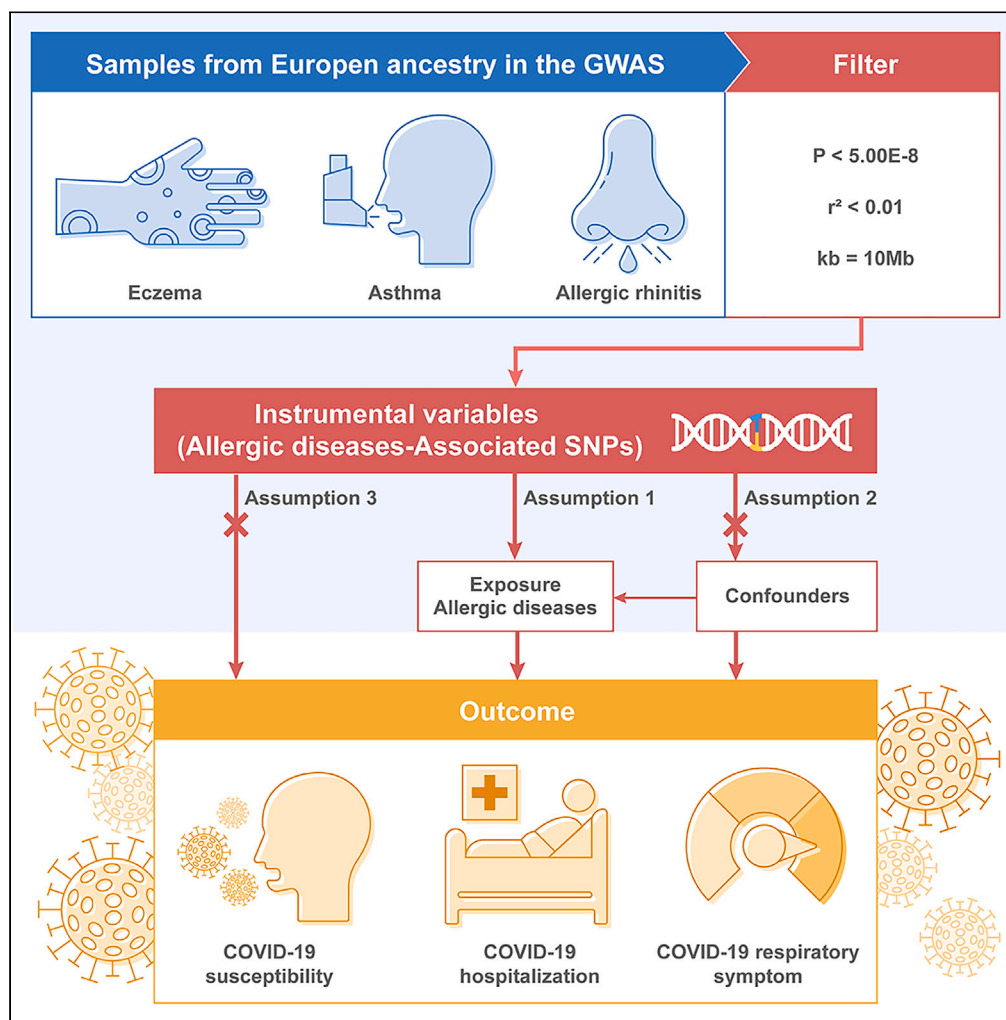


Article

Exploring genetic associations between allergic diseases and indicators of COVID-19 using mendelian randomization



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Highlights

Genetic predisposition to eczema lowers the risk and admission rate of COVID-19

Genetic predisposition to asthma reduces the risk and severity of COVID-19

Allergic rhinitis is not genetically associated with any of the COVID-19 indicators

Article

Exploring genetic associations between allergic diseases and indicators of COVID-19 using mendelian randomization

Yujie Wang,^{1,2,3,4,5} Xiaoyu Gu,^{1,2,3,4,5} Xinquan Wang,^{1,2,3,4,5} Wu Zhu,^{1,2,3,4,*} and Juan Su^{1,2,3,4,6,*}

