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Mendelian randomization analysis establishes a causal relationship between COVID-19 and cardiometabolic diseases

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ABSTRACT

Objective: The causal impacts of COVID-19 on cardiometabolic diseases remained uncertain. This study utilized the two-sample Mendelian randomization (MR) method to evaluate causal relationships between COVID-19 (susceptibility and severity) and four primary cardiometabolic diseases (type 2 diabetes, coronary heart disease, ischemic stroke, and heart failure).

Methods: MR analysis was conducted using genome-wide association study (GWAS) results. Susceptibility and severity were defined as COVID-19-positive and COVID-19-hospitalization, respectively. Data from the COVID-19 Host Genetics Initiative were used for susceptibility and severity analysis. Consortium data from Spracklen CN, Nikpay, Malik R, and Neale lab were employed for type 2 diabetes, coronary heart disease, ischemic stroke, and heart failure, respectively.

Results: For COVID-19 susceptibility, the inverse variance weighted (IVW) method showed the odds ratio (OR) (95% confidence interval [CI], *P*-value) for type 2 diabetes was 1.719 (1.510–1.956, $P = 0.000$). For COVID-19 severity, the IVW method estimate indicated that the OR (95% CI, P-value) for ischemic stroke was 1.051 (1.008–1.095, $P = 0.020$). Moreover, the OR for heart failure was slightly higher in the hospitalized population than in the control population (1.001, 95% CI 1.000–1.002, $P = 0.010$). The remaining results were negative.

Conclusion: This MR study establishes that genetically predicted COVID-19 susceptibility causally increases type 2 diabetes risk, while severe infection shows suggestive causal links with ischemic stroke and heart failure, redefining COVID-19 as an independent cardiometabolic risk factor.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to significant morbidity and mortality, as well as widespread social and economic disruptions.[1] Individuals with cardiometabolic diseases such as obesity, diabetes, atherosclerotic cardiovascular disease, hypertension, and heart failure, were at higher risk of COVID-19-related complications.[2] In the USA, an estimated 63.5% of severity was attributable to hypertension, diabetes mellitus, obesity, and heart failure.[3]

Meanwhile, the relationship between COVID-19 and cardiometabolic health might not be a one-way street. The pandemic itself had a significant deleterious impact on the cardiometabolic health of the population, including declines in physical activity, increases in smoking and alcohol use, worsening blood pressure and glycemic control, and detrimental effects on mental health.[4] In addition, SARS-CoV-2 caused myocardial injury in patients through various pathological mechanisms.[5] There might have been a bidirectional causality between COVID-19 and cardiometabolic diseases.

While early reports were crucial to inform clinical decision-making

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and public health policy during a pandemic of a new pathogen, correlative observational data could be plagued by residual confounding. Thus, inherent challenges remained in inferring causal impact from these epidemiological studies. Mendelian randomization (MR) is an epidemiological method that uses genetic variants to proxy an exposure predicting its causal association with an outcome.[6] It aims to overcome reverse causality and confounding to draw causal inferences from observational data.[7] It has been widely applied to unresolved questions in epidemiology, utilizing summary statistics from genome-wide association studies (GWAS) on an increasing number of human traits.[8] Aaron Leong et al. evaluated the associations of 17 cardiometabolic traits with COVID-19 susceptibility and severity using two-sample MR analyses. They found that higher body mass index was the only cardiometabolic risk factor among the 17 cardiometabolic traits they studied associated with a higher risk of severity for COVID-19. If the other 16 cardiometabolic risk factors had causal associations with COVID-19 illness, their effects were likely modest.[9] This indicates that some cardiometabolic diseases may serve as etiological factors for COVID-19.

In the present day, with the implementation of a diverse array of robust measures, including vaccination drives, public health advisories, and in-depth technical guidance, the global management of this cataclysmic pandemic has witnessed a remarkable improvement. However, the causal effect of COVID-19 on cardiometabolic diseases remains uncertain, and to uncover it still makes sense. Our hypothesis suggests a causal relationship between COVID-19 and certain cardiometabolic conditions. In this study, we utilized the two-sample MR method to evaluate causal associations between COVID-19 (susceptibility and severity) and four primary cardiometabolic diseases (type 2 diabetes, coronary heart disease, ischemic stroke, and heart failure).

