

Causal associations between type 1 diabetes and COVID-19 infection and prognosis: a two-sample Mendelian randomization study

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ABSTRACT

Introduction It has been suggested that type 1 diabetes was associated with increased COVID-19 morbidity and mortality. However, their causal relationship is still unclear. Herein, we performed a two-sample Mendelian randomization (MR) to investigate the causal effect of type 1 diabetes on COVID-19 infection and prognosis.

Research design and methods The summary statistics of type 1 diabetes were obtained from two published genome-wide association studies of European population, one as a discovery sample including 15 573 cases and 158 408 controls, and the other data as a replication sample consisting of 5913 cases and 8828 controls. We first performed a two-sample MR analysis to evaluate the causal effect of type 1 diabetes on COVID-19 infection and prognosis. Then, reverse MR analysis was conducted to determine whether reverse causality exists.

Results MR analysis results showed that the genetically predicted type 1 diabetes was associated with higher risk of severe COVID-19 (OR=1.073, 95% CI: 1.034 to 1.114, $p_{FDR}=1.15\times 10^{-3}$) and COVID-19 death (OR=1.075, 95% CI: 1.033 to 1.119, $p_{FDR}=1.15\times 10^{-3}$). Analysis of replication dataset showed similar results, namely a positive association between type 1 diabetes and severe COVID-19 (OR=1.055, 95% CI: 1.029 to 1.081, $p_{FDR}=1.59\times 10^{-4}$), and a positively correlated association with COVID-19 death (OR=1.053, 95% CI: 1.026 to 1.081, $p_{FDR}=3.50\times 10^{-4}$). No causal association was observed between type 1 diabetes and COVID-19 positive, hospitalized COVID-19, the time to the end of COVID-19 symptoms in the colchicine treatment group and placebo treatment group. Reverse MR analysis showed no reverse causality.

Conclusions Type 1 diabetes had a causal effect on severe COVID-19 and death after COVID-19 infection. Further mechanistic studies are needed to explore the relationship between type 1 diabetes and COVID-19 infection and prognosis.

INTRODUCTION

COVID-19 is a highly infectious disease caused by SARS-CoV-2. Up to July 2022, the cumulative number of confirmed COVID-19 cases has reached over 540 million, and the death toll of COVID-19 has arrived at 6.3 million across 200 countries. Many factors could affect the

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ COVID-19 poses a serious threat to human health and it is urgent to find the risk factors for COVID-19. At present, many studies have explored the relationship between type 1 diabetes and COVID-19. However, most of the studies are observational and lack causal inference. So we used a two-sample Mendelian randomization analysis to infer causality between them.

WHAT THIS STUDY ADDS

⇒ Type 1 diabetes was genetically associated with severe COVID-19 and COVID-19 death. On the other hand, type 1 diabetes did not have a causal relationship with COVID-19 positive and hospitalized COVID-19.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study provides a new insight for the prevention of COVID-19, and the protection of patients with COVID-19 with type 1 diabetes should also be strengthened. Further mechanistic studies such as molecular mechanism analysis, mouse model construction and further therapeutic studies are needed to confirm our view.

severity of COVID-19 infection, including old age, smoking, pre-existing diseases and so on.¹⁻⁴ Although the majority of patients with COVID-19 have mild symptoms, some of them will develop serious complications, such as acute respiratory distress syndrome⁵ or even death.⁶

Given the severity of COVID-19, many studies are currently focusing on risk factors for COVID-19. Retrospective observational studies have shown that patients with diabetes have higher rates of hospitalization, severe illness⁷⁻⁹ and mortality compared with patients without diabetes in the same situation with COVID-19 infection.^{5 10} COVID-19 infection may also cause ketosis in people with diabetes

and then may increase the length of hospital stays.¹¹ However, as most of the current studies of diabetes are about type 2 diabetes and COVID-19, there are very few studies on the association between type 1 diabetes and COVID-19.