SUMMARY

We carried out a bidirectional Mendelian randomization (MR) including cases of eczema (N = 218,792), asthma (N = 462,933), and allergic rhinitis (N = 112,583). COVID-19 susceptibility (N = 1,683,768), COVID-19 hospitalization (N = 1,887,658), and COVID-19 severe respiratory symptom (N = 1,388,342) were sampled from GWAS database. The MR analysis was primarily based on inverse variance weighted (IVW), supplemented by several other algorithms. In the bidirectional MR analysis, eczema was negatively associated with COVID-19 susceptibility (odds ratio (OR)_{IVW} = 0.92; p = 0.031) and COVID-19 hospitalization (OR_{IVW} = 0.81, p = 0.010); asthma was negatively associated with COVID-19 susceptibility (OR_{IVW} = 0.65, p = 0.005) and COVID-19 severe respiratory symptom (OR_{IVW} = 0.20, p = 0.001). No significant association was found between allergic rhinitis and COVID-19 susceptibility (OR_{IVW} = 0.80, p = 0.174), COVID-19 hospitalization (OR_{IVW} = 0.71, p = 0.207), or COVID-19 severe respiratory symptom (OR_{IVW} = 0.56; p = 0.167). The reverse MR analysis showed no potential reverse causal association. Our findings provided new evidence that allergic diseases might be associated with different risks of COVID-19 susceptibility, hospitalization, and severe respiratory symptom.

INTRODUCTION

The COVID-19 pandemic has imposed a substantial burden on global public health, significantly increasing the rate of hospitalizations for pneumonia and multi-organ diseases worldwide. As of April 19, 2023, the incidence of COVID-19 reached 763,740,140, resulting in 6,908,554 deaths (<https://covid19.who.int/>). Studies have shown that most underlying conditions could increase the risk of developing COVID-19.¹ However, the association of allergic diseases with the development of COVID-19 and the causal relationship between them is still under discussion. In a recent Mendelian randomization (MR) study, Larsson et al.² suggested that genetic susceptibility to allergic diseases is associated with reduced COVID-19 susceptibility. However, this association was insignificant with regard to COVID-19 hospitalization and single subgroup analyses on patients with eczema, asthma, and allergic rhinitis did not show any causal associations with COVID-19 susceptibility and hospitalization either.

On this basis, we performed a bidirectional MR analysis lately (Figure 1). MR is a statistical method to investigate causal relationships between exposure and outcome variables using the genetic variation of exposures as Instrumental variables (IVs) to eliminate the interference of confounding factors.³ We included the latest publications of genome-wide association study (GWAS) on the susceptibility and severe respiratory symptom of COVID-19 as well as COVID-19-related hospitalization, and used multiple algorithms and sensitivity analyses to test the previous hypothesis.

RESULTS

MR analysis

The MR analysis was conducted with eczema, asthma, and allergic rhinitis as exposure factors and COVID-19-related factors as the outcomes (Figure 2). When eczema was used as an exposure factor, 12 valid single nucleotide polymorphisms (SNPs) (OR_{IVW} = 0.92, 95% confidence interval (CI): 0.85–0.99, p = 0.031) were

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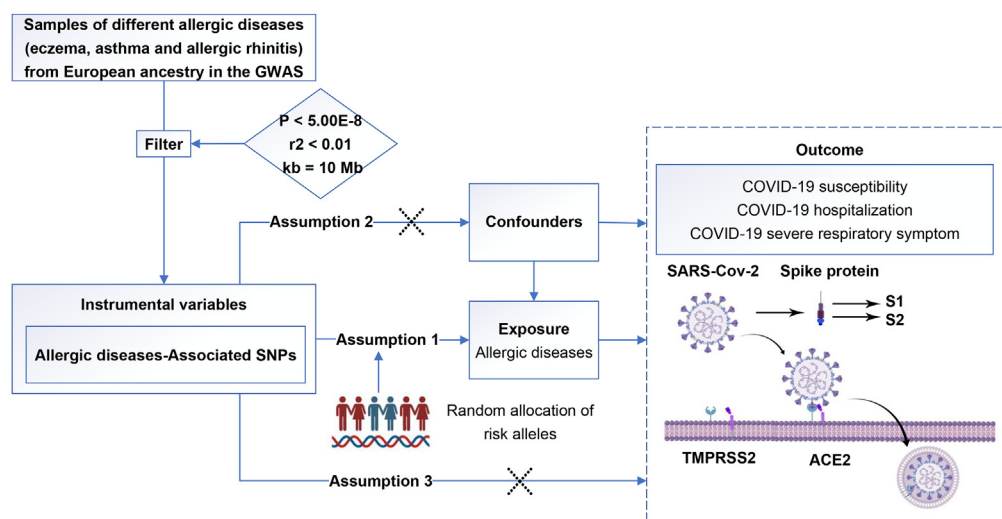


