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Original Article

Effects of COVID-19 on the cardiovascular system: A mendelian randomization study

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ABSTRACT

Infections with the coronavirus disease 2019 (COVID-19) and disorders of the heart and blood vessels are causally related. To ascertain the causal relationship between COVID-19 and cardiovascular disease (CVD), we carried out a Mendelian randomization (MR) study through a method known as inverse variance weighting (IVW). When analyzing multiple SNPs, MR can meta-aggregate the effects of multiple loci by using IVW meta-pooling method. The weighted median (WM) is the median of the distribution function obtained by ranking all individual SNP effect values according to their weights. WM yields robust estimates when at least 50% of the information originates from valid instrumental variables (IVs). Directed gene pleiotropy in the included IVs is permitted because MR–Egger does not require a regression straight line through the origin. For MR estimation, IVW, WM and MR-Egger were employed. Sensitivity analysis was conducted using funnel plots, Cochran's *Q* test, MR–Egger intercept test, MR–PRESSO, and leave-one-out analysis. SNPs related to exposure to COVID-19 and CVD were compiled. CVD for COVID-19 infection, COVID-19 laboratory/self-reported negative, and other very severe respiratory diagnosis and population were randomly assigned using MR. The COVID-19 laboratory/self-reported negative results and other very severe respiratory confirmed cases versus MR analysis of CVD in the population ($p > 0.05$); COVID-19 infection to CVD ($p = 0.033$, $OR = 1.001$, 95%*CI*: 1.000–1.001); and the MR–Egger results indicated that COVID-19 infection was associated with CVD risk. This MR study provides preliminary evidence for the validity of the causal link between COVID-19 infection and CVD.

1. Introduction

The World Health Organization (WHO) dubbed the novel coronavirus pneumonia (CoronaVirus Disease 2019, COVID-19), "Coronavirus Disease 2019," the cause of the COVID-19 pandemic, and it had an unprecedented effect worldwide.[1] COVID-19 is a communicable illness that is brought on by the SARS-CoV-2 virus and is responsible for 19% of infectious disease-related deaths among individuals aged younger than 70 years.[2] According to two WHO statistics, COVID-19 or its complications claimed the lives of 14.9 million people between 2020 and 2021 and severely affected people's health and quality of life.[3] Cardiovascular diseases (CVDs) accounted for one-third of all deaths worldwide in 2019. CVDs are circulatory diseases that affect the heart and blood arteries.[4] As a consequence of population aging, population growth, and changes in disease epidemiology, CVDs have evolved into one of the most significant social health burdens. Risk factors, such as diabetes, hypertension, dyslipidemia, and others, contribute to the increased incidence and mortality of CVDs.[5] We aim to investigate the consequences of these disorders and the resulting medical costs.[6]

The pathological causes of COVID-19 infection can affect the cardiovascular system as well as cause myocardial injury, myocardial infarction, arrhythmia, and heart failure.[7,8] These processes involve systemic inflammation (cytokine storm), coagulation dysfunction, hypoxemia, endothelial injury, fever, and electrolyte imbalance.[9] Individuals have been less likely to exercise because of the rapid and widespread spread of COVID-19, and they have substantial body mass indices and negative emotions, such as depression and worry about the pandemic. Both variables can exacerbate heart-related symptoms, such as palpitations, shortness of breath, and chest pain.[10] Cardiovascular physicians

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List of abbreviations:

COVID-19	CoronaVirus Disease 2019
CVDs	Cardiovascular diseases
CMR	cardiac magnetic resonance imaging
MR	Mendelian randomization
SNPs	single nucleotide polymorphisms
IVs	instrumental variables
MR-PRESSO	Mendelian Random Pleiotropic Residuals and Outliers

need to standardize the evaluation and treatment of heart problems and symptoms after coronavirus infection. Inflammation, intraluminal megakaryocytes, macrovascular and microvascular thrombosis, and other pathological abnormalities were found in 47.8% of 277 patients who died from COVID-19 infection.[11] The results of an endocardial myocardial biopsy in conjunction with cardiac magnetic resonance imaging (CMR) showed that 97 (0.2%) of 56 963 hospitalized patients with COVID-19 infection encountered myocarditis; of which, 54 (55.7%) had a proper diagnosis of myocarditis.[12] Whether the memoir coronavirus can infect cardiomyocytes and cause CVD, such as myocarditis, remains controversial.

