; O, outcomes; EAF, the effect allele frequency; No, sample size; chr, chromosome; pos, position; beta.E, beta value of exposure; beta.O, beta value of the outcome; eaf.O, EAF (the effect allele frequency) of the outcome; eaf.E, the EAF in our exposure; SNP, single nucleotide polymorphism; se.O, the standard error in the outcome; pval.O, the p-value in an outcome; se.E, the standard error in the exposure; pval.E, the p-value in the exposure; F, the values of F statistics; rs, the references SNPs.

potential underlying mechanisms.

SARS-CoV-2, which was first reported in December 2019 and rapidly spread worldwide, is responsible for causing COVID-19 [13]. The World Health Organization declared COVID-19 a global pandemic on 11 March 2020, due to its exceptional transmissibility [14]. While several hypotheses have been proposed to explain its pathogenesis, COVID-19 appears to affect men more severely than women [15].

Therefore, there has been increasing concern regarding the potential association between COVID-19 and male reproductive health [16]. Several recent studies have shown that while SARS-CoV-2 primarily targets the respiratory system, it may also cause damage to other systems in the body, including the male reproductive system [17, 18]. The virus enters human cells through angiotensin-converting enzyme II (ACE-2) receptors, which are present in many organs throughout the body, not just in the lungs [16]. Nevertheless, the exact mechanism through which the virus affects the male reproductive system requires further investigation.

Several studies have reported that COVID-19 can lead to a significant decrease in sperm count and motility, potentially resulting in male infertility [16, 17]. It was also reported that after a COVID-19 infection, sperm production may decrease, resulting in reduced male fertility for a period of 72 to 90 days [16]. One study found that Connexin 43 (Cx43) expression, both in terms of protein and mRNA levels, was reduced in azoospermia. Specifically, men with non-obstructive azoospermia showed a decline in Cx43 mRNA expression, and a correlation was observed between the severity of seminiferous tubule damage and the reduction in the number of Cx43 cells [17]. Thus, these findings suggested that Cx43 might play a crucial role in male fertility. Given the significant reduction in Cx43 expression observed in COVID-19 patients [17], Cx43 is thus considered an important factor linking COVID-19 infection to male fertility.

Recent evidence suggests that male patients, especially those who had severe cases and were hospitalized due to COVID-19, may experience a negative impact on their sexual function and fertility even after recovery [18]. Moreover, studies have shown that the virus can enter the testes [19–21], possibly due to an inflammatory response caused by the infection that disrupts the blood-testes barrier. Additionally, the concept of testicular immunological privilege and the presence of regulatory T cells may contribute to the virus's ability to persist in testicular tissue [22]. Recent studies have raised concerns about the potential for male genital tract infection, viral shedding in semen, and the need for reproductive therapies for COVID-19 patients [20] because the presence of SARS-CoV-2 in semen samples and autopsies of COVID-19 patients' testes have revealed congestion, interstitial edema, red blood cell exudation, T-lymphocyte, and macrophage infiltration, as well as elevated inflammatory responses in both the testis and epididymis. Additionally, elevated ACE-2 expression was observed in the Leydig cells of males who died of COVID-19 [23]. However, most fertility-related COVID-19 studies were performed in a small cohort of single-center and observational settings, making it difficult to draw widely applicable conclusions. Thus, more definitive investigations regarding this issue are yet to be provided by major follow-up studies [18].

Observational studies investigating the association between COVID-19 and male infertility have had several limitations, including potential confounding factors and reverse causation [9]. Other factors, such as age, comorbidities, and medication