Figure 1. The overview of study design and assumptions of the Mendelian randomization (MR) design

Assumption 1: Instrumental variables are strongly associated with allergic diseases. Assumption 2: Instrumental variables are independent of any confounders. Assumption 3: Instrumental variables affect COVID-19 susceptibility, COVID-19 hospitalization and COVID-19 severe respiratory symptom through allergic diseases only and not through any other pathways. Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; GWAS, genome-wide association study; SNP, single nucleotide polymorphism; TMPRSS 2, transmembrane protease serine S1 member 2; SARS-CoV-2, acute respiratory syndrome coronavirus 2.

extracted with COVID-19 susceptibility being the outcome, 12 valid SNPs ($OR_{IVW} = 0.81$, 95% CI: 0.70–0.95, $p = 0.010$) were extracted with COVID-19 hospitalization being the outcome, and 13 valid SNPs ($OR_{IVW} = 0.82$, 95% CI: 0.64–1.04, $p = 0.099$) were extracted with COVID-19 severe respiratory symptom being the outcome that was not statistically significant.

When asthma was used as an exposure factor, 143 valid SNPs ($OR_{IVW} = 0.65$, 95% CI: 0.49–0.88, $p = 0.005$) were extracted with COVID-19 susceptibility being the outcome, 143 valid SNPs ($OR_{IVW} = 0.20$, 95% CI: 0.08–0.50, $p = 0.001$) were extracted with COVID-19 severe respiratory symptom being outcome, and 143 valid SNPs ($OR_{IVW} = 0.70$, 95% CI: 0.38–1.27, $p = 0.237$) were extracted with COVID-19 hospitalization being the outcome that showed no statistical significance.

When allergic rhinitis was used as an exposure, 32 valid SNPs ($OR_{IVW} = 0.80$, 95% CI: 0.59–1.10, $p = 0.174$) were extracted with COVID-19 susceptibility being the outcome, 32 valid SNPs ($OR_{IVW} = 0.71$, 95% CI: 0.41–1.21, $p = 0.207$) were extracted with COVID-19 hospitalization being the outcome, and 32 valid SNPs ($OR_{IVW} = 0.56$, 95% CI: 0.25–1.27, $p = 0.167$) were extracted with COVID-19 severe respiratory symptom being the outcome, none of which were statistically significant.

Sensitivity and pleiotropy analysis

The MR sensitivity analysis and heterogeneity test showed that, with eczema and asthma as exposure factors, the Cochran's Q statistic and MR Egger regression intercept were not significant ($p > 0.05$), indicating no heterogeneity or horizontal pleiotropy (Table 1). The visualization analysis showed that the association between eczema and COVID-19 susceptibility and COVID-19 hospitalization and the association between asthma and COVID-19 susceptibility and severe respiratory symptom were not driven by a single SNP, but by all functional SNPs together (Table S1 and Figures S1–S3).

Reverse MR analysis

The reverse MR analysis was performed with COVID-19 susceptibility, COVID-19 hospitalization, and COVID-19 severe respiratory symptom as exposures and allergic diseases as the outcome, respectively. No statistically significant reverse association was found ($p > 0.05$), indicating that all the associations observed were unidirectional.