Although the causal relationship between COVID-19 infection and CVD is unclear, the two conditions are closely related. The correlation between COVID-19 infection and CVD is generally supported by current research and pertinent observational studies.[13] However, whether reverse causality bias or common multicausal factors alone account for the association between COVID-19 infection and CVD risk remains unclear because of the inherent limitations of clinical observational studies. Furthermore, conducting randomized controlled trials on this subject is labor intensive and time-consuming. In contrast to observational studies, Mendelian randomization (MR) studies use genetic variation in exposure, such as single nucleotide polymorphisms (SNPs), as instrumental variables (IVs) to evaluate the causal relationship between exposure and outcome and minimize the possibility of confounding and reverse causality. MR is a reasonably accurate epidemiological strategy that reduces the repercussions of reverse causality and possible confounding. Meiosis-based random classification of genetic variants forms the basis of molecular recognition (MR) by using exposure-associated genetic variants as IVs to infer associations between risk factors (COVID-19 infection) and disease outcomes (e.g., CVD).[14] MR analysis can prevent confounding factors, reverse causality, and identify causal determinants of particular outcomes because of the random assignment of genetic variants prior to the onset of disease.[15] The present research aims to use two-sample MR analysis to examine the connection between COVID-19 infection and CVD.

2. Materials and methods

2.1. Study design

Two-sample MR analysis was performed to assess the causal relationship between the risk of COVID-19 infection and CVD. MR analysis relies on inverse variance weighting to estimate causal effects between exposure and outcome. The fundamental concept of MR analysis involves determining if a causal relationship exists by leveraging genetic variants associated with the exposure and outcome as IVs. In this study, COVID-19 infection was considered the exposure factor, SNPs significantly linked to COVID-19 infection were utilized as IVs, and CVD was the outcome. The MR study adhered to three key hypotheses: the correlation hypothesis, the independence hypothesis, and the exclusion restriction hypothesis, as illustrated in Fig. 1.[16,17]

2.2. Research environment

Two independent researchers collected data at the China Academy of Chinese Medical Sciences (Beijing Campus). One researcher downloaded relevant information, including exposure and outcome factors, from the GWAS database, while the other researcher compiled exposure and outcome data by using RStudio software. Study participants were

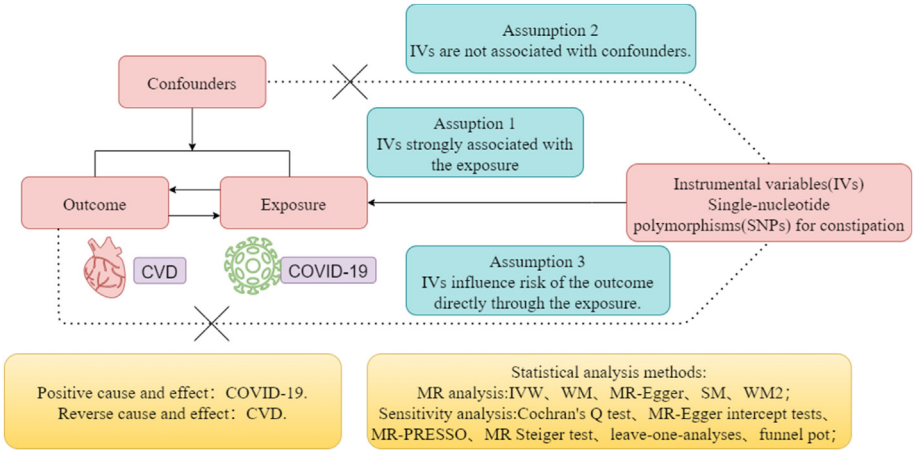

Fig. 1. Graphical representation of the three main hypotheses of Mendelian randomization studies
Note: MR, Mendelian randomization. IVW, inverse variance-weighted. WM, weighted median.MR-Egger, MR-Egger regression.SM, simple mode. WM2, weighted mode.

Table 1
A summary of the data for Mendelian randomization analysis.

