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Leveraging large-scale genetic data to assess the causal impact of COVID-19 on multisystemic diseases

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Abstract

Background The long-term impacts of COVID-19 on human health are a major concern, yet comprehensive evaluations of its effects on various health conditions are lacking.

Methods This study aims to evaluate the role of various diseases in relation to COVID-19 by analyzing genetic data from a large-scale population over 2,000,000 individuals. A bidirectional two-sample Mendelian randomization approach was used, with exposures including COVID-19 susceptibility, hospitalization, and severity, and outcomes encompassing 86 different diseases or traits. A reverse Mendelian randomization analysis was performed to assess the impact of these diseases on COVID-19.

Results Our analysis identified causal relationships between COVID-19 susceptibility and several conditions, including breast cancer (OR = 1.0073, 95% CI = 1.0032–1.0114, $p = 5 \times 10 - 4$), ER + breast cancer (OR = 0.5252, 95% CI = 0.3589–0.7685, $p = 9 \times 10 - 4$), and heart failure (OR = 1.0026, 95% CI = 1.001–1.0042, $p = 0.002$). COVID-19 hospitalization was causally linked to heart failure (OR = 1.0017, 95% CI = 1.0006–1.0028, $p = 0.002$) and Alzheimer's disease (OR = 1.5092, 95% CI = 1.1942–1.9072, $p = 0.0006$). COVID-19 severity had causal effects on primary biliary cirrhosis (OR = 2.6333, 95% CI = 1.8274–3.7948, $p = 2.059 \times 10 - 7$), celiac disease (OR = 0.0708, 95% CI = 0.0538–0.0932, $p = 9.438 \times 10–80$), and Alzheimer's disease (OR = 1.5092, 95% CI = 1.1942–1.9072, $p = 0.0006$). Reverse MR analysis indicated that rheumatoid arthritis, diabetic nephropathy, multiple sclerosis, and total testosterone (female) influence COVID-19 outcomes. We assessed heterogeneity and horizontal pleiotropy to ensure result reliability and employed the Steiger directionality test to confirm the direction of causality.

Conclusions This study provides a comprehensive analysis of the causal relationships between COVID-19 and diverse health conditions. Our findings highlight the long-term impacts of COVID-19 on human health, emphasizing the need for continuous monitoring and targeted interventions for affected individuals. Future research should explore these relationships to develop comprehensive healthcare strategies.

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Keywords Genome-Wide Association Study (GWAS), Mendelian randomization, Cancer, Long-term effect, Coronavirus disease-2019 (COVID-19), Heart failure Alzheimer's disease

Introduction

As of June 10, 2023, there have been over 676 million confirmed cases of COVID-19 worldwide, with approximately 6.88 million related deaths (source: https://coronavirus.jhu.edu/map.html) [1]. While most individuals infected with COVID-19 can achieve recovery [2], the infection may lead to persistent effects on the human body and affect the risk of other diseases [3, 4]. Previous studies have indicated potential links between COVID-19 and conditions like chronic obstructive pulmonary disease (COPD) [5], myocardial infarction (MI) [6], stroke [7], and diabetes [8]. However, prior investigations have primarily relied on retrospective and observational studies and are often limited to a single disease category. There is a lack of comprehensive research on the causal relationships between COVID-19 and multiple systemic diseases.

Mendelian randomization employs exposure-related single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to analyze causal relationships between exposures and outcomes [9, 10], thereby providing a method to mitigate the influence of confounding factors and achieving effects similar to randomized controlled studies [11, 12]. Previous studies have explored the causal effects of COVID-19 on the risk of various diseases, such as gout [13], cancer [14], psoriasis [15], diabetes [16], and atrial fibrillation [17] using MR. However, there remains a dearth of comprehensive research exploring the causal association between COVID-19 and the risk of multisystem diseases.

In this study, we aim to evaluate the role of various diseases in relation to COVID-19 susceptibility, hospitalization, and severity by analyzing genetic data from a large-scale population. We employed Mendelian randomization to comprehensively investigate the causal relationships between COVID-19 and a range of diseases, including cancer, autoimmune diseases, cardiovascular diseases, digestive diseases, endocrine diseases, mental and nervous system diseases, pulmonary diseases, renal diseases, and reproductive and sexual function. Additionally, reverse Mendelian randomization was conducted to explore the reverse effects of multisystem diseases on COVID-19.

Methods

Data sources

Exposure data

The GWAS summary results for SARS-CoV-2 infection, hospitalized COVID-19, and critically ill COVID-19 were derived from the COVID-19 host genetics initiative (HGI) GWAS meta-analysis (RELEASE 7) (https://www.covid19hg.org/results/r7/) [18] as the exposure data. HGI represents a meta-analysis conducted using publicly available GWAS data for COVID-19. The dataset included 112,612 individuals with SARS-CoV-2 infection and 2,474,079 controls, 88.9% of whom were of European origin. It also included 24,274 hospitalized COVID-19 patients and 2,474,079 controls, with 88.9% being of European origin. Additionally, 8,779 critically ill COVID-19 patients and 1,001,875 controls, 94.9% of whom were European, were included. We categorized SARS-CoV-2 infection as COVID-19 susceptibility, hospitalized COVID-19 as COVID-19 hospitalization, and critical COVID-19 as COVID-19 severity. We extracted single

nucleotide polymorphisms (SNPs) associated with COVID-19 susceptibility, COVID-19 hospitalization, and COVID-19 severity as instrumental variables (IVs).

Outcome data

The GWAS summary-level data of multisystem diseases used in this study were obtained from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/, updated until April 19, 2023). These data were sourced from various projects, including UK Biobank [19], FINNGEN [20], MRC-IEU [21], IIBDGC [22], Bipolar Disorder Working Group of the Psychiatric Genomics Consortium [23], International Genomics of Alzheimer's Project (IGAP) [24], Ovarian Cancer Association Consortium (OCAC) [25], Oncoarray Oral and Oropharyngeal Cancer [26], Breast Cancer Association Consortium (BCAC) [27], CKDGen [28], and the Neale Lab (http://www.nealelab.is/uk-biobank/). Detailed information can be found in Supplementary Table 1.