Type 1 diabetes is a kind of autoimmune disease, whose pathogenesis is the destruction of islet β cells due to immune disorder.¹² The destruction of islet β cells leads to a lack of insulin production, which causes the poor control of blood glucose.¹³ In recent years, the incidence of type 1 diabetes rises consistently worldwide.¹⁴ Besides, it is reported that compared with people without type 1 diabetes, patients with type 1 diabetes have a higher incidence of various infections.¹⁵

According to observational studies, during the COVID-19 pandemic, the number of confirmed cases of type 1 diabetes in children has increased significantly¹⁶ and the prevalence of type 1 diabetes among patients with COVID-19 is 0.15%–28.98%.¹⁷ The TEDDY Study indicates that respiratory infections, including coronavirus infection, may lead to a greater risk of islet autoimmunity,¹⁸ which may in turn lead to the development of type 1 diabetes. Moreover, it is reported that patients with type 1 diabetes with poor blood glucose control is a risk factor for the infection of COVID-19.¹⁹ Different opinions have emerged in an observational study that the risk of severe prognosis is low among people with type 1 diabetes who require hospitalization due to COVID-19.²⁰

The above studies have shown that there are some connections between type 1 diabetes and COVID-19 infection and prognosis; however, these observational studies cannot infer a causal relationship due to various confounding factors. Mendelian randomization (MR) is a way to access the causal relationship using genetic variation as instruments. Due to an individual's genetic variation is randomly assorted at conception, it is usually unaffected by confounding factors such as environment. Therefore, an unconfounded estimate of causal inference could be made from MR analysis.

In the present study, we performed a bidirectional MR analysis to identify the causal relationship between type 1 diabetes and COVID-19 infection and prognosis, in which the genome-wide association study (GWAS) summary data were obtained from publicly available studies.

RESEARCH DESIGN AND METHODS

STROBE-MR (Strengthening the Reporting of Observational Studies in Epidemiology-MR) guidelines²¹ were used to strengthen the reporting of this study (online supplemental file 1). The research framework of this study is shown in figure 1.

GWAS summary statistics

We first extracted type 1 diabetes GWAS data from previously published study, which consisted of 15 573 cases and 158 408 controls.²² To validate our results, we chose another GWAS data as replication sample, which

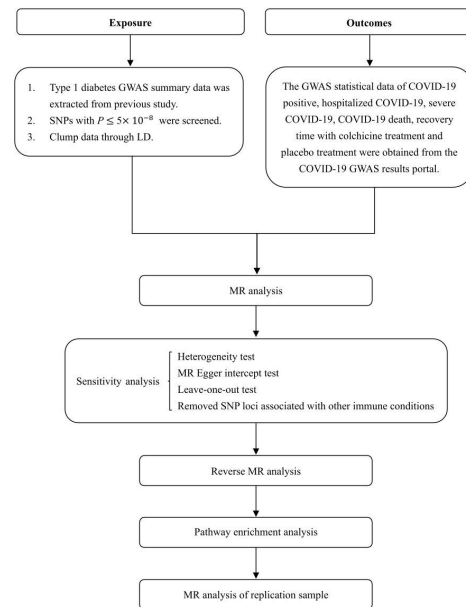


Figure 1 Outline of the MR analysis. GWAS, genome-wide association study; LD, linkage disequilibrium; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms.

included 5913 cases diagnosed before the age of 17 years and 8828 controls.²³ Both GWAS data of European population and potential population structure were already been adjusted by genetic principal components in the original analyses.