2. Methods

2.1. Summary of genome-wide association study (GWAS) data

The COVID-19 Host Genetics Initiative was an international genetics collaboration about COVID-19 susceptibility and severity.[10] Susceptibility (sample size = 1,299,010) was defined as COVID-19-positive (n = 14,134) versus population controls (n = 1,284,876). Severity (sample size = 908,494) was defined as COVID-19 hospitalization (n = 6,406) versus population controls (n = 902,088).[10] The above GWAS data were used to test COVID-19 (susceptibility and severity) against four cardiometabolic diseases (type 2 diabetes, coronary heart disease, ischemic stroke, and heart failure). Spracklen CN consortium data were used for type 2 diabetes,[11] Nikpay consortium data were utilized for coronary heart disease,[12] Malik R consortia data were utilized for ischemic stroke.[13] We chose the Neale lab consortium data for heart failure. Table 1 showed more details.

2.2. Two-sample MR and causal effect assessment

The MR analysis relies on three fundamental assumptions: (1) the genetic variant must exhibit a strong and consistent association with the exposure; (2) the genetic variant should not be associated with confounding factors that may affect the relationship between the exposure and the outcome; and (3) the genetic variant must affect the outcome exclusively through its impact on the exposure, without involvement in any direct or alternative pathways.[14]

The MR was performed in a two-sample MR strategy using results from GWAS.[15] The causality was explored on the MR-based platform (https://www.mrbase.org),[16] (1) Causality: The conventional MR approach (inverse variance weighted method, IVW), MR Egger, weighted median, simple mode, and weighted mode method were used. (1.1) Causality between genetically determined COVID-19 susceptibility and four cardiometabolic diseases (type 2 diabetes, coronary heart disease, ischemic stroke, and heart failure). (1.2) Causality between genetically determined COVID-19 severity and four cardiometabolic diseases (type 2 diabetes, coronary heart disease, ischemic stroke, and heart failure). (2) Heterogeneity. (3) Horizontal pleiotropy. (4) Leave-one-out analysis. (5) Funnel plots.

Following previous MR studies,[17,18] a comprehensive set of sensitivity analyses were conducted, which include leave-one-out analysis, funnel plots, and the application of both the weighted median method and the weighted mode method.

The causality was established if the IVW method was statistically significant and had no heterogeneity or horizontal pleiotropy. If all MR models were similar, the results would be more confident.[19]

2.3. Statistical analysis

P values were 2-sided, and evidence of association was declared at $P < 0.05$. Bonferroni corrections were used to make allowance for multiple testing.

3. Results

3.1. Causality between genetically determined COVID-19 susceptibility and four cardiometabolic diseases (type 2 diabetes, coronary heart disease, ischemic stroke, and heart failure)

The characteristics of the single-nucleotide polymorphisms (SNPs) were detailed in Supplement Table 1. For COVID-19 susceptibility, the IVW method revealed that the odds ratio (OR) (95% confidence interval [CI], P-value) for type 2 diabetes was 1.719 (1.510–1.956, P = 0.000) (Table 2 and Fig. 1A). Consistent results were obtained using the weighted median method (OR, 1.736; 95% CI, P = 0.000), simple mode method (OR, 1.770; 95% CI, P = 0.045), and weighted mode method (OR, 1.751; 95% CI, P = 0.039) (Table 2). Both IVW and MR-Egger methods indicated no heterogeneity (P = 0.513 and P = 0.261, respectively) (Table 2). A plot of the SNP-COVID-19 susceptibility associations and the SNP-type 2 diabetes associations with standard error bars, was shown in Figure Supplement 1A. No obvious outlier SNPs were found, indicating small heterogeneity among these SNPs.

Moreover, MR-Egger regression suggested no directional horizontal pleiotropy. (MR-Egger intercept P = 0.854) (Table 2). Furthermore, no horizontal pleiotropy was observed. (Figure Supplement 1)

In conclusion, the genetically determined COVID-19 susceptibility positively increased type 2 diabetes risk only, but not the other three cardiometabolic diseases (coronary heart disease, ischemic stroke, and heart failure). (Table 2, Fig. 1C, E, 1G, and Figure Supplement 1).