Statistical analyses

Instrumental variable selection

The flowchart of the study is depicted in Fig. 1. In summary, we investigated the causal relationship between COVID-19 and multisystem diseases. In this study, we extracted SNPs related to COVID-19 susceptibility, COVID-19 hospitalization, and COVID-19 severity as instrumental variables. To ensure the accuracy and reliability of the causal relationship, we performed quality control and selected the IVs based on previous studies [12]. Firstly, we identified SNPs that were significantly associated with COVID-19

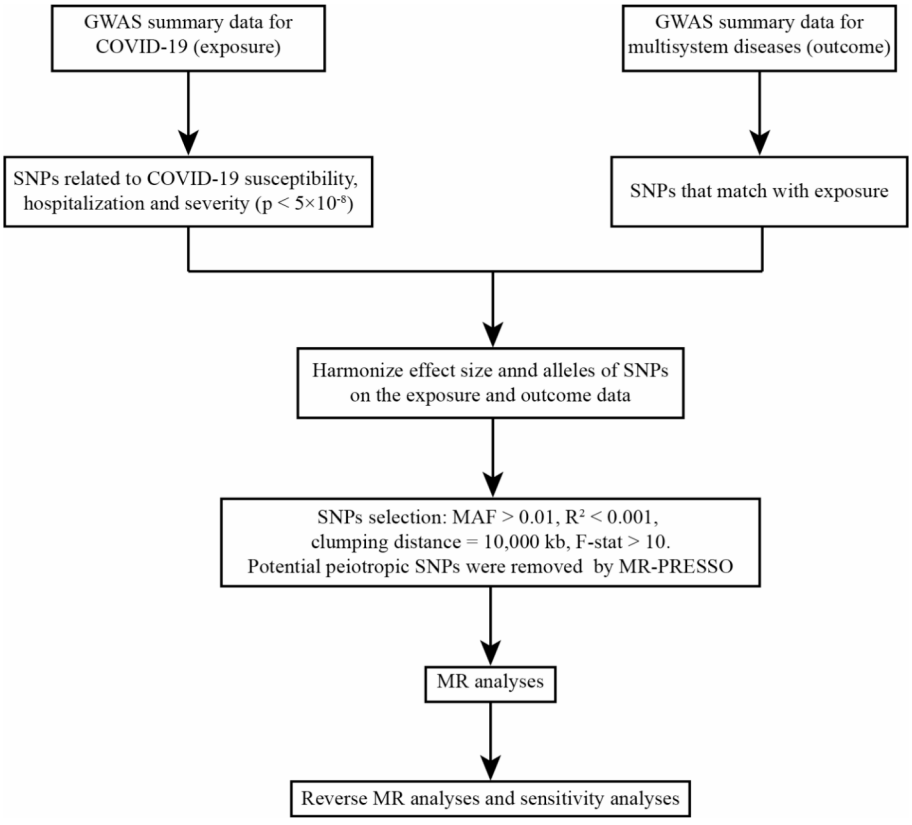

Fig. 1 Study design and workflow

($p<5\times10^{-8}$) as instrumental variables. Secondly, we set a minor allele frequency (MAF) threshold of 0.01 for the variants of interest. Thirdly, as strong linkage disequilibrium (LD) between instrumental variables can introduce bias in MR analysis [29], it is essential to ensure no LD between the selected IVs. Therefore, in this study, we ensured that the R^2 value was <0.001 and the clumping distance was 10,000 kb when selecting the SNPs. Furthermore, we removed palindrome SNPs, which are SNPs with allele combinations A/T, T/A, G/C, or C/G. Besides, to avoid weak instrument bias, we excluded instrumental variables with an F statistic less than or equal to 10 [30]. Lastly, we employed the MR-PRESSO and MR-Egger regression tests to monitor potential horizontal pleiotropic effects, and only the remaining SNPs after removing pleiotropic SNPs were used for subsequent MR analysis (both MR-PRESSO global test $p>0.05$ and MR-Egger regression $p>0.05$).

MR and reverse MR analyses

We conducted Mendelian randomization analyses using COVID-19 as the exposure and multisystem diseases as the outcomes. Subsequently, we performed reverse Mendelian randomization analyses, with multisystem diseases as the exposure and COVID-19 as the outcome, to demonstrate the direction of the causal relationship. Additionally, we employed the MR Steiger directionality test to assess the directional nature and correctness of the causal effects [31]. For features involving multiple instrumental variables (IVs), we utilized five MR methods for analysis, including the inverse-variance weighting (IVW) test [32], the MR-Egger regression [33], the weighted median estimation (WME) [34], the weighted mode [35], and the MR-PRESSO [36]. It has been reported that the IVW method is more accurate than other methods [34], and so we primarily utilized the IVW method for analysis and reported its results, while the other four methods served as supplementary analyses. For features with only one IV, we employed the Wald ratio test to estimate the causal relationship between the IV and multi-system diseases [37]. In addition, We performed Cochran's Q statistics to evaluate the heterogeneity. If the p-value in Cochran's Q statistics was less than 0.05, we considered the presence of heterogeneity in that analysis [38]. We employed the MR-PRESSO global test to evaluate the presence of horizontal pleiotropy, and if the p-value was greater than 0.05, we concluded that there was no evidence of horizontal pleiotropy [39].

Statistical analysis

All the analyses were performed with the R packages "TwoSampleMR" [40], "MRPRESSO", "forestplot", and "ggplot2" [41], in R software (v4.2.3) (http://www.r-project.org). The p-value<0.05/n (n refers to the disease number of the system) was considered significant, and the p-value between 0.05 and 0.05/n was regarded as suggestive evidence. A p-value<0.05 was used as a significant threshold in sensitivity analysis.

Results

SNP selection

Firstly, we applied the following thresholds to select SNPs: p-value$<10^{-8}$, $R^2<0.001$, and clumping distance=10,000 kb, minor allele frequency (MAF)≥0.01. We selected a total of 7 SNPs associated with COVID-19 susceptibility, 5 SNPs associated with COVID-19 hospitalization, and 8 SNPs associated with COVID-19 severity. Subsequently, we

removed 2 palindrome SNPs associated with COVID-19 susceptibility, 1 palindrome SNP associated with COVID-19 hospitalization, and 1 palindrome SNP associated with COVID-19 severity. These SNPs were used as instrumental variables. Subsequently, we calculated the F-statistics for each SNP, and all SNPs had F-values greater than 10 (Supplementary Table 2). The F-values for COVID-19 susceptibility IVs ranged from 32.4943 to 107.4253, for COVID-19 hospitalization IVs, they ranged from 34.433 to 69.5504, and for COVID-19 severity IVs, they ranged from 35.6082 to 83.5852, indicating no evidence of weak instrument bias. We conducted an MR-PRESSO global test to assess pleiotropic effects and found no evidence of pleiotropy ($p>0.05$). Additionally, we removed pleiotropic SNPs identified by the MR-PRESSO outlier test or MR-Egger regression and performed another round of the MR-PRESSO global test and the MR-Egger regression, both yielding p-values>0.05, indicating no evidence of horizontal pleiotropy among the instrumental variables.

