

## LETTER TO THE EDITOR

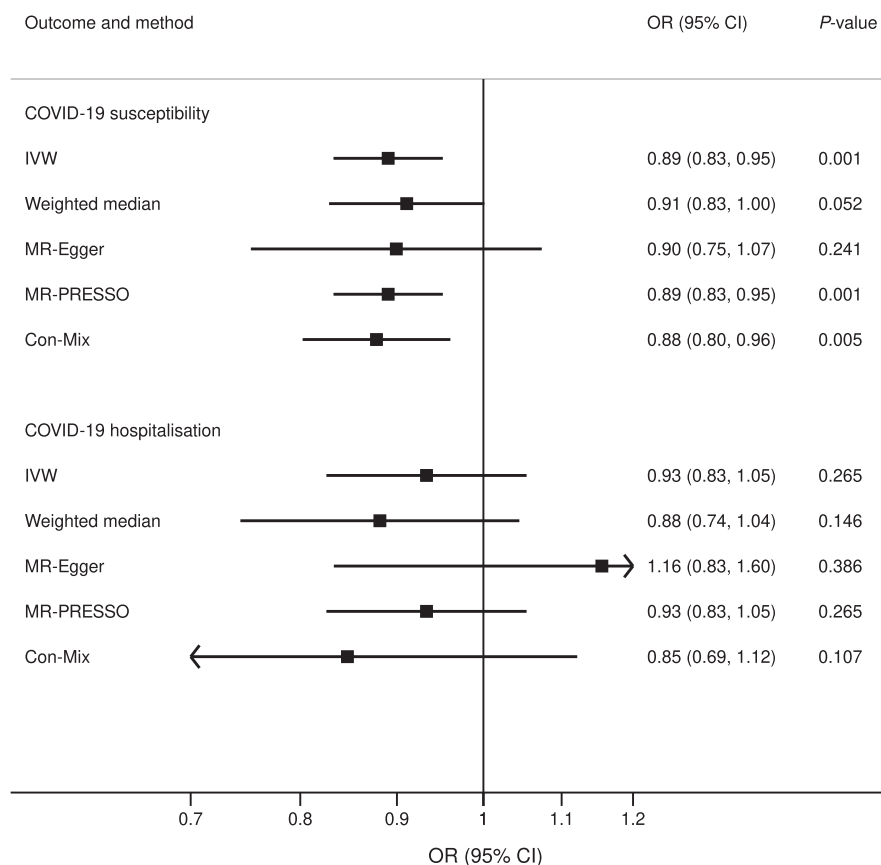
# Genetic predisposition to allergic diseases is inversely associated with risk of COVID-19

To the Editor,

The host immune response is integral to determining susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severity of consequent coronavirus disease 2019 (COVID-19).<sup>1</sup> Allergic diseases such as allergic rhinitis (hay fever), atopic dermatitis (eczema) and asthma tend to cluster together in individuals, partly because of shared genetic factors that navigate the immune system.<sup>2</sup> However, it is not yet known whether genetic predisposition to

allergic disease also relates to COVID-19 susceptibility. Understanding this relationship may provide mechanistic insight towards uncovering preventative and therapeutic strategies for COVID-19. To this end, we performed a Mendelian randomization analysis investigating how genetic predictors of allergic disease relate to COVID-19 susceptibility.

As genetic instruments for the primary analysis, we considered 136 uncorrelated ( $r^2 < 0.02$ ) single nucleotide polymorphisms associated with a broad allergic disease phenotype (presence of at least



**FIGURE 1** Associations of genetic predisposition to any allergic disease with COVID-19 with different Mendelian randomization statistical analysis methods with different assumptions. The  $I^2$  value for heterogeneity between individual genetic variants was  $\leq 27\%$ . The  $p$  value for the intercept in the MR-Egger analyses was  $>0.16$  in all analyses. No outlier SNP was detected in the MR-PRESSO analysis. CI: confidence interval; Con-Mix, contamination mixture; IVW, inverse-variance weighted; MR, Mendelian randomization; OR: odds ratio; PRESSO, Pleiotropy RESidual Sum and Outlier

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one allergic disease, including allergic rhinitis, atopic dermatitis and asthma) at  $p < 3 \times 10^{-8}$  in a meta-analysis of 13 genome-wide association studies with a total of 180 129 cases and 180 709 controls (without the three allergic diseases), all of European descent.<sup>2</sup> Information on allergic disease was self-reported. The number of cases with each allergic disease is shown in Table S1. The association estimates were adjusted for age, sex and genetic principal components of ancestry.<sup>2</sup> In secondary analyses, we separately considered single nucleotide polymorphisms associated with each allergic disease (Appendix S1).

Genetic association estimates for COVID-19 susceptibility were obtained from the COVID-19 Host Genetics Initiative genome-wide association meta-analyses (round 4, release October 20, 2020).<sup>3</sup> To minimize population stratification bias, we restricted the analyses to individuals of European ancestry. The publicly available datasets comprising European-descent individuals included 14 134 cases with laboratory-confirmed COVID-19 infection (RNA and/or serology-based) or physician confirmed COVID-19 vs. 1 284 876 population controls (everyone that is not a case) and 6406 cases of hospitalized laboratory-confirmed COVID-19 infection versus 902 088 population controls. Of the 136 single nucleotide polymorphisms associated with any allergic disease, 130 were available in the COVID-19 outcome datasets. Details of the single nucleotide polymorphisms and their associations with COVID-19 are shown in Table S2.

We conducted two-sample summary-level Mendelian randomization analyses using the random-effects inverse-variance weighted method (primary analysis) and several statistical sensitivity analysis methods that make different assumptions.<sup>4</sup> Analyses were conducted in Stata/SE (version 14.2) and R (version 3.4.3) using summary-level data only. Ethical approval and participant consent had previously been obtained.

Genetic predisposition to any allergic disease was associated with reduced susceptibility to COVID-19 but not clearly with risk of being hospitalized with COVID-19 (Figure 1). Similar results were observed in statistical sensitivity analyses, although with wider confidence intervals that were likely attributable to lower statistical power (Figure 1). The associations of each single nucleotide polymorphism with allergic disease and COVID-19 susceptibility are displayed in Figure S1. Secondary analyses based on genetic variants associated with different allergic diseases did not reveal associations with any particular allergic disease specifically, although the magnitude of the inverse association was most pronounced for allergic rhinitis albeit with broad confidence intervals (Figure S2).

Our results provide evidence to support that the genetic factors underlying predisposition to allergic disease are protective against COVID-19. The pathophysiological process underlying COVID-19 involves an exaggerated host immune response.<sup>5</sup> Previous work has highlighted genetic associations between obesity and smoking with both allergic disease and severe COVID-19,<sup>2,6</sup> supporting immune dysregulation as a common underlying mechanism. Further work is required to unravel the specific pathways linking susceptibility to

allergic disease with risk of COVID-19, for the purpose of identifying opportunities for clinical intervention.

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## CONFLICT OF INTEREST

Dr. Gill is employed part-time by Novo Nordisk, outside the submitted work. Dr. Larsson has nothing to disclose.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.