Six traits were selected to represent COVID-19 infection and prognosis. The GWAS summary statistics of these six traits were obtained from the COVID-19 GWAS results portal,²⁴ all of which were of European population. The first trait was 'positive versus negative (tested)', which included 16 551 COVID-19-positive cases and 81 826 COVID-19-negative controls. The second one contained 2884 hospitalized COVID-19-positive cases and 13 667 non-hospitalized COVID-19-positive controls, which was called 'hospitalized positive versus non-hospitalized positive'. The third one was called 'severe positive versus non-severe positive', which included 1120 severe COVID-19-positive cases and 14 695 non-severe COVID-19-positive controls. A severe positive COVID-19 case was defined as COVID-19 death or with inpatient diagnosis of both COVID-19 and dependence on respirator, or a COVID-19 case with advanced respiratory support. The fourth one contained 1001 COVID-19 deaths and 14 814 COVID-19-positive survivors, which were called 'positive and death versus positive survivor'. The fifth one was the time to the end of COVID-19 symptoms in 872 patients with COVID-19 treated with colchicine. The last one was the time to the end of COVID-19 symptoms in 851 patients with COVID-19 not treated with colchicine. For ease of description, the above six traits were abbreviated as COVID-19 positive, hospitalized COVID-19, severe COVID-19, COVID-19 death, recovery time with colchicine treatment and recovery time with placebo treatment.

Instrumental variables selection

The choice of instrumental variables (IVs) is based on three hypotheses: (1) IVs are closely related to exposure; (2) IVs are not correlated with any confounding factors; (3) IVs are not directly related to the outcome, and their effect on the outcome can only be reflected through exposure. To satisfy these three hypotheses statistically, we performed a series of quality control. First, we selected single-nucleotide polymorphisms (SNPs) at the genome-wide significance level ($p \leq 5 \times 10^{-8}$) so that they were strongly associated with exposure. Second, palindromic SNPs were discarded due to their ambiguous effect direction. Then, we conducted a linkage disequilibrium clumping to retain independent SNPs by setting the r^2 threshold as 0.01 and the clumping window size as 1000 kb. SNPs with r^2 greater than 0.01 with the lead SNP within 1000 kb were removed. Moreover, we tested the overall pleiotropy through MR-Pleiotropy RESidual Sum and Outlier (PRESSO) global test. If the global test p value is < 0.05 , then we performed the MR-PRESSO outlier test and removed the pleiotropic SNPs with $p_{\text{outlier}} < 0.05$. Finally, we evaluated the strength of IVs by F statistic,²⁵ which was defined as $F = \frac{R^2(n-k-1)}{k(1-R^2)}$, where R^2 was the degree of exposure explained by IVs, n was the sample size of exposure, and k was the number of IVs. An F statistic ≥ 10 indicated that the IVs were strongly correlated with the exposure. SNPs after rigorous screening were used as IVs in subsequent MR analyses.

Bidirectional MR analysis and sensitivity analysis

We first evaluated the causal effect of type 1 diabetes on COVID-19 infection and prognosis in discovery sample. For exposures having only one IV, we used the Wald ratio test to perform the MR analysis. For exposures having two or more IVs, we conducted inverse variance weighted (IVW) model. OR, 95% CI and p values were used to estimate the causal effect.

Significant results discovered in the discovery sample were subjected to be replicated in the replication sample with the same analyses.

To estimate the robustness of MR findings, we performed a series of sensitivity analyses, including heterogeneity test, MR-Egger intercept test and leave-one-out test. The heterogeneity among different IVs was evaluated using the Cochran's Q statistic. The Cochran's Q statistic follows a χ^2 distribution with the number of IVs minus 1 df. When heterogeneity existed between IVs, we used the random-effects IVW model to evaluate causality; otherwise, we used the fixed-effects IVW model. MR-Egger regression was performed by a simple modification to the IVW method. Rather than constraining the intercept term to be zero, the term was estimated and a non-zero intercept suggesting possibility of directional pleiotropy.²⁶ The leave-one-out analysis was performed by re-estimating the MR association after removing an SNP. These techniques addressed potential concerns on the causal estimate due to weak violation of MR assumption.

As another sensitivity analysis, we searched the associations of the IVs being used in this study with other autoimmune diseases via the web tool PhenoScanner V.2.^{27,28} Associated IVs ($p < 5 \times 10^{-8}$) were removed and the MR analysis was redone with the remaining IVs.

Finally, to determine whether there was a reverse causal relationship between identified significant COVID-19 traits and type 1 diabetes, we conducted a reverse MR analysis and chose IVs at significance of $p \leq 1 \times 10^{-5}$.