Phenotype	Dataset	Year	Population	Sample size	Number of SNPs	PMID
COVID-19	ebi-a-GCST010776	2020	European	1 299 010	11 435 708	32404885
COVID-19 (covid vs lab/self-reported negative)	ebi-a-GCST010778	2020	European	110 624	12 832 272	32404885
Cardiovascular disease	ukb-d-I9_K_CARDIAC	2020	European	361 194	10 071 648	34594039

sourced from various European locations including electoral rolls, outpatient registries, cancer registries, and tertiary care centers. Data were collected on October 1, 2023, and statistical data were compiled on December 1, 2023. The study concluded on January 31, 2024. The two researchers conducted their respective tasks in separate locations to ensure full compliance with the STROBE-MR guidelines.

2.3. Data sources

Exposome data (COVID-19 infection, COVID-19 laboratory/self-reported negativity) were collected from the IEU Open GWAS database. All relevant ethnicities were from Europe.[18]

Outcome variable data (CVD) and Summary-grade GWAS data related to CVD were obtained from IEU Open GWAS with all participants from Europe,[19] as detailed in Table 1.

2.4. Selection and evaluation of IVs

We extracted SNPs that were significantly correlated with exposed variables from the IEU Open GWAS database as IVs with a screening condition of $p < 5 \times 10^{-8}$ (minimum screening criteria of $p < 5 \times 10^{-6}$). To ensure independence between IVs, we set the parameters of $r^2 < 0.01$ and $kb = 1\ 000$ to exclude those IVs with linkage imbalance (LD). If the number of SNPs screened is insufficient, then we relax the parameters to $p < 5 \times 10^{-6}$. In addition, SNPs with palindromic structures are excluded by correcting for inexpensive and resulting data. The *F*-score for each SNP ($F = \beta^2_{\text{exposure}}/SE^2_{\text{exposure}}$) was used to estimate the likelihood of weak instrumental bias. Table 1 provides a detailed overview of these IVs.[20]

2.5. MR analysis

In this study, five methods including inverse variance-weighted (IVW), weighted median, MR-Egger regression, weighted mode, and simple mode were used to calculate the causal relationship among COVID-19, COVID-19 (COVID vs. lab/self-reported negative) and CVD. In Mendelian random analysis, inverse variance-weighting method based on genotype data pools was used as the main method. The Wald estimates of each single-nucleotide polymorphism were combined by meta-analysis to obtain the overall estimate. The regression slope of the weighted slope of the resulting effect to the exposure effect was representative of the outcome estimate (with zero intercept limit).[21–23] The weighted median method requires at least 50% of the weights to come from valid IVs; this method is best in the presence of heterogeneity but has no transverse multidimensionality.[24] MR–Egger regression allows for multidimensionality of all single-nucleotide polymorphisms and can detect horizontal heterogeneity by intercept test and obtain estimates after adjusting for pleotropy.[25] Simple and weighted model methods can be used as additional MR methods and should be used in conjunction with other methods in the sensitivity analysis framework by using several methods with different assumptions rather than a single method as an effective strategy to ensure the robustness of the assessment results.[26] A causal relationship is considered to exist if the IVW results of the main method are significant ($p < 0.05$) and the results of the other methods are in the same direction as the IVW method.

2.6. Sensitivity analysis

Various quality control methods were employed to test the stability and reliability of the MR results. Cochran's *Q* test was used to assess the heterogeneity of individual estimates of genetic variation. If $p < 0.05$ of the Cochran's *Q* test indicates heterogeneity between SNPs, then a final MR analysis is performed and a random-effects model with inverse variance weighting is deemed necessary.[27] Second, an MR–Egger intercept horizontal polymorphism test is performed, and a *p* value greater than 0.05 of the intercept indicates the absence of horizontal polymorphisms to identify potential polymorphisms.[28] Third, MR Pleiotropic Residuals and Outliers (MR-PRESSO) were used to search for outliers in the consequence and were excluded from the analysis. Fourth, Leave-one-out sensitivity test is mainly used to calculate the MR results of the remaining IVs after the elimination of IVs one by one; if the estimated MR results of other IVs after the elimination of one instrumental variable are very different from the total results, then the MR results are sensitive to the IVs.[29]

2.7. Use SNPs to map core genes

SNP polymorphisms are variations in the genome and are one of the common forms of genetic variation. It is related to SNP differences that exist between individuals in the genome, including the displacement, insertion, or deletion of individual bases.[30] SNPs are commonly used to study genetic differences between people and genomic variants associated with diseases. We screened and retained SNPs that intersected with CVD in the presence of exposure to COVID-19 infection.