Causal relationships between COVID-19 and multisystem diseases

In this study, we employed MR to investigate the potential multisystem effects of COVID-19. Specifically, COVID-19 susceptibility, COVID-19 hospitalization, and COVID-19 severity were considered as exposures, while cancers, autoimmune diseases, cardiovascular diseases, digestive diseases, endocrine diseases, mental and nervous system diseases, pulmonary diseases, renal diseases, and reproductive and sexual function were evaluated as outcomes. Since our study involved multiple rounds of Mendelian randomization analyses, we adjusted the p-values to mitigate Type I errors, utilizing a significance threshold of P=0.05/n, where 'n' represents the number of features included within a particular system. Consequently, the significance thresholds for various systems were set as follows: cancers $p=0.001389$ (0.05/36), autoimmune diseases $p=0.007143$ (0.05/7), cardiovascular diseases $p=0.01$ (0.05/5), digestive diseases $p=0.01$ (0.05/5), endocrine diseases $p=0.01$ (0.05/5), mental and nervous system diseases $p=0.005$ (0.05/10), pulmonary diseases $p=0.0125$ (0.05/4), renal diseases $p=0.00625$ (0.05/8), and reproductive and sexual function $p=0.01$ (0.05/5). However, we acknowledge concerns that such stringent criteria may lead to the omission of meaningful results. Consequently, we also present results using a significance threshold of $P=0.05$, which was considered suggestive evidence. The subsequent section outlines the causal effects of COVID-19 on ten categories of diseases, including cancers, autoimmune diseases, etc.

Category 1: cancer

Using a significance threshold of $P=0.001389$, we found significant causal relationships between COVID-19 susceptibility and breast cancer (OR=1.0073, 95%CI=1.0032–1.0114, $p=5\times10^{-4}$, IVW), as well as ER+breast cancer (OR=0.5252, 95%CI=0.3589–0.7685, $p=9\times10^{-4}$, IVW) (Fig. 2; Table 1). When analyzing with a significance threshold of $p=0.05$, we discovered potential causal relationships between COVID-19 susceptibility and breast cancer (OR=1.0073, 95%CI=1.0032–1.0114, $p=0.0005$, IVW), ER+breast cancer (OR=0.5252, 95%CI=0.3589–0.7685, $p=0.0005$, IVW), endometrial cancer (OR=1.8434, 95%CI=1.0957–3.1015, $p=0.0212$, IVW), head and neck cancer (OR=0.9985, 95%CI=0.9971–0.99996, $p=0.0433$, IVW), lung cancer (OR=0.9985, 95%CI=0.9971–0.99996, $p=0.0433$, IVW), oral and oropharyngeal cancer (OR=0.9976, 95%CI=0.9953–0.9998, $p=0.0303$, IVW), oropharyngeal cancer

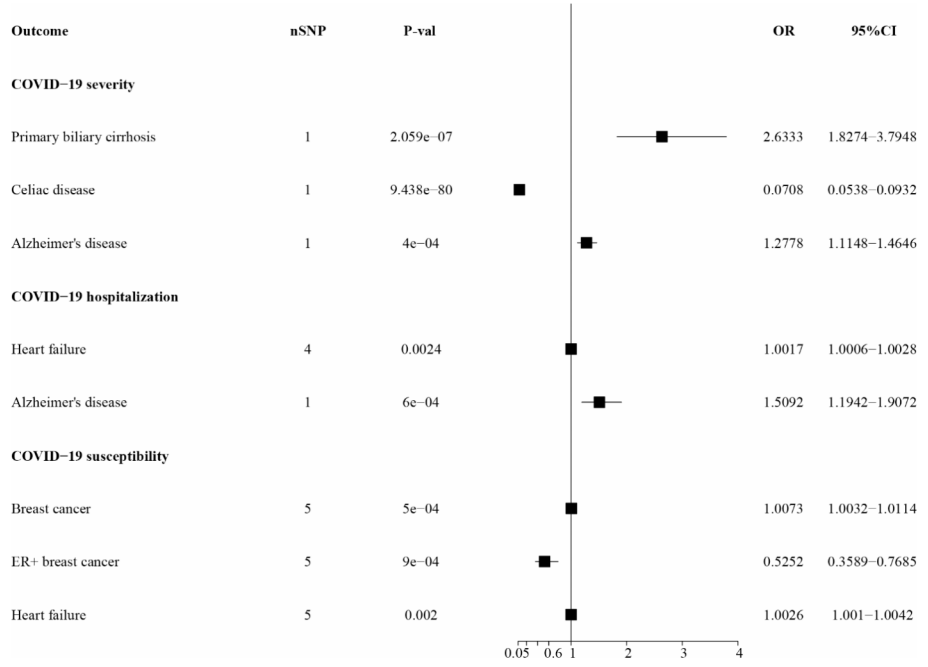

Fig. 2 Mendelian randomization results of causal effects between COVID-19 and multisystem disease risk ($p < 0.05/n$). CI, confidence interval; COVID-19, coronavirus disease-2019; IVW, inverse-variance weighted; OR, odds ratio

Table 1 Mendelian randomisation (MR) results of causal effects between COVID-19 and multisystem diseases ($p < 0.05/n$)

Exposure	Outcome	method	Number of SNPs	b	se	pval	OR	95%CI	Correct causal direction	Steiger *p*-value
COVID-19 severity	Primary biliary cirrhosis	Wald ratio	1	0.9683	0.1864	2.06E-07	2.6333	1.8274-3.7948	TRUE	5.29E-06
	Celiac disease	Wald ratio	1	-2.648	0.14	9.44E-80	0.0708	0.0538-0.0932	TRUE	2.17E-71
	Alzheimer's disease	Wald ratio	1	0.2452	0.0696	0.0004	1.2778	1.1148-1.4646	FALSE	0.06585
COVID-19 hospitalization	Heart failure	IVW	4	0.0017	0.0006	0.0024	1.0017	1.0006-1.0028	TRUE	0.01478
	Alzheimer's disease	Wald ratio	1	0.4115	0.1194	0.0006	1.5092	1.1942-1.9072	FALSE	0.02631
COVID-19 susceptibility	Breast cancer	IVW	5	0.0073	0.0021	0.0005	1.0073	1.0032-1.0114	TRUE	4.46E-07
	ER + breast cancer	IVW	5	-0.644	0.1942	0.0009	0.5252	0.3589-0.7685	TRUE	0.00136
	Heart failure	IVW	5	0.0026	0.0008	0.002	1.0026	1.001-1.0042	TRUE	9.87E-06