Table 1
Details of studies and data sets used for analyses.

Exposure/Outcomes	ID in MR base	Sample size	Pubmed ID	First author	Consortium	Year
COVID-19 susceptibility	ebi-a-GCST010780	1,299,010	32404885	COVID-19 Host Genetics Initiative	NA	2020
COVID-19 severity	ebi-a-GCST010780	908,494	32404885	COVID-19 Host Genetics Initiative	NA	2020
Type 2 diabetes	ebi-a-GCST010118	433,540	32499647	Spracklen CN	NA	2020
Coronary heart disease	ieu-a-7	184,305	26343387	Nikpay	CARDIoGRAMplusC4D	2015
Ischemic stroke	ebi-a-GCST005843	40,328	29531354	Malik R	NA	2018
Heart failure	ukb-d-I50	361,194	NA	Neale lab	NA	2018

NA, Not available.

3.2. Causality between genetically determined COVID-19 severity and four cardiometabolic diseases (type 2 diabetes, coronary heart disease, ischemic stroke, and heart failure)

When comparing hospitalized individuals with population controls, the IVW method estimate indicated that the OR (95% CI, *P*-value) for ischemic stroke was 1.051 (1.008–1.095, $P = 0.020$) (Table 3 and Fig. 1F). Moreover, the OR (1.001, 95% CI 1.000–1.002, $P = 0.010$) for heart failure was slightly higher (Table 3 and Fig. 1H). However, no causal associations were found between COVID-19 severity and type 2 diabetes or coronary heart disease (Table 3 and Fig. 1B and D). The Scatter plots, leave-one-out sensitivity analysis, and funnel plots of causal effects between COVID-19 severity and four cardiometabolic disease risks were shown in Figure Supplement 2.

In conclusion, the findings suggested a potential causal link between genetically determined COVID-19 severity and ischemic stroke and heart failure, but not with type 2 diabetes or coronary heart disease.

4. Discussion

This MR analysis provided evidence supporting a causal relationship between COVID-19 and cardiometabolic diseases. Our study not only focused on COVID-19 susceptibility and severity but also systematically evaluated its causal relationships with four major cardiometabolic diseases. Moreover, our study emphasized the potential long-term impact of COVID-19 on cardiometabolic health, providing new directions for future research and clinical practice. The findings highlighted the need for closer monitoring of cardiometabolic health in COVID-19 patients, especially severe cases, and suggested new strategies for chronic disease management. While not directly focused on medication, this research provided critical insights for advancing drug development and long-term health interventions in integrative pharmacy.

COVID-19 was initially reported in Wuhan, China, in late December 2019, leading to a significant number of deaths.[20] Subsequently, the infection rapidly spread worldwide and was declared a global health emergency by the WHO in March 2020. While many infected patients were asymptomatic or experienced mild symptoms, some cases resulted in severe complications and posed a life-threatening risk. With the majority of the general public gaining immunity through vaccination or previous infection, COVID-19 has transitioned from a pandemic to an endemic phase.[21]

It was important to note that there was an interplay between COVID-19 and cardiometabolic diseases.[22] Cardiometabolic diseases had emerged as independent risk factors for severe COVID-19 outcomes such as hospitalization, mechanical ventilation, and mortality.[23] Previous reports from China found that cardiometabolic diseases and their risk factors were common pre-existing conditions in patients with COVID-19.[24–27] Importantly, cardiometabolic disease patients suffered more compared with general people.[24,28–31] The existing dataset strongly suggested that cardiometabolic diseases, including hypertension, coronary artery disease, diabetes, and obesity, serve as strong comorbidities in COVID-19.[32] The findings indicated that cardiometabolic diseases might play a role in promoting COVID-19 pathogenesis. Conversely, the COVID-19 pandemic itself had caused major adverse repercussions on the cardiometabolic health of the population.[4] Among a cohort of 799 COVID-19 patients in Wuhan, heart failure was the most common critical complication during the exacerbation of COVID-19.[33] However, it was important to note that these findings were primarily based on retrospective and cross-sectional studies. Therefore, caution should be exercised when inferring causal effects from observational studies due to potential confounding factors.