This study used R (version 4.3.1) and dual-sample MR (version 0.5.7 and MR-PRESSO software package (version 1.0.0), with a testing level of $\alpha = 0.05$. The results were analyzed using the MR-PRESSO package (version 1.0.0).

3. Results

3.1. Characteristics of the selected SNP

COVID-19 infection was included in the IV of 20 SNPs as an exposure factor, with *F* statistics ranging from 20.936 to 115.126. The *F*-statistic of each included SNP was greater than the empirical threshold of 10, and instrumental variables are strongly correlated with the exposure, thereby avoiding bias in the results caused by weak instrumental variables. As shown in the supplementary material, all SNPs independently confirmed linkage disequilibrium with genome-wide statistics ($p < 5 \times 10^{-6}$). The IV information on the inclusion of COVID-19 infection as an exposure factor in the 20 SNPs is shown in Table 2.

3.2. Estimates of the causal relationship between genetic predisposition and CVD risk

The statistical results of MR analysis are shown in Table 2. Using a random-effects IVW approach, we found that genetic susceptibility to COVID-19 infection was associated with an increased risk of CVD. The incidence of CVD in patients with COVID-19 is 1.001 times that of the control group (COVID-19 infection to CVD, $p = 0.033$, $OR = 1.001$, 95% *CI*: 1.000–1.001. The robustness of the study was supported by consistent results from the weighted median analysis, MR-Egger regression analysis, weighted pattern analysis, and simple pattern analysis as well as the MR-PRESSO method to identify and handle outliers. Laboratory/self-reported negative was not significantly associated with an increased risk of CVD in the population ($p > 0.05$).

3.3. Sensitivity analysis of MR

First, in the test for heterogeneity, the *p*-value calculated by Cochran's *Q* statistic was less than 0.05, indicating heterogeneity between SNPs (Table 3). In the MR analysis, we used the IVW random-effects method as the primary analytical technique. At the same time, the MR–Egger regression intercept test did not show that COVID-19 infection was multidimensional in any CVD-related IV. In addition, the leave-one-out approach showed that the potential causal relationship between COVID-19 infection and CVD risk was not significantly affected by any single SNP (Fig. 2).

Table 2
SNP information shared by COVID-19-infected individuals with CVD.

number	*PE*	*BE*	*SE*	*SNP*	*EA*	*OA*	*EE*	*F*
1	156 450 719	−0.088 588	0.018 539	rs1185700	A	G	0.273 4	22.833 747 02
2	114 823 998	0.357 23	0.069 421	rs7535387	G	C	0.022 33	26.479 764 39
3	119 176 557	−0.118 02	0.025 793	rs72840835	T	C	0.118 4	20.936 665 01
4	166 368 788	−0.068 714	0.014 483	rs6756041	T	C	0.466 7	22.509 891 4
5	45 839 176	0.225 99	0.034 043	rs73062394	T	A	0.053 39	44.067 944 59
6	45 899 651	0.277 17	0.025 832	rs34326463	G	A	0.083 26	115.126 785 7
7	31 121 232	0.131 91	0.025 594	rs111837807	C	T	0.092 05	26.563 121 54
8	43 199 730	0.119 58	0.025 816	rs114371775	C	T	0.117 1	21.455 527 35
9	107 607 902	0.118 21	0.025 283	rs2237698	T	C	0.099	21.860 053 74
10	122 832 148	−0.067 123	0.014 662	rs10087754	A	T	0.580 4	20.958 311 31
11	136 149 229	0.091 995	0.015 08	rs505922	C	T	0.343 5	37.215 663 35
12	16 874 940	0.257 3	0.055 849	rs116865546	A	T	0.018 04	21.225 052 34
13	113 362 997	0.072 505	0.015 172	rs4766664	G	T	0.672 7	22.837 588 62
14	30 401 179	−0.180 62	0.039 357	rs2761929	A	C	0.081 06	21.061 422 6
15	89 262 657	0.094 01	0.020 14	rs117169628	A	G	0.151 3	21.788 592 32
16	20 925 377	0.086 466	0.017 209	rs8096771	C	T	0.674 3	25.245 237 92
17	4 723 670	0.096 506	0.016 826	rs2277732	A	C	0.316 5	32.896 285 44
18	456 473	0.085 752	0.016 065	rs157807	G	A	0.359 1	28.492 270 32
19	34 611 571	0.092 53	0.016 098	rs12482060	G	C	0.338	33.038 572 79
20	44 089 340	0.255 79	0.053 471	rs73174327	A	G	0.030 06	22.883 924 77