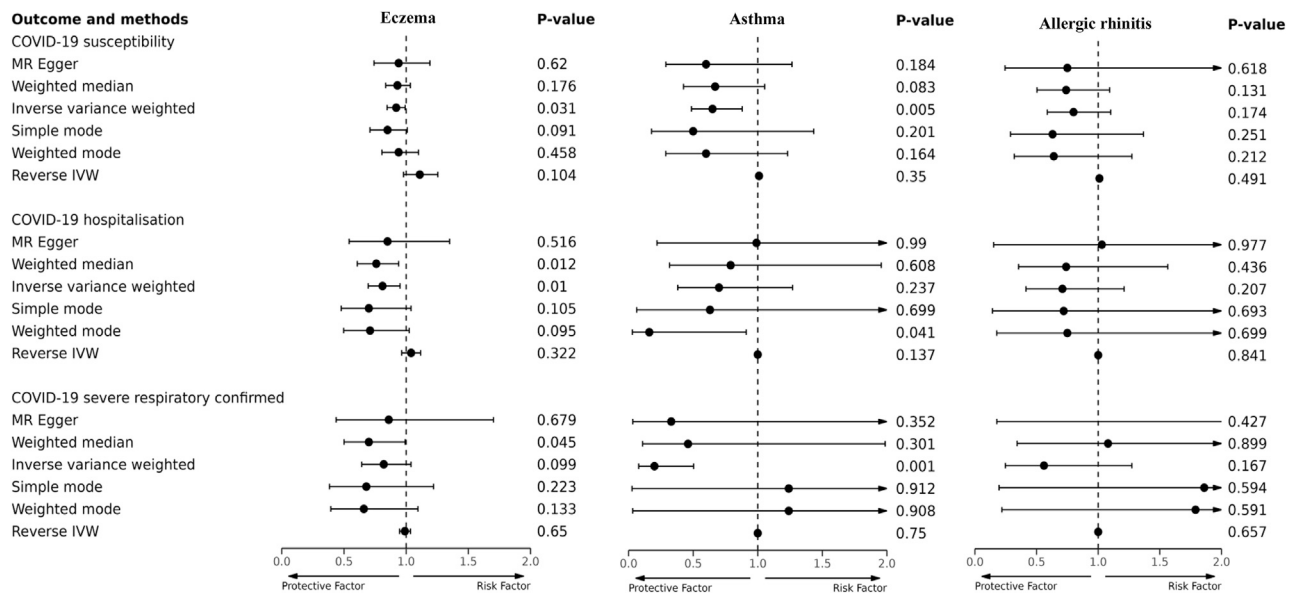


Figure 2. Association of genetic susceptibility to various allergic diseases with different Mendelian randomizations of COVID-19
IVW, inverse-variance weighted; MR, Mendelian randomization. Statistical significance: $p < 0.05$.

DISCUSSION

At present, few studies have been conducted to investigate the potential causal relationship and the pathogenetic association between allergic diseases (e.g., eczema, asthma, and allergic rhinitis) and the development of COVID-19. In the present study, we analyzed the relationship between the three allergic diseases mentioned above and the development of COVID-19 through a bidirectional MR analysis, with the exclusion of the influence of external confounders. We have found that the genetic predisposition of eczema was associated with a significantly lower risk of development of and COVID-19 hospitalization, the genetic predisposition of asthma was associated with a substantially lower risk for COVID-19 susceptibility and severe COVID-19 infection, while allergic rhinitis was not associated with any of the COVID-19 indicators, and there was no potential causal link.

Allergic diseases are likely to coexist as they share some genetic risk variants that dysregulate the expression of immune-related genes.⁴ However, the COVID-19 susceptibility of patients with allergic diseases is not clearly understood. According to centers for disease control and prevention (CDC), asthma has been listed as a risk factor for COVID-19. Epidemiological studies have shown a significantly increased risk of developing COVID-19 in patients with eczema, asthma, and allergic rhinitis.^{5,6} However, some studies during the COVID-19 pandemic did not support allergic diseases as risk factors for developing COVID-19.^{7,8} The disparities between findings might be related to the presence of external confounding factors.

Through an MR analysis, Larsson et al. found that genetic predisposition to allergic diseases was protective factor against COVID-19 but not significantly associated with COVID-19 hospitalization. However, subgroup analysis for single allergic diseases did not show any specific association with COVID-19 susceptibility or COVID-19 hospitalization.² And Baranova et al. also used COVID-19 (Round 4, release on October 20, 2020) to analyze the relationship between asthma and COVID-19 through MR.⁹ They concluded that genetic liability to asthma was associated with decreased COVID-19 susceptibility and severe respiratory symptom. The disparity between our results and the findings by Larsson et al. and Baranova et al. might be attributed to the following reasons. Firstly, we expanded the sample size by using data from the latest GWAS of COVID-19 (Round 5, released on January 18, 2021). On this basis, we found that patients with eczema and asthma were at a decreased risk of developing COVID-19, whereas no statistically significant association was found between allergic rhinitis and COVID-19 susceptibility. Furthermore, the risk of COVID-19 hospitalization was significantly decreased in patients with eczema but not in patients with asthma and allergic rhinitis. We also found that patients with asthma were less likely to have severe