All statistical analyses were performed by using *TwoSampleMR* package in R (V.4.1.3). The false discovery rate (FDR) correction was used to adjust for multiple testing.

Pathway enrichment analysis

To identify the pathways through which IVs may influence outcomes, we performed pathway enrichment analysis. Specifically, the SNPs from the significant MR results were mapped to genes, and then the metabolic pathways of these genes were investigated. The original g:SCS (set counts and sizes) correction method was used by default and those with adjusted p value of < 0.05 were screened for further investigation of their relationship with COVID-19. The pathway enrichment analysis was conducted in g:Profiler (<https://biit.cs.ut.ee/gprofiler/>).²⁹

Data and resource availability

Type 1 diabetes GWAS summary statistics used in this study were obtained from the GWAS catalog (study accession GCST90013791) (from Crouch *et al.*²²) and Dryad repository, doi:10.5061/dryad.ns8q3 (from Cooper *et al.*²³). The GWAS summary statistics of COVID-19 infection and prognosis are publicly accessible at <https://grasp.nhlbi.nih.gov/Covid19GWASResults.aspx>.

RESULTS

Causal effects of type 1 diabetes on COVID-19 infection and prognosis

124 independent SNPs that were associated with type 1 diabetes were selected as IVs to assess the causal relationship between type 1 diabetes and COVID-19 positive, and a total of 123 IVs were selected to estimate the causal effects of type 1 diabetes on hospitalized COVID-19, severe COVID-19 and COVID-19 death. Besides, we chose 72 and 73 IVs to assess the causal effect of type 1 diabetes on recovery time with colchicine treatment and placebo treatment. The F statistics of these IVs were all greater than 159, indicating no evidence of weak instrument bias. Details of IVs are shown in online supplemental table 1.

As shown in table 1, results of IVW method showed that the genetically predicted type 1 diabetes was associated with an increased risk of severe COVID-19 (OR=1.073, 95% CI: 1.034 to 1.114, $p_{\text{FDR}} = 1.15 \times 10^{-3}$). The genetically predicted type 1 diabetes was also associated with higher risk of COVID-19 death (OR=1.075, 95% CI: 1.033 to 1.119, $p_{\text{FDR}} = 1.15 \times 10^{-3}$). Moreover, results showed that type 1 diabetes had no causal relationship with COVID-19 positive, hospitalized COVID-19, or the recovery time

Table 1 MR analysis results of type 1 diabetes and COVID-19 infection and prognosis

Exposure	Outcome	Significance level of the selected IVs	nSNP	β	SE	P value	P-adjusted
Type 1 diabetes (from Crouch <i>et al</i> ²²)	COVID-19 positive	$p \leq 5 \times 10^{-8}$	124	0.004	0.005	0.433	0.470
	Hospitalized COVID-19	$p \leq 5 \times 10^{-8}$	123	0.010	0.013	0.417	0.470
	Severe COVID-19	$p \leq 5 \times 10^{-8}$	123	0.071	0.019	2.11×10^{-4}	1.15×10^{-3}
	COVID-19 death	$p \leq 5 \times 10^{-8}$	123	0.072	0.020	3.83×10^{-4}	1.15×10^{-3}
	Recovery time with colchicine treatment	$p \leq 5 \times 10^{-8}$	72	-0.023	0.032	0.470	0.470
	Recovery time with placebo treatment	$p \leq 5 \times 10^{-8}$	73	0.025	0.033	0.443	0.470
Type 1 diabetes (from Cooper <i>et al</i> ²³)	COVID-19 positive	$p \leq 5 \times 10^{-8}$	83	-0.001	0.004	0.772	0.772
	Hospitalized COVID-19	$p \leq 5 \times 10^{-8}$	83	0.009	0.008	0.264	0.396
	Severe COVID-19	$p \leq 5 \times 10^{-8}$	83	0.053	0.013	2.66×10^{-5}	1.59×10^{-4}
	COVID-19 death	$p \leq 5 \times 10^{-8}$	83	0.052	0.013	1.17×10^{-4}	3.50×10^{-4}
	Recovery time with colchicine treatment	$p \leq 5 \times 10^{-8}$	46	-0.017	0.024	0.461	0.554
	Recovery time with placebo treatment	$p \leq 5 \times 10^{-8}$	45	-0.032	0.022	0.141	0.283

nSNP is the number of SNPs used as IVs; β is the estimated effect coefficient; SE is the standard error of β ; p-adjusted is the p value that has been corrected by false discovery rate.