Note: PE, pos. Exposure; BE, beta. Exposure; SE, se. Exposure; EA, effect_allele. Exposure; OA, other_allele. Exposure; EE, eaf. Exposure.

Table 3
Pleiotropy and Heterogeneity test of the COVID-19 IVs from CVD GWAS.

Outcomes	Heterogeneity test						Pleiotropy test			MR-PRESSO global pleiotropy test	
	MR-Egger			IVW			MR-Egger			*p*-Value	Outliers
	Q	*Q df*	*Q pval*	*Q*	*Q df*	*Q pval*	Intercept	*SE*	*p*		
COVID-19	18.85	17	0.33	20.84	18	0.28	1.59e-04	1.18 e−04	0.19	0.206	none

Note:MR, Mendelian randomization. *Q*, Cochran's *Q* test.

4. Discussions

This study uses five MR methods (IVW, MR-Egger, WM, horizontal pleiotropy test, and Cochran's *Q* test for heterogeneity) to investigate the association between CVD and COVID-19 infection and COVID-19 laboratory/self-report negative. According to the MR results, a positive association was found between COVID-19 infection and CVD. This finding suggests that COVID-19 infection, as a risk factor, may contribute to the development of CVD.[31] According to a meta-analysis, patients infected with the novel coronavirus had a 22.3% incidence of myocardial injury. Patients with myocardial injury have an 8.21-fold increased risk of fatal events, and myocardial injury is directly linked to increased disease severity and risk of mortality.[32] Patients infected with the novel coronavirus prospective cohort studies may have an imbalance between the oxygen supply and demand in their hearts due to fever, hypoxia, tachycardia, and sympathetic hyperexcitability; in severe cases, it can result in myocardial infarction.[33] Instances of acute coronary artery syndrome with normal or near-normal coronary arteries are more common during the epidemic period than they are during the non-epidemic period. Additionally, 50%–60% of patients who suffer myocardial injury do not have severe coronary artery stenosis, a condition that some academics refer to as acute novel coronavirus infection–cardiovascular syndrome.[34] The potential mechanisms are (1) anemia, hyperthermia, tachyarrhythmia, severe hypoxemia, respiratory failure, shock, or hypotension as a result of myocardial injury caused by an imbalance in the oxygen supply and demand in the heart.[35] (2) Right ventricular dysfunction and elevated right ventricular afterload can be due to positive pressure mechanical ventilation and acute respiratory distress syndrome.[36] (3) Microthrombosis in cardiac tissues is caused by an abundance of cytokines and inflammatory factors released by histiocytes and inflammatory cells. Table 4 lists the common cardiac and non-cardiac causes of myocardial injury and acute cardiovascular events in patients infected with COVID-19.[37]