(OR = 2.2239, 95%CI = 1.1253–4.3953, $p = 0.0215$, IVW), and ovarian cancer (OR = 1.367, 95%CI = 1.0064–1.8568, $p = 0.0454$, IVW) (Fig. 3; Table 2). Furthermore, we observed a potential causal relationship between COVID-19 hospitalization and uterine/endometrial cancer (OR = 1.0008, 95%CI = 1.000003–1.0016, $p = 0.0493$, IVW), oral cavity and

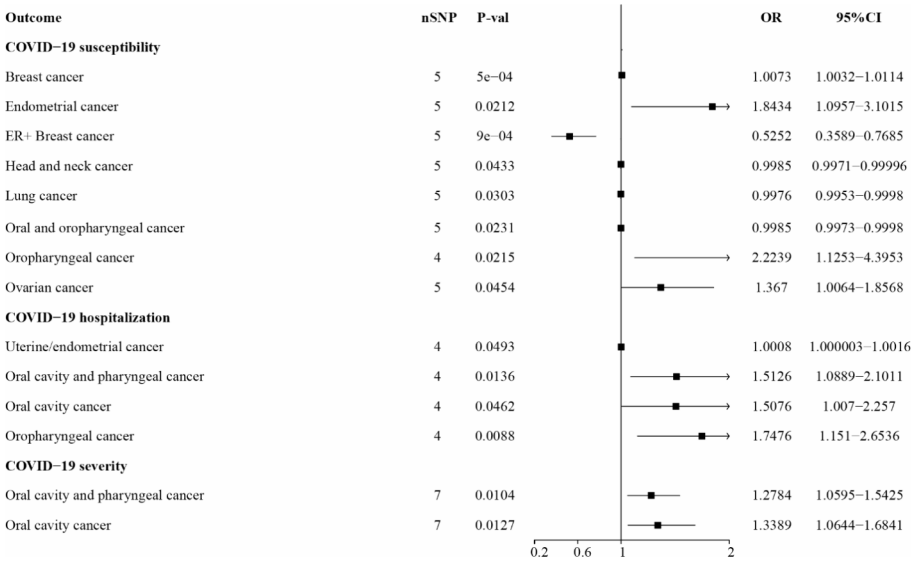

Fig. 3 Mendelian randomization results of causal effects between COVID-19 and cancer risk ($p < 0.05$). CI, confidence interval; COVID-19, coronavirus disease-2019; IVW, inverse-variance weighted; OR, odds ratio

pharyngeal cancer (OR=1.5126, 95%CI=1.000003–1.0016, $p=0.0493$, IVW), oral cavity cancer (OR=1.5126, 95%CI=1.000003–1.0016, $p=0.0462$, IVW), and oropharyngeal cancer (OR=1.7476, 95%CI=1.151–2.6536, $p=0.0088$, IVW) (Table 2; Fig. 3). Additionally, COVID-19 severity was found to have a potential causal relationship with oral cavity and pharyngeal cancer (OR=1.2784, 95%CI=1.0595–1.5425, $p=0.0104$, IVW) and oral cavity cancer (OR=1.3389, 95%CI=1.0644–1.6841, $p=0.0127$, IVW) (Table 2; Fig. 3). Moreover, the Steiger directionality test indicated that all these causal relationships exhibited a causal direction from the exposure to the outcome (Tables 1 and 2).

Category 2: autoimmune diseases

Using a significance threshold of $P=0.007143$, we identified a significant causal relationship between COVID-19 severity and primary biliary cirrhosis (OR=2.6333, 95%CI=1.8274–3.7948, $p=2.059\times10^{-7}$, Wald ratio) (Fig. 2; Table 1). When we expanded the threshold to $p=0.05$, we found a causal relationship between COVID-19 severity and psoriasis (OR=0.9979, 95%CI=0.9963–0.9995, $p=0.0109$, IVW) (Fig. 4; Table 3). However, we did not observe any causal relationships between COVID-19 and multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, or primary sclerosing cholangitis.

Category 3: cardiovascular diseases

In analysis using a significance threshold of $P=0.01$, we found a significant causal relationship between COVID-19 hospitalization and heart failure (OR=1.0017, 95%CI=1.0006–1.0028, $p=0.0024$, IVW), as well as between COVID-19 susceptibility and heart failure (OR=1.0026, 95%CI=1.001–1.0042, $p=0.0026$, IVW) (Fig. 2; Table 1). This study also analyzed the impact of COVID-19 on myocarditis, coronary heart disease, essential (primary) hypertension, and atrial fibrillation and flutter, but we did not find evidence of causal relationships between them. However, we did not find any causal

Table 2 Mendelian randomization (MR) results of causal effects between COVID-19 and cancers ($p < 0.05$)

Exposure	Outcome	method	Number of SNPs	b	se	pval	OR	95%CI	Correct causal direction	Steiger *p*-value
COVID-19 susceptibility	Breast cancer	IVW	5	0.007	0.002	5E-04	1.007	1.0032-1.0114	TRUE	4.46E-07
	ER + Breast cancer	IVW	5	-0.64	0.194	9E-04	0.525	0.3589-0.7685	TRUE	0.0014
	Endometrial cancer	IVW	5	0.612	0.265	0.021	1.843	1.0957-3.1015	TRUE	0.0058
	Head and neck cancer	IVW	5	-0	7E-04	0.043	0.999	0.9971-0.99996	TRUE	0.0263
	Lung cancer	IVW	5	-0	0.001	0.03	0.998	0.9953-0.9998	TRUE	0.0052
	Oral and oropharyngeal cancer	IVW	5	-0	6E-04	0.023	0.999	0.9973-0.9998	TRUE	0.0061
	Oropharyngeal cancer	IVW	4	0.799	0.348	0.022	2.224	1.1253-4.3953	TRUE	0.0005
	Ovarian cancer	IVW	5	0.313	0.156	0.045	1.367	1.0064-1.8568	TRUE	0.0223
COVID-19 hospitalization	Uterine/endometrial cancer	IVW	4	8E-04	4E-04	0.049	1.001	1.000003-1.0016	TRUE	0.0014
	Oral cavity and pharyngeal cancer	IVW	4	0.414	0.168	0.014	1.513	1.0889-2.1011	TRUE	0.0364
	Oral cavity cancer	IVW	4	0.411	0.206	0.046	1.508	1.007-2.257	TRUE	0.0009
	Oropharyngeal cancer	IVW	4	0.558	0.213	0.009	1.748	1.151-2.6536	TRUE	0.0278
COVID-19 severity	Oral cavity and pharyngeal cancer	IVW	7	0.246	0.096	0.01	1.278	1.0595-1.5425	TRUE	0.0110
	Oral cavity cancer	IVW	7	0.292	0.117	0.013	1.339	1.0644-1.6841	TRUE	0.0099

relationships between COVID-19 and other cardiovascular diseases, even after expanding the threshold to $p=0.05$.