$P_{FDR} < 0.05$ is marked in bold.

IVs, instrumental variables; MR, Mendelian randomization; SNP, single-nucleotide polymorphism.

in patients with COVID-19 treated with colchicine and placebo.

Sensitivity analysis

Detailed sensitivity analysis results are provided in online supplemental table 2. No heterogeneity was detected by the heterogeneity test. No evidence suggested the existence of pleiotropy through MR-Egger intercept test (all $p > 0.05$). The leave-one-out test showed that none of the identified causal associations were driven by any single SNP (figures 2 and 3).

To determine whether the causal relationship between type 1 diabetes and COVID-19 was specific, we removed IVs associated with the following autoimmune diseases: rheumatoid arthritis, inflammatory bowel disease, self-reported psoriasis, primary sclerosing cholangitis, primary biliary cirrhosis, celiac disease, self-reported multiple sclerosis and primary biliary cholangitis. We removed 61 SNPs that were associated with other immune conditions. MR analysis of the remaining SNPs showed no change in the association between type 1 diabetes and severe COVID-19 (OR=1.126, 95% CI: 1.036 to 1.223, $p=0.005$), and the association with COVID-19 death was also consistent with the above results (OR=1.131, 95% CI: 1.037 to 1.234, $p=0.005$). Specific SNP exclusion information is detailed in online supplemental table 3.

To mitigate the potential impact of reverse causality of COVID-19 infection and prognosis on type 1 diabetes, we conducted reverse MR analyses. The 15, 11, 8, 4, 13 and 15 IVs were, respectively, chosen to represent six

phenotypes of COVID-19 infection and prognosis (online supplemental table 4). The F statistics were all larger than 25, which indicated that the IVs were strongly correlated with COVID-19-related phenotypes. MR results showed that six phenotypes of COVID-19 infection and prognosis had no causal effects on type 1 diabetes. Detailed results are shown in table 2.

Pathway analysis results

The IVs used in the significant MR results were mapped to 68 corresponding genes. GO biological process results showed 45 possible metabolic pathways. By eliminating duplicate metabolic pathways as well as metabolic pathways unrelated to severe COVID-19 and COVID-19 death, one metabolic pathway remained, namely GO:0002682 (online supplemental table 5).

Replication sample results

In replication phase, 83 IVs were chosen to assess the causal relationship between type 1 diabetes and COVID-19 positive, hospitalized COVID-19, severe COVID-19, and COVID-19 death. In addition, 46 and 45 IVs were, respectively, obtained to evaluate the causal effects of type 1 diabetes on the recovery time with colchicine treatment and placebo treatment. All of the F statistics were also more than 357. Details of IVs are shown in online supplemental table 6.

MR results for replicate sample were in accordance with the discovery sample, that is, type 1 diabetes and severe COVID-19 were positively causally related