In a U.S. study, 153 760 patients infected with the novel coronavirus showed that within the first 12 months following infection, the risk of composite endpoint events, including myocardial infarction, stroke, and all-cause death, increased by 55%. Additionally, the burden of cardiovascular events per 1 000 people increased by 23.48%, including 63% increase in the risk of myocardial infarction, 2.91% increase in the burden of myocardial infarction, 52% increase in the risk of stroke, 4.03 cases of stroke per 1 000 people, and 72% increase in the risk of heart failure. Even in cases without underlying cardiovascular disease prior to infection, the cardiovascular risk of COVID-19 patients increased significantly. The increase included an increase in the risk of pulmonary embolism of 193%, an increase in the burden of pulmonary embolism of 5.47 cases per 1 000 people, an increase in the risk of cardiac arrest of 145%, an increase in the burden of cardiac arrest per 1 000 people, and an increase in the risk of atrial fibrillation of 71%.[38] A study conducted in UK biobanks from 16 March to November 30, 2020 involving 7 584 COVID-19 patients, 75 790 contemporaneous normal controls, and 75 774 historically normal controls revealed that patients with COVID-19 had a significantly higher risk of all-cause mortality (HR 5.0 and 4.5, respectively) and of developing CVD (compared with contemporaneous and historically normal controls, HR 1.4 and 1.3).[39] These investigations suggest a potential positive correlation between COVID-19 and CVD; however, prior research had small sample sizes, shaky correlations, ambiguous causal relationships, and no solid evidence. Consequently, this study used MR analysis to strengthen the associations that were found. By using IVs, this approach enables a trustworthy evaluation of causality. By utilizing genetic data, additional causal links between COVID-19 and CVD can be established and possible confounders can be minimized.

This study offers several noteworthy benefits. This study is the first to use MR to ascertain CVD outcomes in COVID-19 infection exposure. Additionally, the study makes use of the largest set of publicly available GWAS data to date. Furthermore, by replicating the MR results in a sizable cohort, the genes in the GWAS cohort must also achieve significance under the predetermined conditions. This finding verifies the