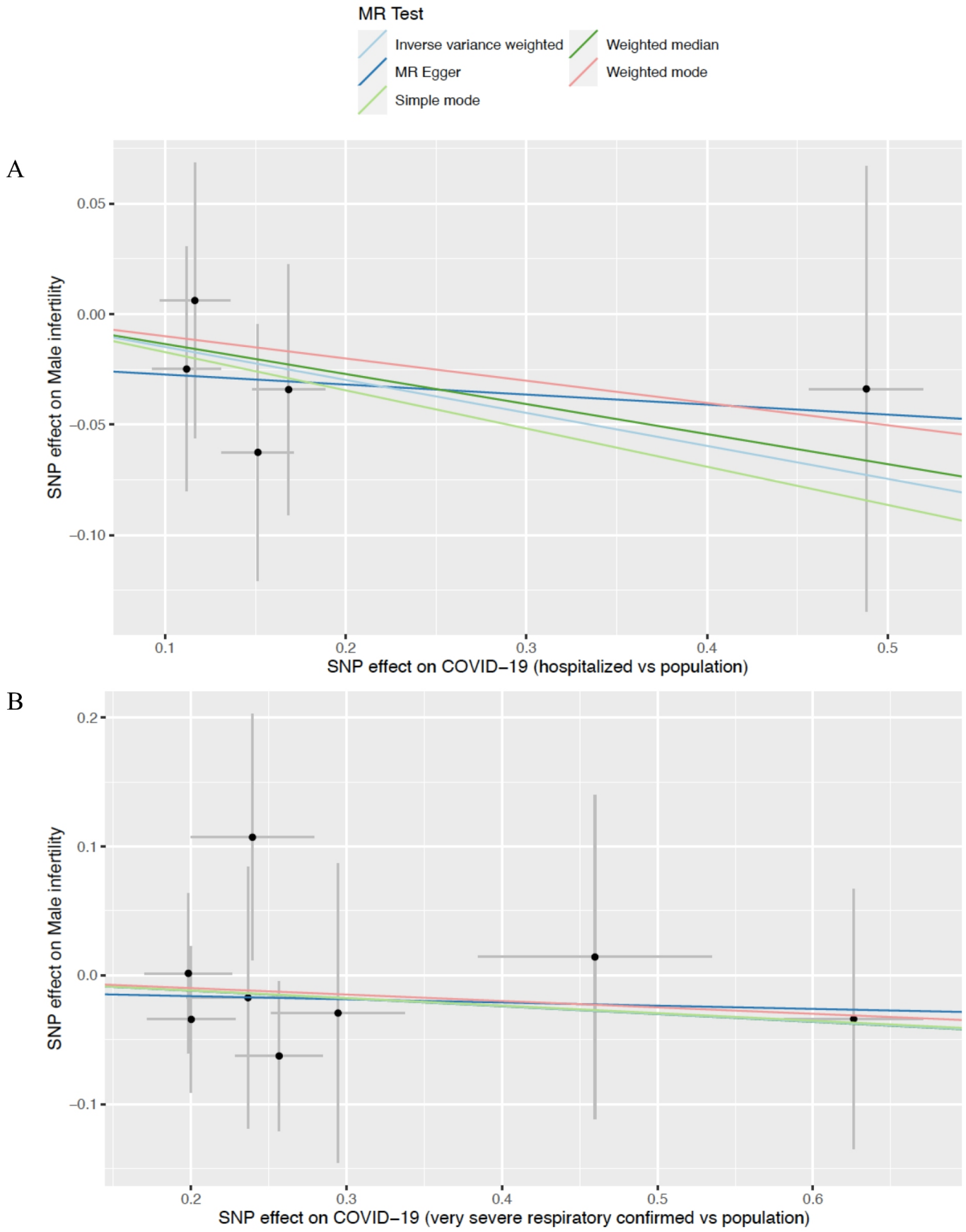

FIGURE 1. Scatter plot for the causal effect of COVID-19 on the risk of male infertility. (A) Scatter plot for the causal effect of hospitalized COVID-19 patients on the risk of male infertility, and (B) scatter plot for the causal effect of severe COVID-19 patients on the risk of male infertility. MR, Mendelian randomization; SNP, single nucleotide polymorphism.

use, may confound the observed association between COVID-19 and male infertility [8]. Furthermore, reverse causation can occur, where infertility or poor semen quality increases the risk of COVID-19 infection rather than COVID-19 infection causing infertility [18]. Therefore, cautious interpretations of these observational findings are important, and further research is necessary to confirm any observed associations and explore potential causal mechanisms. Mendelian randomization (MR) analysis is a valuable tool to establish a causal relationship between COVID-19 and male infertility, overcoming some limitations of observational studies [11].