Table 1. Heterogeneity test and horizontal pleiotropy test

Exposure	Outcome	Heterogeneity test			Horizontal pleiotropy test		
		Method	Cochran's Q	Q_ pval	Egger_intercept	Se	pval
Eczema	COVID-19 (RELEASE 5)	MR Egger	5.986	0.816	−0.002	0.010	0.829
		IVW	6.035	0.871			
	COVID-19 (hospitalized vs. population) RELEASE 5	MR Egger	9.934	0.446	−0.005	0.020	0.824
		IVW	9.987	0.532			
	COVID-19 (very severe respiratory confirmed vs. population) RELEASE 5	MR Egger	9.552	0.571	−0.005	0.030	0.870
		IVW	9.580	0.653			
Asthma	COVID-19 (RELEASE 5)	MR Egger	149.356	0.299	0.001	0.003	0.817
		IVW	149.413	0.319			
	COVID-19 (hospitalized vs. population) RELEASE 5	MR Egger	154.900	0.200	−0.003	0.005	0.616
		IVW	155.178	0.212			
	COVID-19 (very severe respiratory confirmed vs. population) RELEASE 5	MR Egger	159.643	0.135	−0.004	0.008	0.642
		IVW	159.888	0.145			
Allergic Rhinitis	COVID-19 (RELEASE 5)	MR Egger	45.051	0.038	0.001	0.008	0.899
		IVW	45.076	0.049			
	COVID-19 (hospitalized vs. population) RELEASE 5	MR Egger	33.000	0.322	−0.006	0.014	0.693
		IVW	33.175	0.362			
	COVID-19 (very severe respiratory confirmed vs. population) RELEASE 5	MR Egger	32.529	0.343	−0.027	0.022	0.224
		IVW	34.198	0.317			

IVW, inverse-variance weighted; MR, Mendelian randomization. Statistical significance: $p < 0.05$.

COVID-19, but such association was not found in patients with eczema or allergic rhinitis. Taken together, our results were only partially consistent with prior findings.

At present, some mechanisms of allergic diseases affecting the susceptibility to COVID-19 have been proposed. Angiotensin-converting enzyme 2 (ACE2) has been identified as the primary recognition receptor for SARS-CoV to date. When the pathogen enters the respiratory tract via droplets, SARS-CoV2 binds to the respiratory mucosa and fuses the cell membrane to enter the cell via surface-bursting proteins with the help of ACE2 receptors and the cellular transmembrane protease serine S1 member 2 (TMPRSS2).¹⁰ Studies have shown that the expression of ACE2 is negatively correlated with the integrity of the nasal mucosal epithelium in patients with allergies, which might be a molecular mechanism for the lower susceptibility to infection by SARS-CoV-2 in these patients. However, the varied ACE2 expression and local protective effects may also affect the susceptibility to COVID-19 in patients with allergic rhinitis and asthma^{11,12}.

There are several strengths of our study. First, we used MR studies to identify the potential causal relationship between the genetic predisposition of allergic diseases and COVID-19. To improve the accuracy of our study, we also excluded the influence of external confounding factors and applied reverse verification to ensure the unidirectionality of the association. Second, by exploring different databases of GWAS, we used a relatively larger sample as well as non-overlapping and independent data for exposures and outcomes to ensure the robustness and scope of assessment. Finally, multiple statistical methods were used for validation to improve the accuracy of the results, and parallel sensitivity analysis was performed to verify the reliability of our findings.