Category 4: digestive diseases

We found a significant causal relationship between COVID-19 severity and celiac disease (OR = 0.0708, 95%CI = 0.0538–0.0932, $p=9.438\times10–80$, Wald ratio) using a significance threshold of $P=0.01$ (Fig. 2; Table 1). When we expanded the threshold to $p=0.05$, we also found potential causal relationships between COVID-19 hospitalization and Crohn's disease (OR = 1.3052, 95%CI = 1.0447–1.6306, $p=0.019$, Wald ratio), as well as between COVID-19 severity and ulcerative colitis (OR = 0.8958, 95%CI = 0.8075–0.9937, $p=0.0375$, IVW) (Fig. 4; Table 3). However, when we analyzed COVID-19 and inflammatory bowel disease, we did not find evidence of a causal relationship.

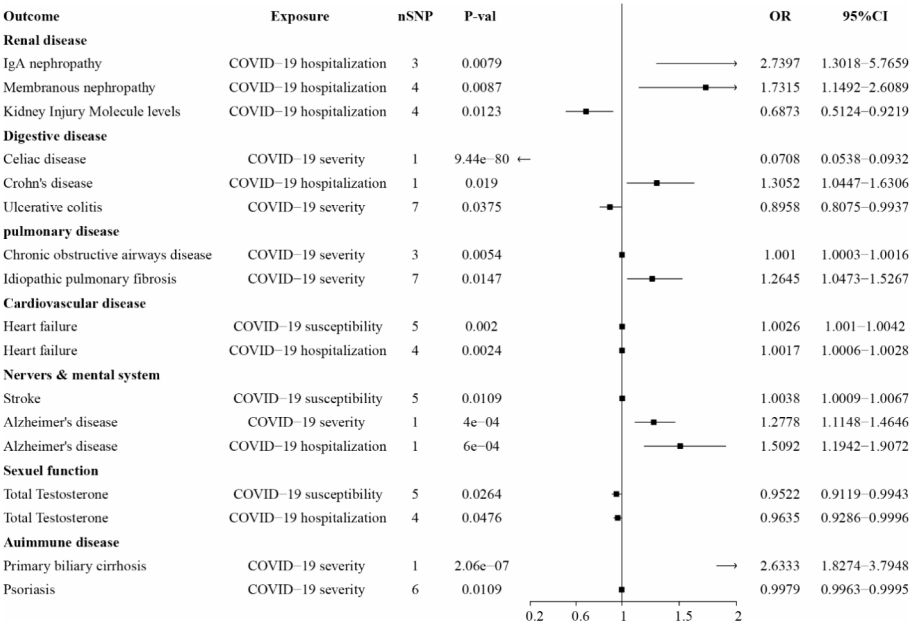

Fig. 4 Mendelian randomization results of causal effects between COVID-19 and cancer risk ($p < 0.05$). CI, confidence interval; COVID-19, coronavirus disease-2019; IVW, inverse-variance weighted; OR, odds ratio

Category 6: endocrine diseases

We analyzed the causal relationship between COVID-19 and five endocrine disorders: type 2 diabetes, hyperthyroidism/thyrotoxicosis, hypothyroidism, hyperaldosteronism, and Cushing's syndrome. However, regardless of whether we used a significance threshold of $p=0.01$ or $p=0.05$, we did not find any evidence of a relationship between COVID-19 susceptibility, COVID-19 hospitalization, COVID-19 severity, and the aforementioned endocrine disorders.

Category 7: mental and nervous system diseases

When $P=0.005$ was used as the significance threshold, there was a significant causal relationship between COVID-19 severity and Alzheimer's disease (OR=1.2778, 95% CI=1.1148–1.4646, $p=0.0004$, Wald ratio), as well as between COVID-19 hospitalization and Alzheimer's disease (OR=1.5092, 95% CI=1.1942–1.9072, $p=0.0006$, Wald ratio) (Fig. 2; Table 1). However, the Steiger test suggests that the causal effects of COVID-19 severity and COVID-19 susceptibility on Alzheimer's disease may not be directional (Table 1). When the p-value of 0.05 was used, we found a possible causal relationship between COVID-19 susceptibility and stroke (OR=1.0038, 95% CI=1.0009–1.0067, $p=0.0109$, IVW) (Fig. 4; Table 3). We also analyzed the causal relationships between COVID-19 and bipolar disorder, schizophrenia, depression, amyotrophic lateral sclerosis, malaise and fatigue, disturbances of smell and taste, and cerebral infarction, but there was no evidence that suggests a causal relationship between COVID-19 and any of them.

Category 8: pulmonary diseases

We did not find a causal relationship between COVID-19 and the pulmonary diseases included in our study using, $p=0.0125$ as the significance threshold. However, when $p=0.05$ was used as the significance threshold, we found a causal effect of COVID-19

Table 3 Mendelian randomization (MR) results of causal effects between COVID-19 and nonmalignant diseases ($p < 0.05$)