The clinical implications of our findings suggest that there may not be a direct causal relationship between COVID-19 and male infertility, and healthcare professionals should be careful when interpreting the findings of observational studies reporting an association between COVID-19 and male infertility. Comparatively, our study emphasizes the importance of considering potential confounding factors when investigating the relationship between COVID-19 and male infertility, and the findings may assist in guiding clinical decision-making and reduce concerns regarding the potential impact of COVID-19 on male reproductive health. However, additional research is necessary to validate our results and clarify the mechanisms underlying any observed associations.

There are several limitations in this study that should be considered when interpreting the results. Firstly, since we relied on summary-level data and didn't have access to individual-level data, our ability to control for possible confounders and investigate potential causal pathways in more depth was limited. Secondly, our analysis assumed that the instrumental variables were valid and free of pleiotropy, which may not always be accurate. Thirdly, our study only explored the potential causal impact of COVID-19 on male infertility and did not examine the potential causal effects of male infertility on COVID-19 susceptibility or severity. Moreover, we did not evaluate the acceptable probability of mutation as one of our SNP inclusion criteria, which could potentially influence our conclusions. Importantly, since genetic characteristics differ among different ethnic groups [24], our conclusions apply solely to European populations. Therefore, careful considerations should be made when extrapolating the findings to other populations. In terms of future directions, further research is essential to confirm our findings and investigate potential causal pathways in greater detail [25], which could involve larger-scale MR analyses with more robust instrumental variables and the integration of individual-level data. Furthermore, it is necessary to investigate the possible mechanisms linking COVID-19 and male infertility, such as the influence of SARS-CoV-2 on the male reproductive system and systemic inflammation. Finally, future research could also examine the

