Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Genetic variation of allergic disease is associated with the susceptibility to COVID-19

Editor: Prof. R. Read

Dear Editor,

In this journal, Garcia-Pachon and colleagues reported that patients with asthma had low prevalence of post-COVID-19 syndrome[1] and Han and colleagues described that COVID-19 patients with asthma had a significantly higher risk for ICU admission.[2] However, it is still unclear whether allergic disease affects the susceptibility to COVID-19.

A study reported no physician-diagnosed asthma among 1590 patients with COVID-19 in China.[3] Another report on 140 COVID-19 patients (Wuhan, China) showed no patients had asthma or other allergic diseases.[4] In addition, Italy has also shown relatively low prevalence of asthma.[5] Furthermore, type 2 immune response such as IL-4 and IL-13 might provide potential protective effects against COVID-19.[6] Thus, we propose that pre-existing asthma may reduce the susceptibility to COVID-19.

To test our proposal, we used two-sample Mendelian randomization (MR), which used genetic variants are independent of many factors that bias observational studies,[7,8] to assess whether the genetic variation of allergic disease affected the susceptibility to COVID-19.

To perform the two-sample MR study, we used, to date, the largest GWAS for allergic disease (asthma, hay fever, and eczema). The GWAS (180,129 cases and 180,709 controls from European ancestry) was provided by Ferreira and colleagues in 2017.[9] The summary dataset of allergic disease GWAS is available in https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST005038. We selected 74 independent genome-wide significant variants as genetic instrumental variants (IVs) for allergic disease using the following criteria: (1) p value ($< 5 \times 10^{-8}$) on allergic disease; (2) linkage disequilibrium (LD) ($r^2 < 0.001$) between SNPs; (3) no effects of other potential risk factors including smoking, body mass index, and blood pressure. These IVs are shown in **Suppl. Table 1**.

To date, the largest GWAS for COVID-19 was produced by the COVID-19 Host Genetics Initiative in 2020.[10] Primarily, this GWAS is to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. The summary dataset of COVID-19 GWAS (14,134 cases and 1284,876 controls from European ancestry) is available in https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST010780 and shown in **Suppl. Table 2**.

Potential proxy SNPs were identified by the LD proxy Tool ($r^2 > 0.8$) when allergic disease IVs could not be found in COVID-2019 summary statistics. Seventy-four independent allergic disease genetic IVs were successfully extracted from COVID-2019. The association of 74 independent allergic disease genetic IVs with COVID-2019 GWAS dataset is shown in **Suppl. Table 3**.

Both MR-egger_intercept and PRESSO methods suggested no significant pleiotropy of 74 independent genetic IVs of allergic disease in COVID-19 GWAS (**Suppl. Table 4**). Both MR Egger and IVW in Cochran's Q statistic showed no significant heterogeneity of 74 independent genetic IVs of allergic disease in COVID-19 GWAS (**Suppl. Table 4**). Therefore, all selected allergic disease-associated genetic variants can be taken as the effective IVs in our MR study.

MR analysis demonstrated that as allergic disease genetically increased, the risk of COVID-19 decreased using MR_egger (Beta = −0.211, p = 0.033; OR = 0.810), weighted median (Beta = −0.106, p = 0.041; OR = 0.900), and IVW (Beta = −0.089, p = 0.009; OR = 0.915) (**Table 1**). Our analysis suggest that the genetic variant of allergic disease reduces COVID-19 risk.

The individual MR estimates demonstrated that as the effect of single SNP on allergic disease increased, the suppressive effect of single SNP on COVID-19 risk increased using MR Egger, weighted median, and IVW **(Suppl. Fig. 1)**. Each effect size **(Suppl. Fig. 2)** and leave-one-out sensitivity **(Suppl. Fig. 3)** suggested that each effect of allergic disease-associated SNPs on COVID-19 risk were robust without obvious bias.

This study has several limitations. First, because allergic disease genetic IVs and COVID-19 GWAS are from European ancestry, our results need be proven in other ancestries. Second, it is necessary to clarify whether allergic disease could reduce the risk of COVID-19 by randomized controlled trials. Third, the underlying mechanism by which allergic disease genetically reduced the

Table 1
The causal association of allergic disease with COVID-19.

Method	nsnp	Beta	SE	p val	OR	OR_lci95	OR_uci95
MR Egger	74	−0.211	0.097	0.033	0.810	0.669	0.979
Weighted median	74	−0.106	0.052	0.041	0.900	0.813	0.995
IVW	74	−0.089	0.034	0.009	0.915	0.856	0.978

COVID-19: corona virus disease 2019; IVW: Inverse variance weighted; nsnp: the number of single-nucleotide polymorphisms; Beta: the regression coefficient based on allergic disease raising effect allele; SE: standard error. $p < 0.05$ represents the causal association of the increased levels of allergic disease genetic IVs with COVID-19; OR: Odds ratio; OR_lci95: Lower limit of 95% confidence interval for OR; OR_uci95: Upper limit of 95% confidence interval for OR.

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risk of COVID-19 is still unclear and worth to be explored in the future.

In summary, our analysis suggested that genetic variation of allergic disease reduced the risk of COVID-19 susceptibility. Thus, allergic disease may be a protective effect against COVID-19.

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Ethical approval

Our study was approved by the Ethics Committee of Beijing Institute of Brain Disorders in Capital Medical University. This article contains human participants collected by several studies performed by previous studies. All participants gave informed consent in all the corresponding original studies, as described in the Methods.

Availability of data and materials

The summary statistics for allergic disease (asthma, hay fever or eczema) GWAS (ID: ebi-a-GCST005038) and for COVID-19 GWAS (ID: ebi-a-GCST010780) are available in ieu open gwas project at https://gwas.mrcieu.ac.uk/datasets/. The MR analysis code can be found at https://mrcieu.github.io/TwoSampleMR/articles/index.html.

Declaration of Competing Interest

The authors have no potential conflicts of interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.01.015.

References

1. Garcia-Pachon E, Grau-Delgado J, Soler-Sempere MJ, Zamora-Molina L, Baeza–Martinez C, Ruiz-Alcaraz S, et al. Low prevalence of post-COVID-19 syndrome in patients with asthma. *J Infect* 2021;**82**(6):276–316.
2. Han X, Xu J, Hou H, Yang H, Wang Y. Significant association of pre-existing asthma with an increased risk for ICU admission among COVID-19 patients: evidence based on a meta-analysis. *J Infect* 2021.
3. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020;**55**(5).
4. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020;**75**(7):1730–41.
5. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region. *Italy. JAMA.* 2020;**323**(16):1574–81.
6. Liu S, Zhi Y, Ying S. COVID-19 and asthma: reflection during the pandemic. *Clin Rev Allergy Immunol* 2020;**59**(1):78–88.
7. Wang R. Genetic variation of interleukin-1 receptor type 1 is associated with severity of COVID-19 disease. *J Infect* 2021.
8. Wang R. Mendelian randomization study updates the effect of 25-hydroxyvitamin D levels on the risk of multiple sclerosis. *J Transl Med* 2022;**20**(1):3.
9. Ferreira MA, Vonk JM, Baurecht H, Marenholz I, Tian C, Hoffman JD, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nat Genet* 2017;**49**(12):1752–7.
10. COVID-19 Host Genetics Initiative The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. *Eur J Hum Genet* 2020;**28**(6):715–18.

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