Limitations of the study

Despite the strengths, there are also some limitations to the study. Firstly, as all our subjects were of European descent, the generalizability of our results is still unclear. Moreover, the data from different institutions might have been collected using different diagnostic criteria for diseases, and diagnostic or coding errors could not be eliminated. Secondly, the diagnostic route of the disease may have an impact on

causality. The diagnosis of asthma in this study was based on the self-report of the patient rather than the diagnosis of the clinician, which could bring about misclassification bias.¹³ Thirdly, some sample overlap is involved in this two-sample study, which may lead to bias, such as type I errors¹⁴ that contribute to pleiotropy. But one study noted that the two-sample MR methodology can be safely applied to a single large dataset (UK Biobank) for causality assessment,¹⁵ and our test showed no pleiotropy in MR analysis. Fourthly, after performing sensitivity analysis using multiple methods, we were still unable to rule out potential genetic variation or eliminate the interference of environmental factors. Fifthly, due to the limitations of GWAS dataset, this study did not further stratify the COVID19-related confounders to further clarify associations of atopic diseases with COVID-19 in different subgroups, such as hypertension,¹⁶ lifestyle,¹⁷ and diabetes.¹⁸ Finally, the database resources were limited and needed to be supported by more clinical data and basic mechanistic studies.

In summary, the present study provided new evidence for the potential causal relationship between allergic diseases and a decreased risk of COVID-19. As our results were produced through statistical analysis only, further mechanistic and clinical studies are warranted to verify these findings.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.isci.2023.106936>.

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AUTHOR CONTRIBUTIONS

Conceptualization, X.G., J.S.; methodology, X.G., W.Z.; software, X.W.; validation, Y.W. and X.G.; formal analysis, X.W.; investigation, X.W.; resources, X.G. and X.W.; data curation, Y.W. and X.W.; writing—original draft, Y.W. and X.W.; writing—review & editing, X.G., J.S., W.Z.; visualization, Y.W. and X.W.; supervision, J.S., W.Z.; project administration, Y.W. and X.W.; funding acquisition, J.S., W.Z.

DECLARATION OF INTERESTS

The authors declare no competing interests.

INCLUSION AND DIVERSITY

We support inclusive, diverse, and equitable conduct of research.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
GWAS database	MRC Integrative Epidemiology Unit (IEU)	https://gwas.mrcieu.ac.uk/
Software and algorithms		
TwoSampleMR	https://mrcieu.github.io/TwoSampleMR/	N/A
R Studio	https://www.r-project.org/	Version 4.0.3

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Juan Su (sujuanderm@csu.edu.cn).

Materials availability

The study did not generate any new materials.

Data and code availability

- All data reported in this paper will be shared by the [lead contact](#) upon request.
- This study did not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the [lead contact](#) upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Observational analysis participants

The present study presented relevant primary data from the GWAS database (<https://gwas.mrcieu.ac.uk/>). The data for eczema were extracted from the FinnGen Biobank ($N=218,792$, $N_{\text{case}}=20,052$ and $N_{\text{control}}=198,740$), and the data for asthma ($N=462,933$, $N_{\text{case}}=53,598$ and $N_{\text{control}}=409,335$) and allergic rhinitis ($N=112,583$, $N_{\text{case}}=25,486$ and $N_{\text{control}}=87,097$) were extracted from the UKB. The data for COVID-19 characteristics were extracted from the GWAS Catalog dataset (Round 5, released on January 18, 2021), including three outcomes: COVID-19 susceptibility (38,984 cases of infection vs. 1,644,784 healthy controls), hospitalizations due to COVID-19 (9,986 hospitalizations vs. 1,877,672 healthy controls), and COVID-19 severe respiratory symptom (5,101 severe cases vs. 1,383,241 healthy controls).¹⁹ COVID-19 susceptibility was represented by cases infected with acute respiratory syndrome coronavirus (SARS-CoV-2), COVID-19 hospitalization was represented by the number of patients hospitalized for COVID-19 infection, and COVID-19 severe respiratory symptom was represented by the number of patients infected with SARS-CoV-2 who required respiratory support or who died as a result. None of the healthy controls had infection with SARS-CoV-2. The data were pooled from the respective datasets, the resulting variables were obtained, and the screened single nucleotide polymorphisms (SNPs) were pooled. All the subjects included were of European ancestry to reduce the effect of race-related factors on the outcome (Table 2). Ethical approval is not required for this study because the original GWAS had previously received authorization from the ethics and institutional review board.