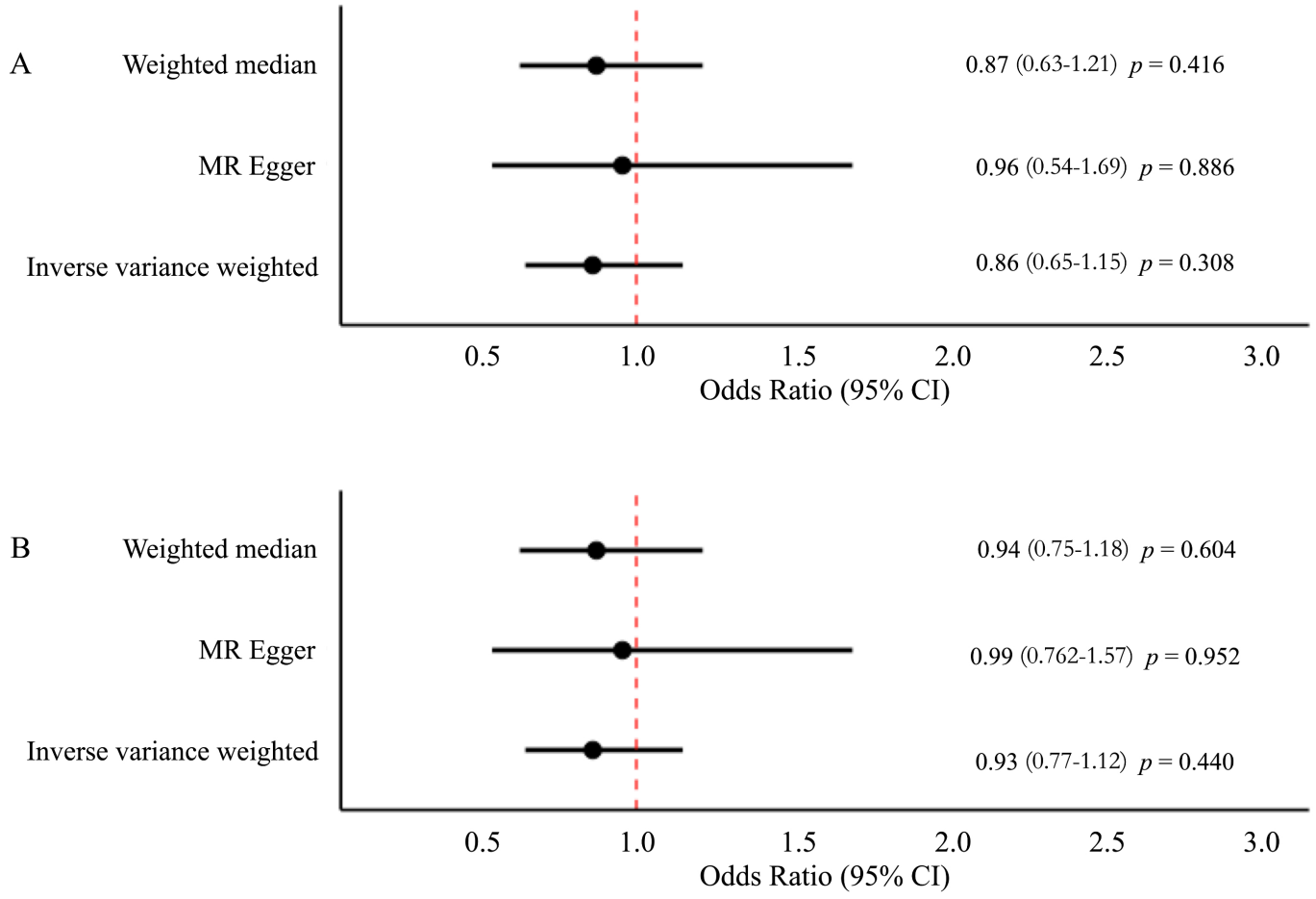

FIGURE 2. MR analysis for the causal effect of COVID-19 on male infertility. (A) MR analysis for the causal effect of COVID-19 on male infertility in hospitalized patients and (B) MR analysis for the causal effect of severe COVID-19 on male infertility. MR, Mendelian randomization; CI, confidence interval.