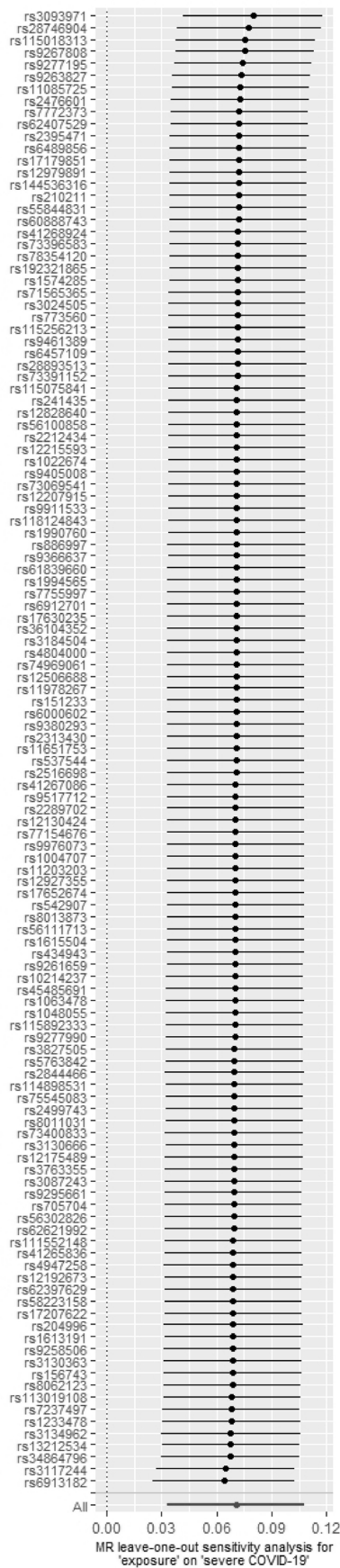


Figure 2 Result of leave-one-out test of type 1 diabetes on severe COVID-19. The bottom black line represents the estimated value of the IVW analysis. IVW, inverse variance weighted; MR, Mendelian randomization.

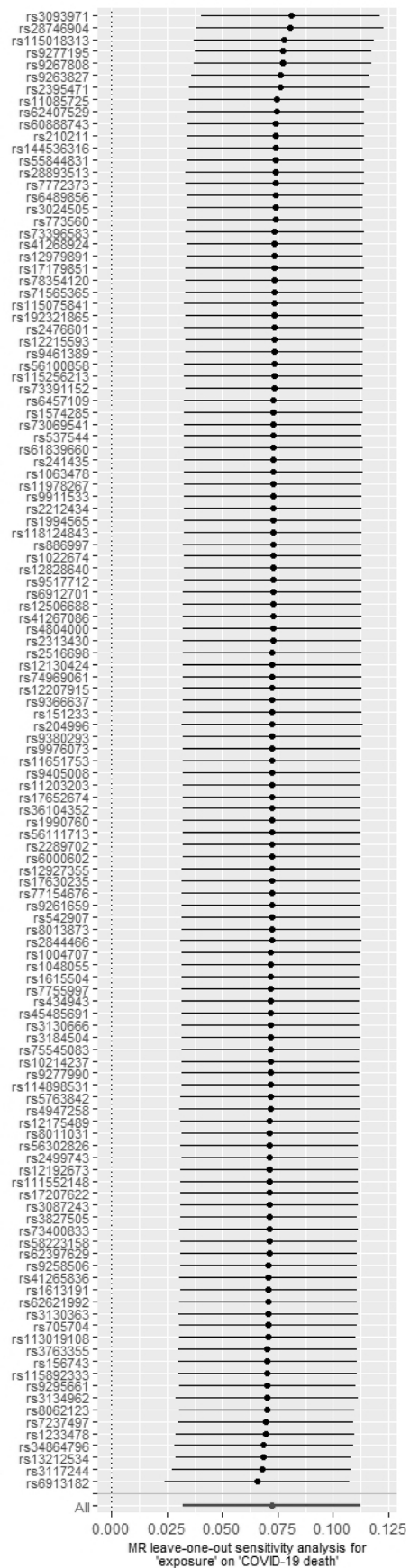


Figure 3 Result of leave-one-out test of type 1 diabetes on COVID-19 death. The bottom black line represents the estimated value of the IVW analysis. IVW, inverse variance weighted; MR, Mendelian randomization.