MR utilized genetic variation linked to modifiable exposures or risk factors to address biases affecting traditional observational study designs. By comparing outcomes among individuals with different genetic variants, researchers could make causal inferences about the effects of specific risk factors.[34] Several MR studies suggested higher body mass index increased COVID-19 susceptibility and severity.[9,35,36] It indicated that targeting obesity might serve as an arrangement to diminish the risk of severe COVID-19 outcomes. However, there was limited understanding of the impact of COVID-19 on cardiometabolic conditions. This study aimed to utilize MR methodology to establish a causal relationship between COVID-19 (susceptibility and severity) and the four cardiometabolic diseases (including type 2 diabetes, coronary heart disease, ischemic stroke, and heart failure) by MR method.

Type 2 diabetes mellitus was a multifaceted health concern encompassing obesity, high cholesterol, high blood pressure, and chronic inflammation, which collectively elevate the risk of cardiovascular diseases.[37] This condition could contribute to an increased pathogenicity of the SARS-CoV-2 virus due to metabolic disturbances. Consequently, individuals with diabetes were at a heightened susceptibility and severity for COVID-19, rendering them a high-risk population. SARS-CoV-2 infection might lead to hyperglycemia or new-onset

Table 2
Causal associations between genetically determined COVID-19 susceptibility and four cardiometabolic diseases (type 2 diabetes, coronary heart disease, ischemic stroke, and heart failure).

Trait	Method	nSNP	OR	95% CI		*P* value	Heterogeneity *P*	MR-Egger intercept *P*
COVID-19 susceptibility -Type 2 diabetes	MR Egger	3	1.614	0.934	2.791	0.336	0.261	0.854
	Weighted median	**3**	**1.736**	**1.407**	**2.141**	**0.000**		
	Inverse variance weighted	**3**	**1.719**	**1.510**	**1.956**	**0.000**	0.513	
	Simple mode	**3**	**1.770**	**1.384**	**2.264**	**0.045**		
	Weighted mode	**3**	**1.751**	**1.401**	**2.189**	**0.039**		
COVID-19 susceptibility -Coronary heart disease	MR Egger	3	0.758	0.535	1.072	0.362	0.102	0.218
	Weighted median	3	1.131	1.012	1.264	0.030		
	Inverse variance weighted	3	1.173	0.833	1.652	0.360	0.000	
	Simple mode	3	1.660	1.249	2.207	0.073		
	Weighted mode	3	0.989	0.871	1.123	0.881		
COVID-19 susceptibility -Ischemic stroke	Inverse variance weighted	2	1.117	0.982	1.271	0.093	0.587	NA
	MR Egger	NA	NA	NA	NA	NA		
	Weighted median	NA	NA	NA	NA	NA		
	Simple mode	NA	NA	NA	NA	NA		
	Weighted mode	NA	NA	NA	NA	NA		
COVID-19 susceptibility -Heart failure	MR Egger	3	1.000	0.992	1.007	0.953	0.060	0.664
	Weighted median	3	1.002	0.999	1.004	0.136		
	Inverse variance weighted	3	1.002	0.999	1.004	0.249	0.093	
	Simple mode	3	1.002	0.999	1.005	0.369		
	Weighted mode	3	1.002	0.999	1.004	0.314		

NA, Not available; SNP, Single-nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval.