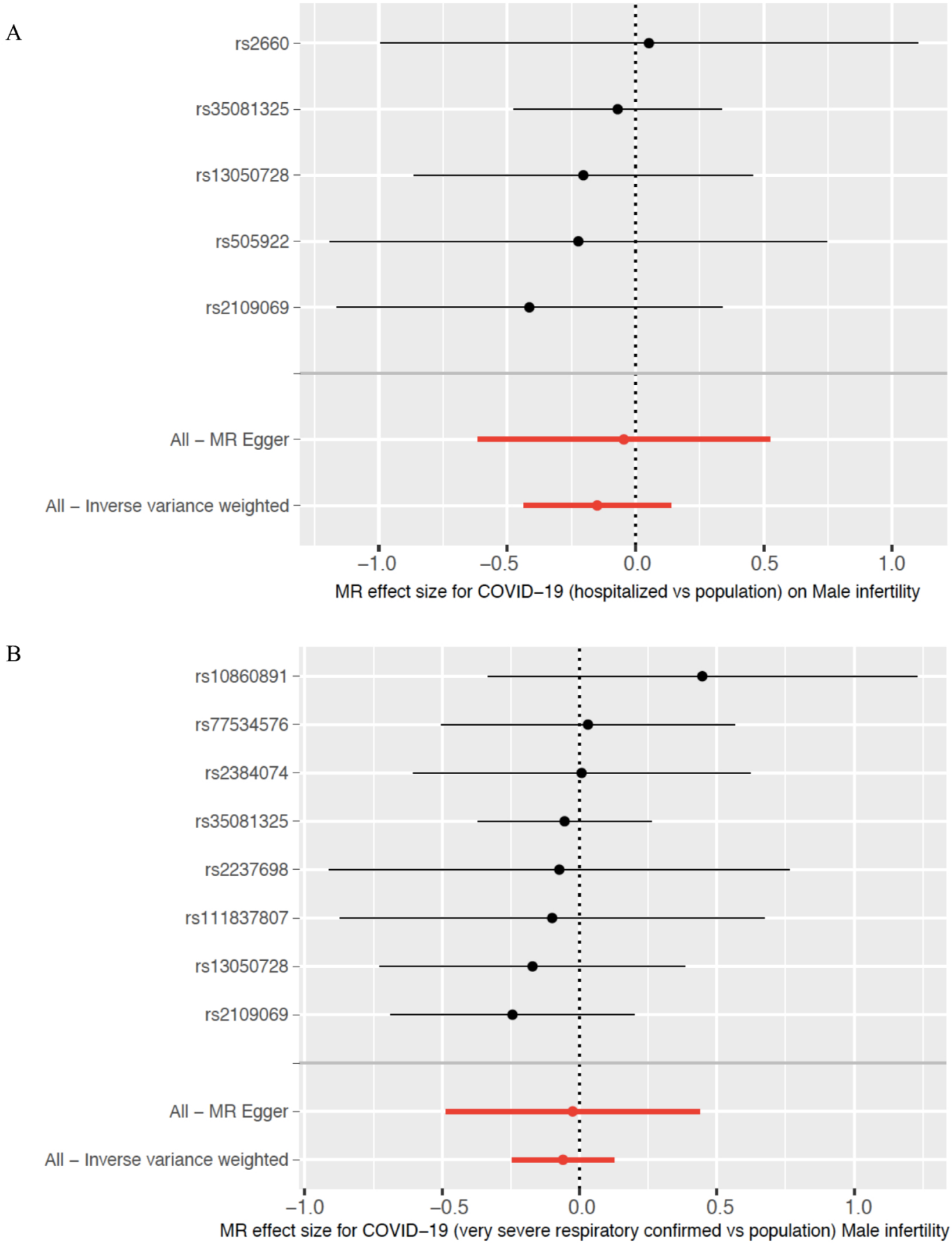

FIGURE 3. Forest plot for the causal effect of COVID-19 on the risk of male infertility. (A) Scatter plot for the causal effect of COVID-19 on the risk of male infertility in hospitalized patients, and (B) scatter plot for the causal effect of severe COVID-19 on the risk of male infertility. MR, Mendelian randomization.