Table 2 Reverse MR analysis results

Exposure	Outcome	Significance level of the selected IVs	nSNP	β	SE	P value
COVID-19 positive	Type 1 diabetes	$p \leq 1 \times 10^{-5}$	15	0.038	0.071	0.595
Hospitalized COVID-19		$p \leq 1 \times 10^{-5}$	11	0.002	0.043	0.971
Severe COVID-19		$p \leq 1 \times 10^{-5}$	8	0.014	0.021	0.506
COVID-19 death		$p \leq 1 \times 10^{-5}$	4	0.053	0.043	0.217
Recovery time with colchicine treatment		$p \leq 1 \times 10^{-5}$	13	0.028	0.017	0.090
Recovery time with placebo treatment		$p \leq 1 \times 10^{-5}$	15	0.010	0.016	0.548

nSNP is the number of SNPs used as IVs; β is the estimated effect coefficient; SE is the standard error of β . IVs, instrumental variables; MR, Mendelian randomization; SNP, single-nucleotide polymorphism.

(OR=1.055, 95% CI: 1.029 to 1.081, $p_{FDR}=1.59 \times 10^{-4}$). Type 1 diabetes and COVID-19 death have a positive relationship in causality (OR=1.053, 95% CI: 1.026 to 1.081, $p_{FDR}=3.50 \times 10^{-4}$).

DISCUSSION

In the present study, we used two separate sets of GWAS data to identify the relationship between type 1 diabetes and COVID-19 infection and prognosis. Our results showed that type 1 diabetes had a causal effect on severe COVID-19 and COVID-19 death.

Type 1 diabetes is caused by an extreme lack of insulin that causes hyperglycemia. The virus of COVID-19, namely SARS-CoV-2, enters the body and interacts with ACE2, thus causing infection. An animal study has shown that the non-obese diabetic mouse model, that is, the autoimmune diabetic model similar to human type 1 diabetes, has increased ACE2 activity.³⁰ Therefore, it may be the case that patients with type 1 diabetes are more susceptible to COVID-19 infection. Although patients with type 1 diabetes may themselves be more susceptible to COVID-19, their infection rates are similar to those of the general population, possibly due to their higher hygiene standards, such as less travel to densely populated areas and greater care to protect themselves. A study has also shown no difference in the incidence of COVID-19 among people with type 1 diabetes compared with the general population,³¹ which is consistent with our findings.

Our results showed that type 1 diabetes was not causally related to hospitalized COVID-19. A retrospective observational study showed no increase in COVID-19 hospitalization among patients with type 1 diabetes.³² It is reported that baseline glycemic control and prompt access to treatment are important factors that can alter the risk of COVID-19 hospitalization.³³ Besides, whether or not to be hospitalized after COVID-19 infection is not only affected by the symptoms of the disease, but also by the economic and health conditions of the region. In a word, it is difficult to objectively evaluate the relationship

between type 1 diabetes and hospitalized patients with COVID-19.

A prospective analysis demonstrated that compared with patients without type 1 diabetes, patients with COVID-19 with type 1 diabetes had a higher risk of developing more severe disease.³⁴ Besides, as we all know, patients with type 1 diabetes are prone to hyperglycemia; previous studies showed patients with COVID-19 who have hyperglycemia may develop more severe COVID-19 because hyperglycemia itself leads to changes in immune cell function and regulation of cytokines such as interleukin 6, as well as abnormalities in the coagulation system.^{35 36} Moreover, it is reported that patients with type 1 diabetes have an increased risk of intensive care unit admission compared with patients without type 1 diabetes.^{37 38}

It was reported that after contracting COVID-19, patients with type 1 diabetes experienced poor blood glucose control, leading to increased mortality.^{39–41} Besides, after adjusting for several confounders, the OR for in-hospital COVID-19-related deaths in patients with type 1 diabetes compared with those without type 1 diabetes was 2.86,⁴² and patients with type 1 diabetes had a 5% higher risk of death than patients without type 1 diabetes.³⁷ An observational study also shows patients with type 1 diabetes have a significantly increased risk of fatal COVID-19 compared with those without type 1 diabetes.³⁸

After removal of SNPs associated with other autoimmune diseases, our findings were unchanged, suggesting that IVs of type 1 diabetes independently influence COVID-19 infection and prognosis, which provides a basis for later use of these IVs as well as genes as drug targets.