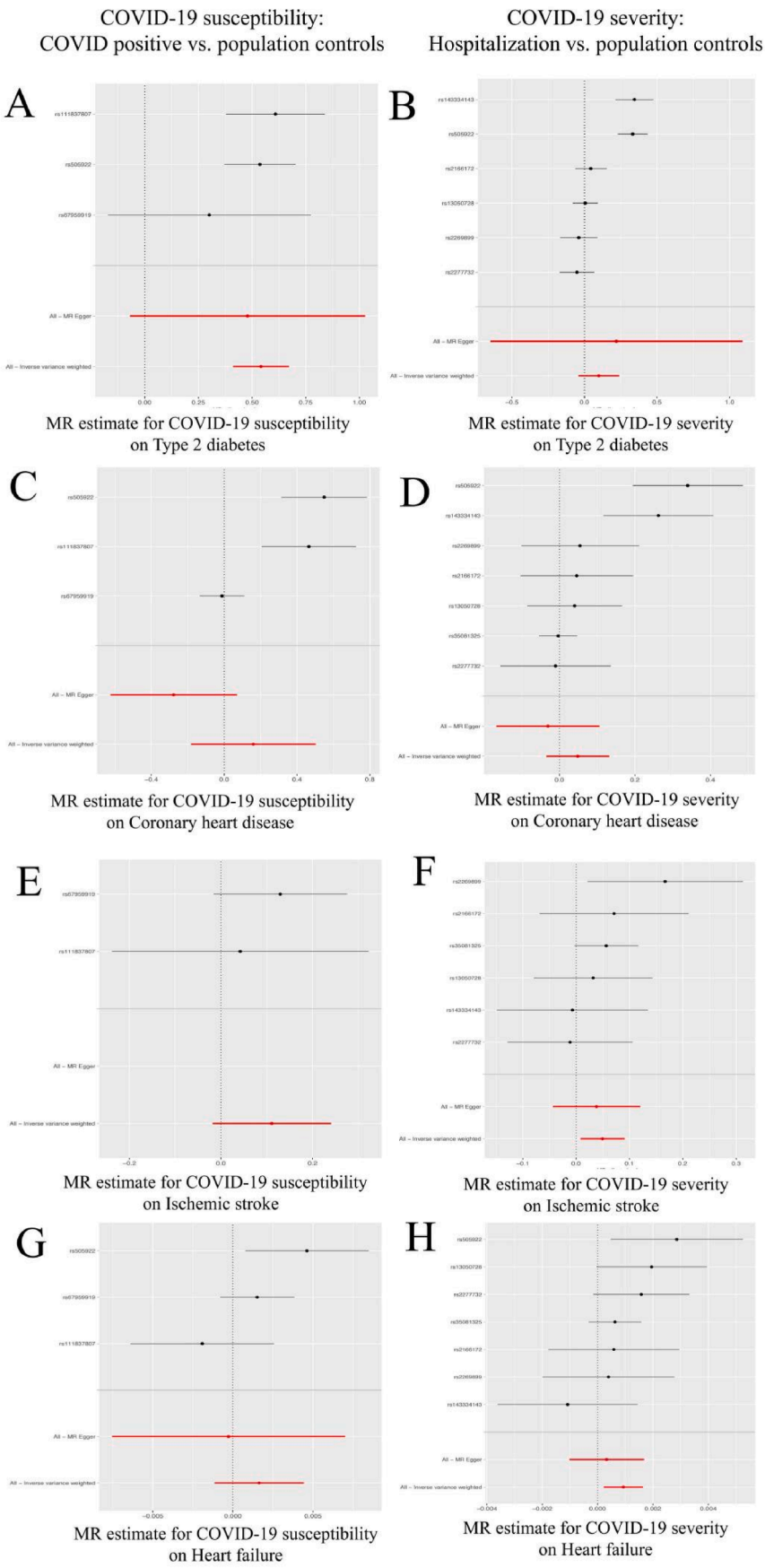

Fig. 1. MR study of the effect of COVID-19 (susceptibility and severity) on four cardiometabolic diseases (type 2 diabetes, coronary heart disease, ischemic stroke, and heart failure). (A, C, E, G) Forest plots of causal effects between COVID-19 susceptibility and risk of four cardiometabolic diseases (type 2 diabetes, coronary heart disease, ischemic stroke, and heart failure). (B, D, F, H) Forest plots of causal effects between COVID-19 severity and risk of four cardiometabolic diseases (type 2 diabetes, coronary heart disease, ischemic stroke, and heart failure). MR, Mendelian randomization; IVW, inverse-variance weighted.

Table 3
Causal associations between genetically determined COVID-19 severity and four cardiometabolic diseases (type 2 diabetes, coronary heart disease, ischemic stroke and heart failure).