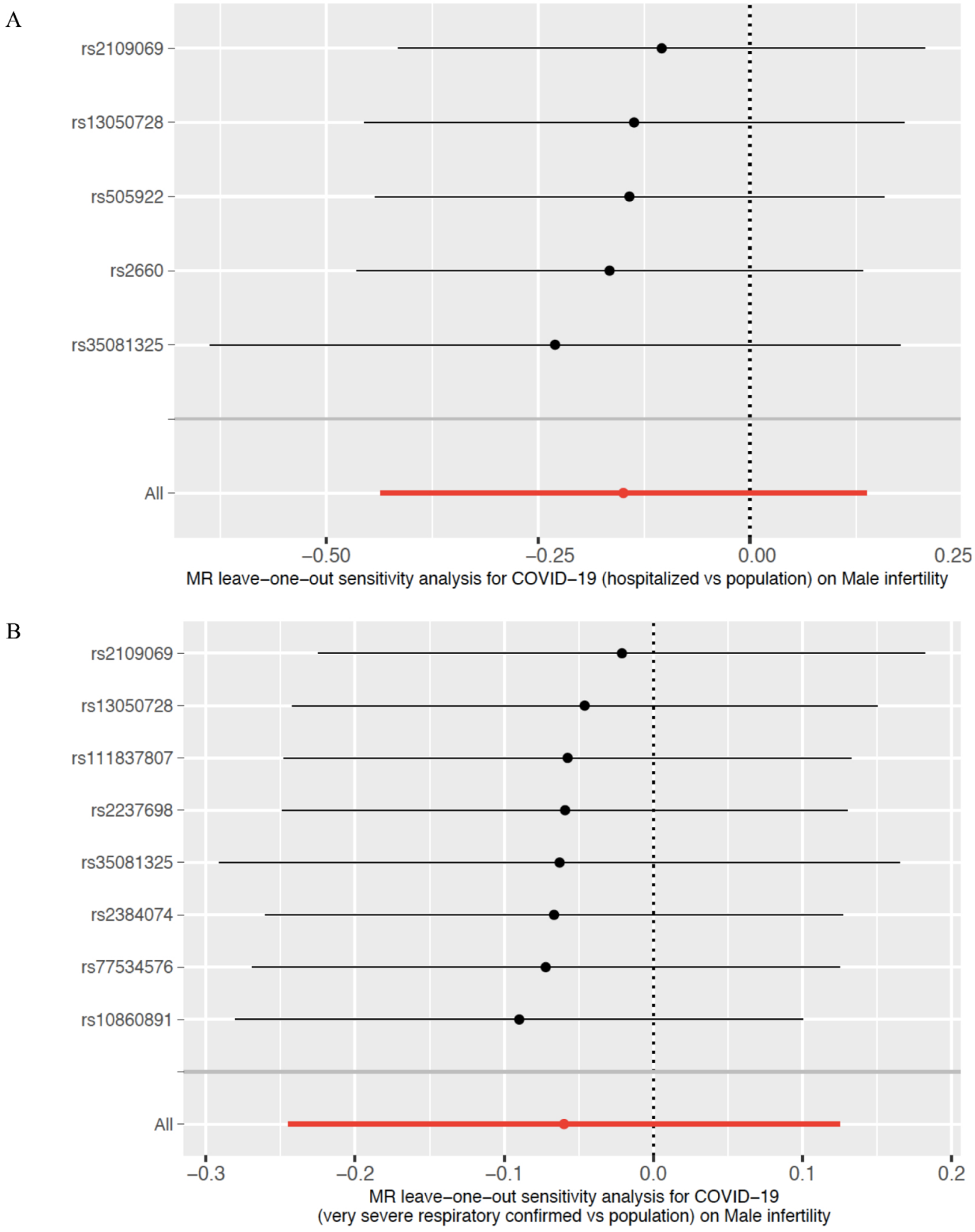

FIGURE 4. Leave-one-out plot for the causal effect of COVID-19 on male infertility. (A) Scatter plot for the causal effect of COVID-19 on the risk of male infertility in hospitalized patients, and (B) scatter plot for the causal effect of severe COVID-19 on the risk of male infertility. MR, Mendelian randomization.