Reverse MR analysis showed that six COVID-19-related phenotypes were not associated with type 1 diabetes. As mentioned in the Introduction section, some observational studies suggested that COVID-19 may be a risk factor for type 1 diabetes. However, our results did not show the causal relationship between COVID-19 positive and type 1 diabetes. An observational study suggested

that the increased incidence of type 1 diabetes observed during the first 18 months of the COVID-19 pandemic may not be a direct effect of COVID-19 infection, but rather a result of confinement and physical distance.⁴³ Besides, during the pandemic of COVID-19, diagnosis of type 1 diabetes may be delayed due to limited access to healthcare. A previous study showed that there is no conclusive evidence that COVID-19 spontaneously induces type 1 diabetes.¹⁹ Moreover, disease progression in type 1 diabetes is a more chronic and long-term process than in COVID-19 infection, so drawing a definitive conclusion on whether COVID-19 is capable of causing type 1 diabetes is difficult and will require longer-term observation at a later date.⁴⁴

The results of the pathway analysis study showed one metabolic pathway may be associated with severe COVID-19 and COVID-19 death, namely regulation of immune system process. It has been shown in the literature that high expression of the monocyte–macrophage chemotactic receptor CCR2 is associated with severe COVID-19 using transcriptome-wide association in lung tissue.⁴⁵ Observational studies have demonstrated a dysregulated immune response in patients with COVID-19, characterized by lymphopenia and cytokine storm. The subsequent dysregulated immune response can lead to septic shock, acute respiratory distress syndrome and/or multiorgan failure, which can result in increased severity and mortality in patients with COVID-19 infection.⁴⁶

Two GWAS summary datasets were used in this study. The discovery dataset included both adolescents and adults with type 1 diabetes, and the replication dataset included patients with type 1 diabetes who were diagnosed at an age younger than 17 years. Results from discovery data showed that type 1 diabetes was a risk factor for COVID-19 severity and mortality. This result was further confirmed by replicate sample. By comparing the results of the two samples, the age of patients with type 1 diabetes was found to have no effect on COVID-19 infection or the severity of post-infection. An available MR analysis study has shown that age is not a risk factor for the severity of COVID-19.⁴⁷

Our study has some advantages. First, we comprehensively analyzed the causal relationship between type 1 diabetes and six COVID-19 infection and prognosis-related traits. Second, the GWAS data used in this study were obtained from published studies with open and reliable data, and the persuasive power to infer causality was relatively strong. Lastly, we conducted a series of sensitivity analyses and reverse MR analysis to validate the robust of our MR results, which makes our results more convincing.

There are also some disadvantages in our study. On one hand, our study focused on European population, lacking studies of other populations, and results may differ somewhat when extrapolated to other populations. On the other hand, as the data we used were summarized and individual information was not available, it was not

possible to estimate the degree of overlap between participants with exposure and outcome data, and in addition, the summary data lacked the patient's level of glycemic control at the time of diagnosis and the specific time of diagnosis, all of which may affect the extrapolation of results to some extent. Besides, GWAS summary data on treatment are currently limited and only available for colchicine treatment and its control group, and further studies will continue if additional data on COVID-19 treatment are available. Finally, the lack of detailed data on the genotype and phenotype of COVID-19 in our study allows us to speculate only on the time of publication of GWAS data that the mutant strains of COVID-19 virus include mainly Alpha, Beta and Delta, which may partially affect the results.

CONCLUSIONS

In summary, our study used a two-sample MR to investigate the causal relationship between type 1 diabetes and COVID-19 infection and prognosis. Our results suggested that the genetically predicted type 1 diabetes was potentially associated with higher risk of severe COVID-19 and COVID-19 death. Further mechanistic studies such as molecular mechanism analysis, mouse model construction and further therapeutic studies are needed to explore the relationship between type 1 diabetes and COVID-19 infection and prognosis.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants. The GWAS summary statistics used in the present study were obtained from published studies. The ethics approval for GWAS was obtained from the original publications. No new ethics approval or informed consent was required. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available in a public, open access repository.

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