	Exposure	Outcome	method	Number of SNPs	b	se	pval	OR	95%CI	Correct causal direction	Steiger *p*-value
Renal disease	COVID-19 hospitalization	IgA nephropathy	IVW	3	1.01	0.38	0.008	2.74	1.3018–5.7659	TRUE	0.0286
	COVID-19 hospitalization	Membranous nephropathy	IVW	4	0.55	0.21	0.009	1.73	1.1492–2.6089	TRUE	0.0011
	COVID-19 hospitalization	Kidney Injury Molecule levels	IVW	4	-0.4	0.15	0.012	0.69	0.5124–0.9219	TRUE	0.0088
Digestive disease	COVID-19 severity	Celiac disease	Wald ratio	1	-2.6	0.14	#####	0.07	0.0538–0.0932	TRUE	2.17×10^{-71}
	COVID-19 hospitalization	Crohn's disease	Wald ratio	1	0.27	0.11	0.019	1.31	1.0447–1.6306	FALSE	0.3085
	COVID-19 severity	Ulcerative colitis	IVW	7	-0.1	0.05	0.038	0.9	0.8075–0.9937	TRUE	0.0059
Pulmonary disease	COVID-19 severity	Chronic obstructive airways disease	IVW	3	0	0	0.005	1	1.0003–1.0016	TRUE	0.0002
	COVID-19 severity	Idiopathic pulmonary fibrosis	IVW	7	0.23	0.1	0.015	1.26	1.0473–1.5267	TRUE	0.0038
Cardiovascular disease	COVID-19 susceptibility	Heart failure	IVW	5	0	0	0.002	1	1.001–1.0042	TRUE	0.00000987
	COVID-19 hospitalization	Heart failure	IVW	4	0	0	0.002	1	1.0006–1.0028	TRUE	0.0148
Nervers & mental system	COVID-19 susceptibility	Stroke	IVW	5	0	0	0.011	1	1.0009–1.0067	TRUE	0.0182
	COVID-19 severity	Alzheimer's disease	Wald ratio	1	0.25	0.07	4E-04	1.28	1.1148–1.4646	FALSE	0.0658
	COVID-19 hospitalization	Alzheimer's disease	Wald ratio	1	0.41	0.12	6E-04	1.51	1.1942–1.9072	FALSE	0.0263
Sexuel function	COVID-19 susceptibility	Total Testosterone (Female)	IVW	5	-0	0.02	0.026	0.95	0.9119–0.9943	TRUE	0.0859
	COVID-19 hospitalization	Total Testosterone (Female)	IVW	4	-0	0.02	0.048	0.96	0.9286–0.9996	TRUE	0.00000139
Auimmune disease	COVID-19 severity	Primary biliary cirrhosis	Wald ratio	1	0.97	0.19	#####	2.63	1.8274–3.7948	TRUE	0.0002
	COVID-19 severity	Psoriasis	IVW	6	-0	0	0.011	1	0.9963–0.9995	TRUE	0.0033

severity on the occurrence of chronic obstructive airways disease (OR=1.001, 95% CI=1.0003–1.0016, p=0.0054, IVW) and idiopathic pulmonary fibrosis (OR=1.2645, 95% CI=1.0473–1.5267, p=0.0147, IVW), with a positive directionality (Fig. 4; Table 3). We did not find evidence of a causal relationship between COVID-19 and forced vital capacity (FVC) or asthma.

Category 9: renal diseases

We analyzed the relationship between COVID-19 and eight kidney diseases: chronic kidney disease, diabetic nephropathy, glomerulonephritis, IgA nephropathy, kidney injury molecule levels, membranous nephropathy, nephrotic syndrome, and unspecified kidney failure. When p=0.00625 was used as the significance threshold, we did not find any causal relationship. When p=0.05 was used as the significance threshold, we found that COVID-19 hospitalization may have a causal effect on IgA nephropathy (OR=2.7397, 95% CI=1.3018–5.7659, p=0.0079, IVW), membranous nephropathy (OR=1.7315, 95% CI=1.1492–2.6089, p=0.0087, IVW), and kidney injury molecule levels (OR=0.6873, 95% CI=0.5124–0.9219, p=0.0123, IVW) (Fig. 4; Table 3). The Steiger test suggests a directional relationship in these cases (Table 3). We did not find any causal relationship between COVID-19 and chronic kidney disease, diabetic nephropathy, glomerulonephritis, nephrotic syndrome, or unspecified kidney failure.

Category 10: reproductive and sexual function

With P=0.001 as the significance threshold, we did not find a causal relationship between COVID-19 and reproductive and sexual function. While using p=0.05 as the significance threshold, we found that COVID-19 susceptibility (OR=0.9522, 95% CI=0.9119–0.9943, p=0.0264, IVW) and COVID-19 hospitalization (OR=0.9635, 95% CI=0.9286–0.9996, p=0.0476, IVW) have a causal impact on total testosterone and show directional effects (Fig. 4; Table 3). We did not find a causal relationship between COVID-19 and age when periods started (menarche), age at menopause (last menstrual period), erectile dysfunction, sex hormone binding globulin (SHBG), or total testosterone (female and male).

Reverse MR between COVID-19 and risk of multisystem diseases

To evaluate reverse causal effects, we conducted Mendelian randomization analyses using multisystem diseases as the exposure, COVID-19 susceptibility, COVID-19 hospitalization, and COVID-19 severity as outcomes. Similarly, we used a significance threshold of p=0.05/n (n being the number of diseases included in this system). We found that rheumatoid arthritis (OR=0.9673, 95% CI=0.9446–0.9906, p=0.0061, IVW) and diabetic nephropathy (OR=0.9492, 95% CI=0.9145–0.9853, p=0.0062, IVW) may reduce COVID-19 susceptibility. Multiple sclerosis may increase the risk of hospitalization due to COVID-19 (OR=7.49×1011, 95% CI=0.9145–0.9853, p=0.0062, IVW). Total testosterone (female) levels have a causal relationship with COVID-19 hospitalization (OR=0.8107, 95% CI=0.6978–0.942, p=0.0062, IVW) and COVID-19 severity (OR=0.6869, 95% CI=0.5349–0.8821, p=0.0033, IVW) (Fig. 5; Table 4). It is worth noting that when using p=0.05 as the significance threshold, COVID-19 susceptibility and COVID-19 hospitalization also have a causal effect on total testosterone (female) (Table 3). Therefore, there may be a bidirectional causal relationship between COVID-19