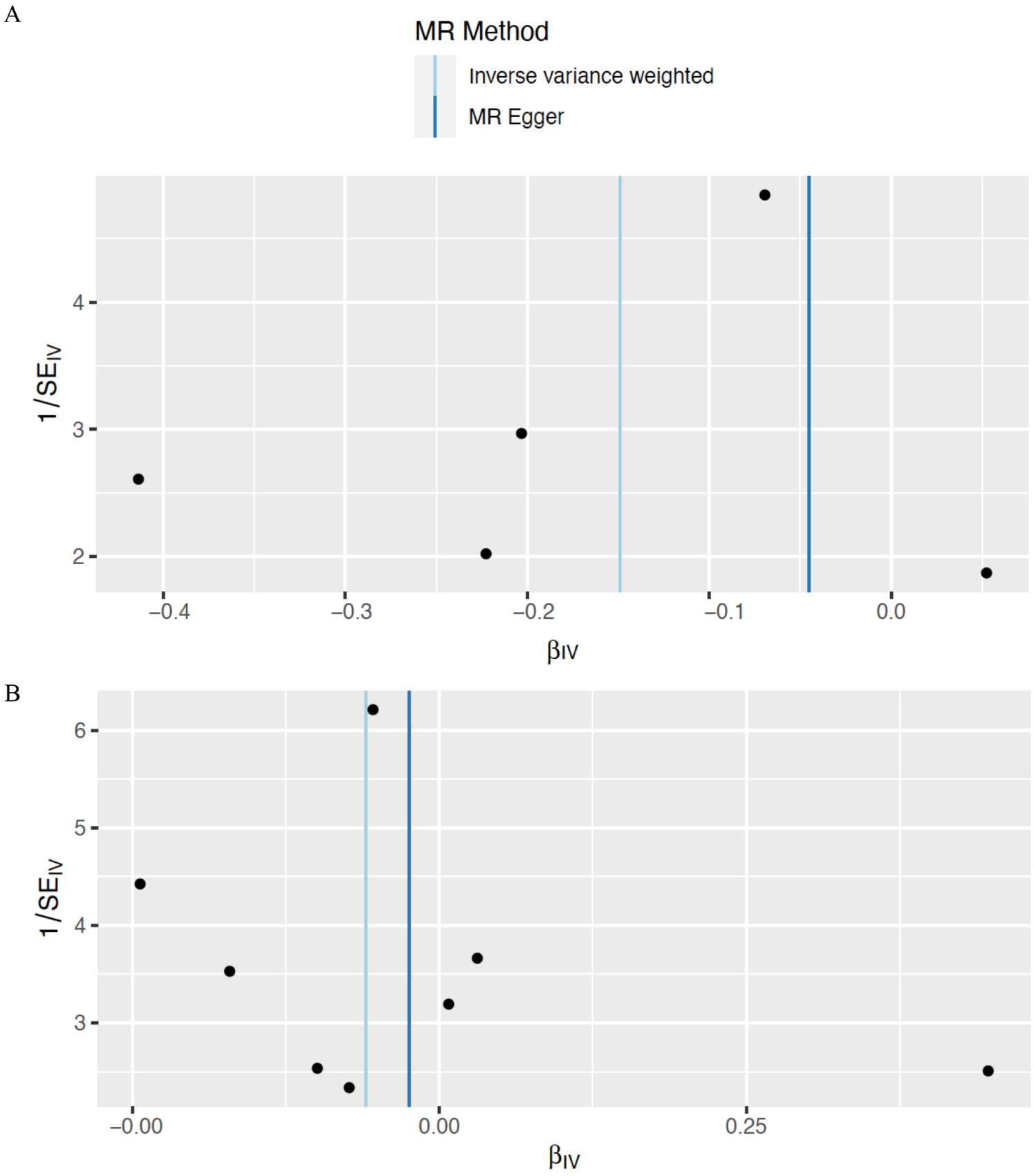

FIGURE 5. Funnel plot for the causal effect of COVID-19 on the risk of male infertility. (A) Scatter plot for the causal effect of COVID-19 on the risk of male infertility in hospitalized patients, and (B) scatter plot for the causal effect of severe COVID-19 on the risk of male infertility. MR, Mendelian randomization; SE_{IV}, the standard error of inverse-variance weighted analysis.

potential long-term effects of COVID-19 on male reproductive health, including fertility outcomes and other reproductive disorders, while accounting for the differences in different populations and ethnicities.

The two-sample MR analysis conducted did not reveal any evidence of a causal relationship between COVID-19 and male infertility. While observational studies have indicated a possible connection, our study implies that such findings may be the result of confounding or reverse causation. Nevertheless, our study has its limitations, including the potential for pleiotropy and the use of imperfect genetic instruments. Further investigation is required to verify these findings and elucidate the mechanisms underlying any observed associations. These results have important implications for the management of COVID-19 patients and the long-term effects of the illness on male reproductive health, underscoring the need for additional research to enhance our understanding of the potential link between COVID-19 and male infertility.

5. Conclusions

This study revealed no evidence of a causal association between COVID-19 (including both hospitalized and severe cases) and male infertility. However, more studies are needed to validate these results.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

QL and BY—designed the research study and wrote the manuscript. XHW and YHC—performed the research and analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Shandong Public Health Clinical Center (No. SPHCC EC-2023-04-03) and conformed to the standards set by the latest revision of the Declaration of Helsinki. Written informed consent was obtained from all study participants in their original study.

ACKNOWLEDGMENT

Union of Researchers (WeChat Subscription) should be acknowledged because we have learned the analysis methods in their WeChat Subscription. We also acknowledged Jiang-Shan Tan in Fuwai Hospital and the reviewers who helped us improve our manuscript.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Qian Liu, Yuehong Cui, Xiaohua Wang, Bo Yang. Genetic association between COVID-19 and male infertility: a two-sample Mendelian randomization analysis. Journal of Men's Health. 2024; 20(1): 62-72. doi: 10.22514/jomh.2024.009.