Trait	Method	nSNP	OR	95% CI		*P* value	Heterogeneity *P*	MR-Egger intercept *P*
COVID-19 severity -Type 2 diabetes	MR Egger	6.000	1.246	0.523	2.966	0.646	0.000	0.795
	Weighted median	6.000	1.012	0.947	1.081	0.726		
	Inverse variance weighted	6.000	1.104	0.960	1.270	0.165	0.000	
	Simple mode	6.000	0.988	0.928	1.052	0.721		
	Weighted mode	6.000	0.996	0.934	1.061	0.898		
COVID-19 severity -Coronary heart disease	MR Egger	7.000	0.970	0.846	1.112	0.679	0.001	0.225
	Weighted median	7.000	1.012	0.964	1.063	0.623		
	Inverse variance weighted	7.000	1.050	0.966	1.141	0.252	0.000	
	Simple mode	7.000	1.028	0.960	1.100	0.460		
	Weighted mode	7.000	1.004	0.962	1.049	0.848		
COVID-19 severity -Ischemic stroke	MR Egger	6.000	1.039	0.957	1.127	0.414	0.368	0.765
	Weighted median	6.000	1.050	0.998	1.105	0.062		
	Inverse variance weighted	**6.000**	**1.051**	**1.008**	**1.095**	**0.020**	0.494	
	Simple mode	6.000	1.030	0.958	1.108	0.457		
	Weighted mode	6.000	1.050	0.990	1.113	0.166		
COVID-19 severity -Heart failure	MR Egger	7.000	1.000	0.999	1.002	0.655	0.314	0.350
	Weighted median	7.000	1.001	1.000	1.002	0.063		
	Inverse variance weighted	**7.000**	**1.001**	**1.000**	**1.002**	**0.010**	0.305	
	Simple mode	7.000	1.001	0.999	1.002	0.289		
	Weighted mode	7.000	1.001	1.000	1.002	0.150		

NA, Not available; SNP, Single-nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval.

diabetes.[38] In addition to the acute impact of pre-existing type 2 diabetes on the course of COVID-19 and exacerbation of dysglycemia following acute infection, there was emerging evidence of long-term consequences resulting from the synergistic interplay between these two conditions - namely the development of COVID-induced diabetes and long-COVID in patients with pre-existing diabetes.[39] Our findings indicated that genetically determined susceptibility to COVID-19 increases the risk of type 2 diabetes (Table 2 and Fig. 1A), revealing COVID-19 as an independent metabolic risk factor beyond acute infection. This finding necessitated systematic post-infection surveillance, particularly glycemic monitoring in recovered patients, to mitigate long-term diabetes progression. We proposed a collaborative care model where primary physicians and endocrinologists implemented longitudinal metabolic tracking, combining routine HbA1c tests with continuous glucose monitoring technology. For diabetic patients who contracted COVID-19, personalized insulin titration protocols were prioritized during the acute phase to counteract infection-induced metabolic dysregulation. These evidence-based recommendations transformed our understanding of COVID-19's enduring health impacts, bridging virology and chronic disease management paradigms.

Furthermore, our findings demonstrated a potential causal association between genetically predicted COVID-19 severity and ischemic stroke (Table 3 and Fig. 1F), consistent with a previous MR study which also suggested an increased risk of ischemic stroke in critical COVID-19 cases (OR = 1.03, 95% CI, 1.00–1.06, $P = 0.03$).[40] More significantly, this study represented the first MR-based identification of a causal link between COVID-19 severity and incident heart failure, a novel mechanistic insight previously unreported in the literature. These findings carried important clinical implications, as they suggested that the prothrombotic and inflammatory cascades triggered by severe SARS-CoV-2 infection might independently contribute to both cerebrovascular and cardiac dysfunction. The results underscored the necessity for enhanced cardiovascular monitoring and preventive strategies (e.g., antithrombotic prophylaxis, hemodynamic optimization) in hospitalized COVID-19 patients, particularly those with pre-existing cardiometabolic risk factors. From a public health perspective, these findings highlighted the potential long-term cardiovascular burden imposed by the pandemic, warranting systematic follow-up of COVID-19 survivors for delayed cerebrovascular and cardiac complications.