Study design

We extracted the data of allergic diseases from the UKB and FinnGen databases in GWAS and the data of COVID-19 from the GWAS Catalog dataset for the MR analysis. Sensitivity analyses (heterogeneity test, horizontal multiplicity test, and leave-one-out analysis) were also performed and visualized. Finally, reverse MR analysis was performed with COVID-19 as the exposure variable and allergic diseases as the outcomes.

Table 2. Details of studies included in the Mendelian randomization analyses for the association between allergic disease and COVID-19

Trait	Database	Year	Consortium	Population	SNP	Sample size
Exposure						
Eczema	finn-b-L12_DERMATITISECZEMA ^a	2021	NA	European	16,380,466	218,792
Asthma	ukb-b-18113 ^b	2018	MRC-IEU	European	9,851,867	462,933
Outcome						
Allergic rhinitis	ukb-b-7178 ^c	2018	MRC-IEU	European	9,851,867	112,583
COVID-19 (RELEASE 5)	ebi-a-GCST011073	2020	NA	European	8,660,177	1,683,768
COVID-19 (hospitalized vs. population) RELEASE 5	ebi-a-GCST011081	2020	NA	European	8,107,040	1,887,658
COVID-19 (very severe respiratory confirmed vs. population) RELEASE 5	ebi-a-GCST011075	2020	NA	European	9,739,225	1,388,342

COVID-19, Coronavirus disease 2019; SNP, single nucleotide polymorphism.

^asourced from https://gwas.mrcieu.ac.uk/datasets/finn-b-L12_DERMATITISECZEMA/.

^bsourced from <https://gwas.mrcieu.ac.uk/datasets/ukb-b-18113/>.

^csourced from <https://gwas.mrcieu.ac.uk/datasets/ukb-b-7178/>.

METHOD DETAILS

MR analysis

Eczema, allergic rhinitis, and asthma were first used as exposure factors in the analysis, respectively, with COVID-19 being the outcome. Before the MR analysis, SNPs at $P < 5E-8$ were abstracted from the pooled SNPs as IVs representing genetic susceptibility to eliminate linkage disequilibrium. We also excluded highly correlated variants with $r^2 < 0.01$ within the range of 10 Mb ($kb > 10,000$) using the clump_data approach to screen out valid SNPs. The MR analysis was then performed using multiple statistical methods, including IVW, MR-Egger,²⁰ and weighted median (WM) methods.²¹ Among them, the random effects model IVW was the most effective statistical method when all IV hypotheses were valid. If there was horizontal pleiotropy, the results might be biased due to additional causal pathways, thereby affecting our test of the IV hypotheses. Therefore, complementary MR-Egger and WM methods were used for different IV assumptions.²² MR-Egger is one of the most commonly used multi-effect treatment methods when all IV assumptions are invalid, but it is prone to result in loss of power. The WM approach provides reliable effect estimates if more than 50% of the IVs are assumed to be valid. For individual SNPs, the Wald method was used for effect estimation.²³

Sensitivity and pleiotropy analysis

To assess the validity and reliability of the MR results, we performed sensitivity analyses, including heterogeneity test, horizontal multiple validity test, and leave-one-out analysis. Data were excluded or corrected for heterogeneity or horizontal multiplicity, and individual SNP tests were performed using leave-one-out analysis to clarify the driving of the overall estimate.²⁴

Reverse MR analysis

Reverse MR analysis was performed using COVID-19 as the exposure and the three allergic diseases mentioned above as outcomes, with the use of the same methods and settings described above ($p < 5.00E-8$, $r^2 < 0.01$, $kb = 10$ Mb).

QUANTIFICATION AND STATISTICAL ANALYSIS

Statistical analysis

All the analyses were performed using the TwoSampleMR package in the R software (Version 1.1.453) according to the guidelines (<https://mrcieu.github.io/TwoSampleMR/>). In the MR analysis, $p < 0.05$ indicated that the difference was statistically significant for all the statistical tests. For heterogeneity tests, $P > 0.05$ indicated that there was no between-group heterogeneity. When the MR-Egger regression intercept was not 0 and showed statistical significance ($P < 0.05$), the IV was then considered to be horizontally pleiotropic. In the reverse MR analysis, $P > 0.05$ indicated that there was no reverse causality between exposure factors and outcome variables.