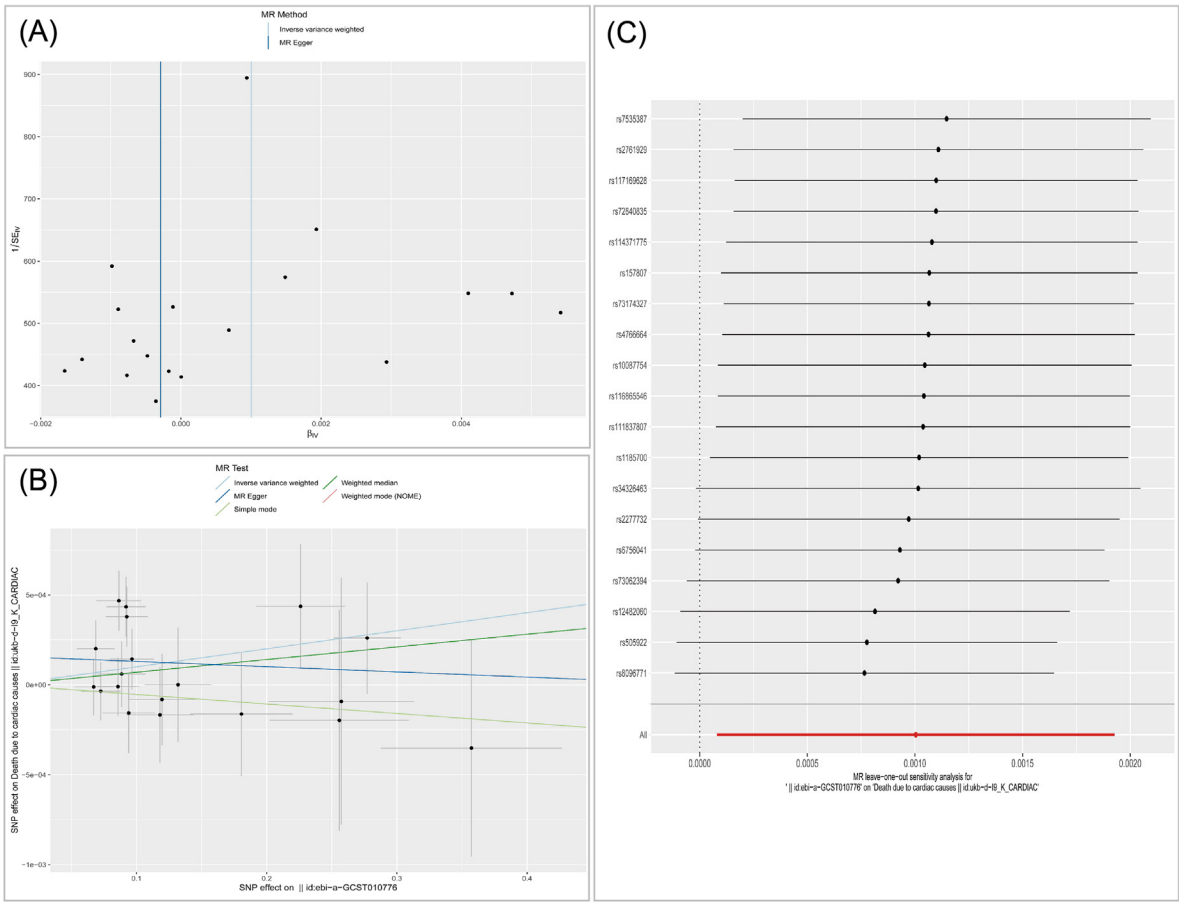

Fig. 2. Scatterplot of Mendelian randomization between COVID-19 and CVD, leave-one-out method, and resultant plots.

Table 4
Common causes of acute cardiovascular events and myocardial injury in patients infected with the novel coronavirus.

Project	Specific causes
Cardiac causes	(1) Type 1 myocardial infarction (including STEMI and NSTEMI); (2) Type 2 myocardial infarction (coronary artery spasm, coronary embolism, spontaneous coronary artery dissection); (3) Acute myocardial injury (direct injury from novel coronavirus and indirect injury from other diseases); (4) Acute coronary syndrome with normal coronary arteries; (5) myocarditis; (6) coronary arteritis; (7) acute heart failure; (8) Acute arrhythmia;
Non-cardiac causes	(1) pulmonary embolism; (2) critical illness; (3) hypoxemia; (4) sepsis; (5) shock; (6) anemia; (7) kidney disease;

Note: STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction;

robustness of the results and significantly decreases the possibility of false positives, thereby increasing the likelihood that clinical trials will be successful.

5. Limitations

Although the results of this study strongly demonstrate a positive correlation between COVID-19 infection and CVD, some limitations should be considered. (1) COVID-19 infection is a complex pathological process that can be influenced by a variety of factors, including age, gender, nutritional status, and physical activity level. Further studies should consider these factors and comprehensively analyze their interactions with CVD. (2) This study identified a causal relationship between COVID-19 infection and CVD, which requires further in-depth studies on the physiological and biochemical mechanisms of COVID-19 infection and CVD. (3) The study cohort had diverse effects because the cohorts of COVID-19 infection and CVD included in the GAWS analysis were made up of Europeans of non-European ancestry. Given differences in genetic background and linkage disequilibrium patterns, such differences in cohort backgrounds may potentially bias MR effect estimates. (4) Participants in this study were all Europeans, and the effect on other racial groups can be very different. (5) The quality of MR is ensured by addressing issues, such as gene-environment interaction, inadequate phenotype definition, time-varying exposures, measurement errors, and possibility of reverse causation, to ensure the quality of MR.

6. Conclusion

This study found a positive causal relationship between COVID-19 infection and CVD. This work can help clinical research on the biological mechanism of this association, and provide medical evidence for exploring the mechanism of CVD caused by COVID-19 infection. Results provide a reference for focusing on cardiac quality and function after COVID-19 infection.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: (i) IEU Open GWAS project (https://gwas.mrcieu.ac.uk/).

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Submission statement

This manuscript is an original work that has not been previously published, nor will it be under consideration for publication by any other journal before a decision has been made by Sports Medicine and Health Science. If accepted, this manuscript will not be published elsewhere. All authors have read and agree with manuscript content.

Ethical approval statement

The data used in this study were obtained from the GWAS public database and did not involve human experimentation or animal manipulation.

CRediT authorship contribution statement

Qingzhi Ran: Writing – review & editing, Writing – original draft, Software, Methodology, Data curation, Conceptualization. **Aoshuang Li:** Formal analysis, Data curation. **Rui Li:** Investigation, Funding acquisition. **Yuyang Dong:** Project administration, Methodology. **Xue Xiao:** Software, Resources. **Kun Wang:** Validation, Supervision. **Hengwen Chen:** Writing – original draft, Visualization. **Benxiang He:** Writing – review & editing, Resources.

Conflict of interest

Benxiang He is an editorial board member for Sports Medicine and Health Science and was not involved in the editorial review or the decision to publish this article. Otherwise, authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smhs.2024.06.001.

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