

Investigating causal relationships between Asthma Phenotypes and Risks for COVID-19

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Dear Editor,

We read with interest the study recently published by Lauren et al.¹ They found that asthma is not a risk factor for more severe COVID-19 disease. Allergic asthmatics were protected from hospitalization with COVID-19. Lower levels of eosinophil counts were associated with a more severe COVID-19 disease trajectory. Additionally, some studies reported that the prevalence of asthma in patients with COVID-19 is lower than expected, suggesting that having asthma may be a protective effect.^{2 3}

However, inconsistent associations between asthma and COVID-19 disease have been observed in epidemiology studies.⁴ The causality of the association between asthma and COVID-19 has not been established. It is difficult to infer causal effects only from observational studies because of confounding. Mendelian randomization (MR) analysis is widely used to assess the presence of causal relationships between genetic variants and selected outcome and is not prone to confounding biases and reverse causality.

Here, we performed MR analysis for the association of asthma phenotypes and three levels of COVID-19 to validate the authors' findings. MR was conducted with inverse variance weighted (IVW), single-nucleotide polymorphisms (SNPs) at $P < 5 \times 10^{-8}$ were selected as instrumental variables. The linkage disequilibrium threshold was set to $r^2 = 0.001$ within a distance of 10,000 kb.

We used data from IEU OpenGWAS project (<https://www.mrbase.org/>),⁵ developed at the MRC Integrative Epidemiology Unit (IEU) at the University of Bristol, including information on asthma (GWAS ID: ukb-b-18113, including 53,598 cases vs. 409,335 controls), allergic diseases (GWAS ID: ebi-a-GCST005038, including 180,129 cases vs. 180,709 controls), eosinophil counts (GWAS ID: bbj-a-20, including 62,076

samples; GWAS ID: ebi-a-GCST90002301, including 8,142 samples), allergic asthma (GWAS ID: finn-b-ALLERG_ASTHMA, including 4,859 cases vs. 135,449 controls), non-allergic asthma (GWAS ID: finn-b-NONALLERG_ASTHMA, including 3,709 cases vs. 135,449 controls) and hayfever allergic rhinitis or eczema (GWAS ID: ukb-a-447, including 77,891 cases vs. 258,891 controls). Genetic association estimates for COVID-19 were obtained from release 7 of the COVID-19 Host Genetics Initiative GWAS.⁶ Three COVID-19 traits were selected: Covid vs. population, which included 159,840 cases versus 2,782,977 controls; Hospitalized covid vs. population, which included 44,986 cases versus 2,356,386 controls; Very severe respiratory confirmed covid vs. population, which included 18,152 cases versus 1,145,546 controls. All summary data used in this work are publicly available.

The MR analyses showed that asthma was associated with decreased risk for either severe COVID-19 (OR = 0.45, 95% CI 0.22-0.91, P = 0.028) or hospitalized COVID-19 (OR = 0.56, 95% CI 0.35-0.90, P = 0.017). There were consistent evidences that higher levels of eosinophil counts could lower the risk of COVID-19 (OR = 0.94, 95% CI 0.90-0.99, P = 0.02), hospitalized COVID-19 (OR = 0.81, 95% CI 0.71-0.93 P = 3.0E-03) and severe COVID-19 (OR = 0.68, 95% CI 0.49-0.94, P = 0.022). Allergic asthma and non-allergic asthma raised the risk for COVID-19 (OR = 1.04, 95% CI 1.00-1.08, P = 0.02 for allergic asthma; OR = 1.04, 95% CI 1.00-1.08, P = 0.039 for non-allergic asthma). The MR analyses showed that hayfever allergic rhinitis or eczema could lower the risk of hospitalized COVID-19 (OR = 0.68, 95% CI 0.52-0.88, P = 3.5E-03) and severe COVID-19 (OR = 0.65, 95% CI 0.44-0.97, P = 0.034) (Table 1).

In the study, we found that asthma may be a causal protective factor for the incidence of severe COVID-19 and hospitalized COVID-19. The higher levels of eosinophil counts is a protective factor for COVID-19 disease. The mechanism is not fully known, may be due to the protective effects of ongoing inflammatory responses against the of COVID-19 disease.

Table 1: Mendelian Randomization Analysis Estimate of Associated between Asthma and COVID-19 Disease with Use of IVW Method.

	COVID-19	COVID-19	COVID-19		Hospitalized COVID-19	Hospita
exposure	SNPs	OR(95%CI)	P-value	SNPs	OR(95%CI)	P-value
Asthma	79	0.88(0.73-1.07)	0.222	97	0.56(0.35-0.90)	0.017
Eosinophil counts	14	0.94(0.90-0.99)	0.020	15	0.81(0.71-0.93)	3.0E-03
Allergic asthma	3	1.04(1.00-1.08)	0.026	5	0.94(0.79-1.12)	0.502
Non-allergic asthma	2	1.04(1.00-1.08)	0.039	2	1.06(0.97-1.16)	0.172
Hayfever allergic rhinitis or eczema	86	0.89(0.77-1.03)	0.140	101	0.68(0.52-0.88)	3.5E-03
Allergic disease	59	1.00(0.97-1.02)	0.977	69	0.92(0.87-0.98)	0.013

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CONFLICT OF INTEREST

None conflict of interest.

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