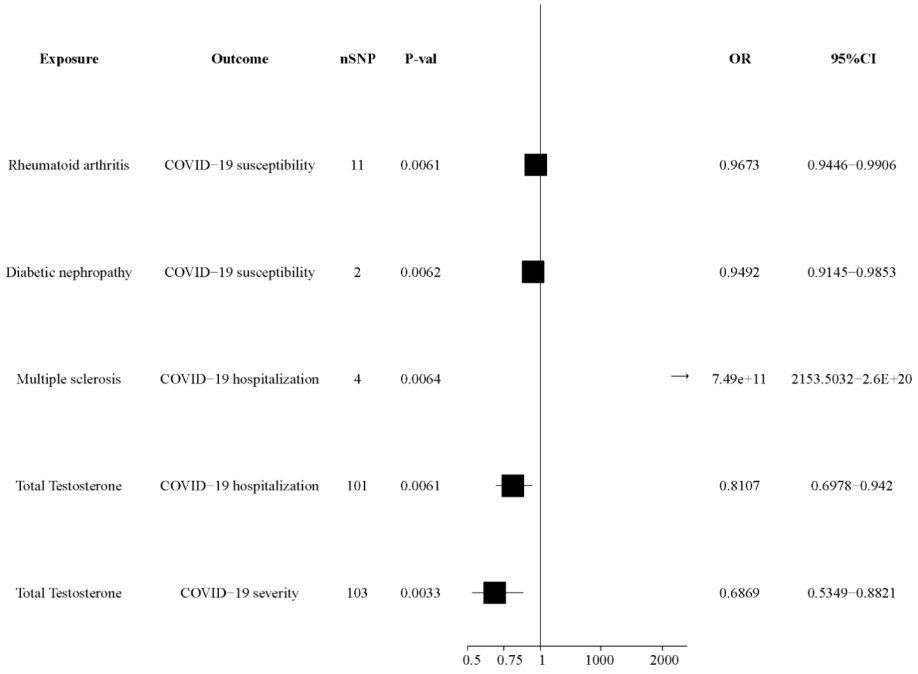

Fig. 5 Mendelian randomization results of causal effects between COVID-19 and multisystem disease risk except cancer ($p < 0.05$). CI, confidence interval; COVID-19, coronavirus disease-2019; IVW, inverse-variance weighted; OR, odds ratio

hospitalization and total testosterone (female). We also show the reverse MR results using $p < 0.05$ as the significance threshold in supplementary Table 3. To better illustrate the mutual causal relationships between COVID-19 and multisystem diseases, we have summarized a causal diagram (Fig. 6).

Sensitivity analyses

MR-Egger, weighted mode, simple mode, and weighted median methods yielded similar causal estimates in terms of magnitude and direction. When using the MR-Egger regression intercept method to test for horizontal pleiotropy in the positive outcomes of the studies, we found no evidence of horizontal pleiotropy ($p > 0.05$) (Supplemental Table 4). MR-PRESSO analysis indicated no outliers in the results. Additionally, the Cochrane Q statistic results showed no significant heterogeneity ($p > 0.05$).

Discussion

In today's global spread of COVID-19, a significant number of patients have either been previously infected or are currently experiencing infections with SARS-CoV-2 [1]. While most patients can recover [42], SARS-CoV-2 infection may have enduring effects on the human body [43, 44], and influence the risk of other diseases, potentially due to the resulting inflammatory responses [45, 46] and changes in immune function [47, 48]. However, the comprehensive impact of COVID-19 on the human body remains uncertain, which is a concern for many individuals who have previously been infected or are currently infected with COVID-19. Therefore, this study conducted a thorough analysis using Mendelian randomization to examine the causal effects of COVID-19 on multiple systems, revealing that COVID-19 may affect the risk of various diseases. To our knowledge, this is the first comprehensive study to investigate the causal relationships between

Table 4 Bidirectional mendelian randomization results of causal effects between multisystem diseases and COVID-19 ($p < 0.05/n$)

Exposure	Outcome	method	Number of SNPs	b	se	*p*-val	OR	95%CI	Correct causal direction	Steiger*p*-value
Rheumatoid arthritis	COVID-19 susceptibility	IVW	11	-0.033	0.0121	0.006	0.9673	0.9446-0.9906	TRUE	1.37E-128
Diabetic nephropathy	COVID-19 susceptibility	IVW	2	-0.052	0.019	0.006	0.9492	0.9145-0.9853	TRUE	5.46E-20
Multiple sclerosis	COVID-19 hospitalization	IVW	4	27.342	10.034	0.006	7.49E+11	2153.5032-2.6E+20	TRUE	4.11E-35
Total Testosterone (Female)	COVID-19 hospitalization	IVW	101	-0.21	0.0766	0.006	0.8107	0.6978-0.942	TRUE	0
Total Testosterone (Female)	COVID-19 severity	IVW	103	-0.376	0.1276	0.003	0.6869	0.5349-0.8821	TRUE	0

COVID-19 and a broad spectrum of multisystem diseases using a bidirectional two-sample Mendelian randomization approach. This study found that COVID-19 severity may increase the risk of primary biliary cirrhosis and Alzheimer's disease while decreasing the risk of celiac disease. COVID-19 hospitalization may increase the risk of heart failure and Alzheimer's disease. COVID-19 susceptibility may increase the risk of developing breast cancer and heart failure but decrease the risk of ER+breast cancer.

It is noteworthy that both COVID-19 hospitalization and COVID-19 severity may increase the risk of developing Alzheimer's disease. Ancha Baranova et al. [49] conducted a Mendelian randomization analysis on the relationship between COVID-19 and Alzheimer's disease and similarly found that hospitalized COVID-19 and critical COVID-19 may increase the risk of developing Alzheimer's disease. However, they also discovered a positive causal relationship between AD and hospitalized COVID-19, which we did not find, possibly due to our stricter significance threshold. Brain volume reduction and cognitive decline are core features of Alzheimer's disease. Douaud et al. [50] performed paired brain scans on 401 COVID-19 patients and compared them with a non-COVID-19 control group, and observed a greater reduction in grey matter thickness and overall brain size in COVID-19 patients than expected, along with changes in olfactory tissue damage markers and a greater decline in cognitive abilities. While we did not find a causal relationship between COVID-19 and olfaction or cognitive function, our study also suggests that COVID-19 may increase the risk of Alzheimer's disease. SARS-CoV-2 infection and induce tau hyperphosphorylation, the damaging "leakage" of RyR2 channels, and structural changes in the brain [51, 52]. However, it is important to note that the Steiger directionality test indicates that the causal effect of COVID-19 on Alzheimer's disease may not have a specific direction.

In addition, we found that both COVID-19 hospitalization and COVID-19 susceptibility increase the risk of heart failure. Previous researchers have also studied the relationship between COVID-19 and heart failure. Marco Zuin et al. [53] found that recovered COVID-19 patients are more likely to experience heart failure compared to those who have not had COVID-19 (HR: 1.90, 95% CI: 1.54–3.24). Zhang et al. [54], in a follow-up study after 85 days, also reached a similar conclusion. These research findings are consistent with the results of our study. The impact of COVID-19 on heart failure may be related to the cytokine storm it induces, which can inhibit myocardial cell function and contractility [55]. Additionally, COVID-19 may directly cause myocardial damage [56].

COVID-19 can activate the NLRP3 inflammasome and increase the levels of inflammatory factors such as IL-1β, exacerbating the body's inflammatory response [57, 58]. Furthermore, COVID-19 is associated with a reduction and functional decline of various immune cells, including CD8+T cells and NK cells [59, 60]. Therefore, COVID-19 may promote tumor development through multiple pathways, including exacerbating inflammatory responses and suppressing anti-tumor immunity.