Several potential mechanisms could account for the association between COVID-19 and cardiometabolic diseases. First, COVID-19 induced a cytokine storm by increasing chemokines and pro-inflammatory cytokines.[22] Recently, a clinical trial reported that the outcomes of hospitalized COVID-19 patients improved when the IL-6 receptor was inhibited.[41] Secondly, the Spike protein and ACE2 interacted with each other. It was considered one of the significant factors in the biological mechanism underlying SARS-CoV-2 infection.[20] ACE2 itself protected against cardiovascular diseases. Downregulation of ACE2 by SARS-CoV-2 infection might be involved in mediating cardiometabolic diseases. So, ACE2 might serve as a potential target for preventing and treating COVID-19 and the following cardiometabolic disorders. Lastly, SARS-CoV-2 infection might directly target endothelial cells, leading to inflammation that could contribute to the development of cardiometabolic disorders.[42]

5. Conclusion

This study demonstrated that genetically predicted susceptibility to COVID-19 increases the risk of type 2 diabetes, while severe COVID-19 infection elevates the risks of ischemic stroke and heart failure. These findings redefine COVID-19 as an independent cardiometabolic risk factor, underscoring the necessity of long-term metabolic screening for recovered patients. This represents a paradigm shift from current guidelines, which primarily focus on acute complications. By employing MR, we mitigated confounding biases inherent in observational studies, such as those arising from pandemic-related lifestyle changes. Our approach generated robust genetic evidence, offering critical insights for public health strategies aimed at mitigating the long-term consequences of COVID-19.

In summary, this study provides genetic validation for a causal link between COVID-19 and cardiometabolic diseases, emphasizing the importance of sustained metabolic surveillance in post-recovery care and informing evidence-based public health interventions.

6. Limitations

However, there were several limitations in this study. Firstly, given the limited power of the MR analysis (with SNPs explaining about 2% of COVID-19), further large-scale studies or longitudinal studies were required to validate the true association between COVID-19 and cardiometabolic diseases. Secondly, the variances explained in the exposures by genetic instruments were modest, though well within the ranges

that were typical for complex traits. The use of weak genetic instruments could have limited our ability to detect subtle causal associations and did not exclude the possibility of modest effects. It was also possible that, with larger sample sizes, the association of COVID-19 and other cardiometabolic outcomes could become significant, and confidence intervals would narrow around true estimates. Thirdly, the MR study could be strengthened by providing more omics information on the SNPs used in the analysis to see if there was any information that exists on these SNPs that could be evidence either for or against the hypothesis of horizontal pleiotropy. It is advisable to include omics data in future studies. Given the large number of COVID-19 patients globally, even a weak positive result, such as the OR of 1.001 (95% CI 1.000–1.002, $P = 0.010$) for the relationship between COVID-19 severity and heart failure, holds clinical significance. Although the effect size may seem minor on an individual level, when extrapolated to the vast population of COVID-19 patients, it can translate into a substantial number of additional cases of heart failure. This could have far-reaching implications for resource allocation, patient management, and long-term healthcare planning.

CRediT authorship contribution statement

Haibo Chen: Formal analysis, Investigation. **Lizhen Liao:** Supervision, Resources. **Zezhi Ke:** Methodology, Data curation. **Xu Zhang:** Resources, Software. **Xiaodong Zhuang:** Resources, Data curation. **Xin Gao:** Writing – review & editing, Supervision. **Litao Pan:** Funding acquisition, Supervision.

Ethical approval and consent to participate

Not applicable. There were no patients or animals included in this study.

Availability of data and materials

For more data and materials, please contact Xin Gao (E-mail: 1027790131@qq.com) and Litao Pan (E-mail: ltpan@email.szu.edu.cn)

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Pan Lit reports administrative support and article publishing charges were provided by Shenzhen Second People's Hospital. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhip.2025.08.001.

List of abbreviations

Mendelian randomization (MR); Genome-wide association study (GWAS); Odds ratio (OR); Confidence interval (CI); Inverse-variance weighted (IVW); Single-nucleotide polymorphism (SNP); Not available (NA).

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