This study found that COVID-19 susceptibility may increase the risk of breast cancer but decrease the risk of ER+breast cancer. Previous studies have shown minimal ACE2 expression in luminal subtypes but significantly higher levels in basal-like and HER2-enriched subtypes of breast cancer [61]. ACE2 serves as both the receptor for SARS-CoV-2 infection and a factor closely associated with the bad prognosis of breast cancer patients [62, 63]. Therefore, we speculate that the lower expression of ACE2 in ER+breast cancer patients may explain the lack of increased risk of ER+breast cancer

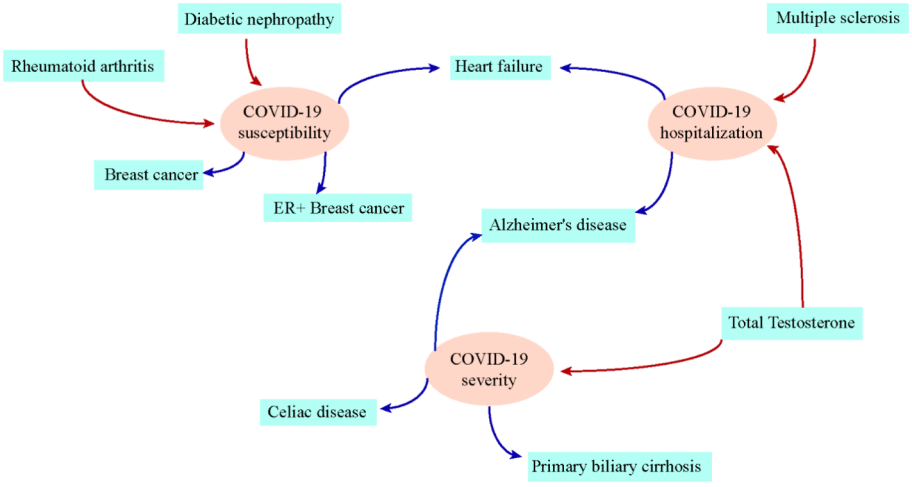

Fig. 6 The causal relationships between COVID-19 and multisystem diseases by bidirectional Mendelian randomization analysis

from COVID-19. Jia Li et al. [14] also conducted a Mendelian randomization study on the relationship between COVID-19 and cancer incidence, which indicated an association between COVID-19 and breast cancer, esophageal cancer, colorectal cancer, gastric cancer, and head and neck cancer. These findings differ from our study, possibly because the GWAS summary results used in their study were solely derived from the Medical Research Council Integrative Epidemiology Unit Open GWAS project, while our data sources include the Neale Lab, OCAC, FINNGEN, UK Biobank, MRC-IEU, and other databases.

Previously, researchers reported COVID-19-induced autoimmune hepatitis-primary biliary cholangitis overlap syndrome, which may be due to an excessive immune response triggered by COVID-19 infection and molecular mimicry between the pathogenic virus and human proteins [64]. COVID-19 can cause abdominal symptoms such as diarrhea and vomiting [65], but there is insufficient evidence in the epidemiological literature to demonstrate that COVID-19 can trigger celiac disease. Previously, researchers speculated that COVID-19 may contribute to the development of celiac disease [66]. COVID-19 enters host cells by utilizing angiotensin-converting enzyme (ACE), specifically ACE2. Cells with increased expression of this protein are more susceptible to viral invasion, and this is particularly relevant to celiac disease as intestinal epithelial cells express ACE2, and viral infection of these cells can lead to increased inflammation, which may further lead to other diseases [67].

To analyze the bidirectional causal relationship between multisystem diseases and COVID-19, we conducted a reverse Mendelian randomization analysis. We found that rheumatoid arthritis and diabetic nephropathy may reduce COVID-19 susceptibility. Total testosterone levels in females were negatively associated with COVID-19 hospitalization and COVID-19 severity. On the other hand, multiple sclerosis may increase the risk of hospitalization due to COVID-19. It is noteworthy that the testosterone levels in females may exhibit a bidirectional causal relationship with COVID-19 hospitalization and severity, whereas this causal relationship does not exist in males.

Our study has several limitations. Firstly, the data on COVID-19 patients are not exclusively from European populations, which may introduce some errors in the experimental

results. Additionally, due to data constraints, the range of diseases included in this study is still not comprehensive enough, and further research is needed to investigate the broader impact of COVID-19. Lastly, when screening SNPs related to traits, we used a threshold of 5×10^{-8}, which may be overly stringent and could result in the omission of some relevant SNPs.

In conclusion, this study comprehensively assessed the causal relationships between COVID-19 and various diseases using large-scale genetic data from the HGI dataset and the IEU Open GWAS project. We identified significant causal effects of COVID-19 on diseases such as primary biliary cirrhosis, celiac disease, Alzheimer's disease, heart failure, and breast cancer. Our findings highlight the long-term impacts of COVID-19 on human health, emphasizing the need for continuous monitoring and targeted interventions for affected individuals. Future research should explore these relationships to develop comprehensive healthcare strategies.

Abbreviations

COVID-19	Corona Virus Disease 2019
COPD	Chronic obstructive pulmonary disease
MI	Myocardial infarction
SNPs	Single nucleotide polymorphisms
IVs	Instrumental variables
MAF	Minor allele frequency
IVW	Inverse-variance weighting
WME	Weighted median estimation
SHBG	Sex hormone binding globulin
ACE	Angiotensin-converting enzyme

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40537-024-00997-4.

Supplementary Material 1

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Figure 6 was developed by summarizing the causal relationships between COVID-19 and various conditions, and then created using Adobe Illustrator (CC 2018).

Author contributions

X.Z., C.C., H.S. designed the study. X.Z., C.C., Z.J., J.M., Y.Q., Y.L., Y.P., C.W. collected the data and performed the analysis. X.Z., H.S., Y.L., Y.C. drafted the manuscript. P.L., J.T., Y.H., S.Z., C.C, H.S. reviewed the manuscript. X.Z., Y.Z. revised the manuscript. All authors read and approved the final manuscript.

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Data availability

The summary level data of multisystem diseases analyzed during the current study are available in COVID-19 Host Genetics Initiative (HGI) GWAS meta-analysis (https://www.covid19hg.org/results/r7/). The summary level data of multisystem diseases analyzed during the current study are available in the IEU dataset (gwas.mrcieu.ac.uk), and the data can be derived by searching the GWAS ID on the website.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publish

Not applicable.

Competing interests
The authors declare no competing interests.

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