# Allergic disease as a causal protective factor for severe covid-19: a multivariable mendelian randomization study

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**Abstract**

Allergic diseases were recently reported related to both SARS-CoV-2 infection and severe COVID-19 through observational studies. However, their causal relationship remains unclear. Herein, we performed univariate and multivariate Mendelian randomization (MR) studies to investigate the causal association between various allergic diseases and COVID-19. Genome-wide association studies (GWAS) summaries were used in this study, with 360838 participants in the allergic disease database, 455449 in asthma, 217914 in allergic rhinitis (AR), and 205764 in atopic dermatitis (AD). In univariate MR analysis, the allergic disease was not causally in connection with SARS-CoV-2 infection but have a causal protective effect on severe COVID-19. In contrast, no significant causal effect was found of SARS-CoV-2 infection/severe COVID-19 on the allergic disease. AD, mixed asthma, and childhood asthma were causal protective factors for severe COVID-19. Multivariate MR analysis further revealed the dominant role of asthma in allergic diseases and the dominance of childhood asthma in asthma subtypes. In summary, this study, based on the population genetic variation model, pointed out the protective effect of allergic diseases against severe COVID-19, which may provide some inspiration for further exploration of the pathophysiological mechanisms of COVID-19.

## 1 Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a novel strain of human coronavirus that surfaced in 2019, which caused a global pandemic of Coronavirus Infectious Disease 2019 (COVID-19)[1]. COVID-19 has great heterogeneity in symptoms, severity, and prognosis, ranging from no symptoms to death[2]. The mortality among critically ill COVID-19 patients has been reported to be 61.5%[3]. Therefore, it is necessary and urgent to explore the related risk and protective factors of severe COVID-19.

Allergic diseases (including allergic rhinitis (AR), eczema/dermatitis, asthma, etc.) were generally considered protective against COVID-19. Analysis of the large prospective cohorts of UK Biobank (UKB) shows that AR was concerned with a lower rate of SARS-CoV-2 infection, but not the severity, while asthma was protective against infection only in people under 65 years[4]. Patients with allergic asthma were reported to have a lower risk of death after SARS-CoV-2 infection than patients with nonallergic asthma in real-world cohorts[5]. However, previous studies are mainly observational studies with possible reverse causality, and the confounding factors cannot be completely removed. Whether the link between allergic diseases and COVID-19 is causal is not yet fully established.

Mendelian randomization (MR) studies use genetic data as a bridge to exploring the causal association between exposure phenotypes and outcomes. Since single nucleotide polymorphisms (SNPs) are used as instrumental variables in MR analysis, the effect of confounding factors will be smaller. Moreover, exposure phenotypes cannot influence SNPs in reserve, so MR analysis is not subject to reverse causality. Importantly, in contrast to traditional epidemiologic methods, the MR study can suggest the directionality of exposure and outcome, and thus a causal relationship rather than an association[6]. A relatively comprehensive MR study showed that physical activity, high education level, never smoking, and asthma were protective factors

against hospitalized COVID-19[7]. It was also suggested through MR analysis that asthma was a protective factor for SARS-CoV-2 infection[8]. To date, no study has comprehensively explored the causal relationship between allergic diseases and COVID-19. Herein, We conducted a bidirectional, two-sample MR analysis for the allergic disease and two COVID-19 outcomes (SARS-CoV-2 infection and severe COVID-19), and then univariate and multivariate MR analyses for the relationships between various allergic diseases (including different subtypes of asthma) and severe COVID-19. This study may shed more light on the pathophysiology of COVID-19 and has potential clinical and public health implications.

## 2 Methods

### 2.1 Study design

A full description of the study design was displayed in Figure 1. A bidirectional, two-sample MR analysis was first conducted to investigate causal associations between the allergic disease, including asthma and/or hay fever (or AR) and/or eczema (or atopic dermatitis(AD)), and the two COVID-19 outcomes (SARS-CoV-2 infection and severe COVID-19). Univariate MR analysis (i.e. two-sample MR analysis) was then designed to explore the causal associations between various allergic diseases (hay fever, AR, or eczema/AR/AD/asthma) and severe COVID-19. Multivariate MR analysis was utilized to assess the independent influence of these allergic diseases on the risk of severe COVID-19. Finally, univariate and multivariate MR analyses were used to explore the causal relationship between various subtypes of asthma and severe COVID-19.

The MR analysis was on the strength of three assumptions: The SNPs utilized as instrumental variables (IVs) have connections with the exposure; The IVs have nothing to do with any confounders; IVs are not directly related to outcome, and they influence the outcome only through the exposure, not through any alternative pathways[9].

### 2.2 Data source

Publicly available genome-wide association studies (GWAS) summaries were used in this study. Data for SNPs associated with the allergic disease was from the largest GWAS to date (meta-analysis of 13 studies), all of the European ancestry, including 180,129 cases with self-reported asthma and/or hay fever and/or eczema and 180,709 controls without any of these symptoms[10]. (Figure 2)

Genetic association estimates for hay fever, AR, or eczema diagnosed by the doctor (104,559 cases and 350,890 controls) and asthma diagnosed by the doctor (52,504 cases and 402,945 controls) were acquired from the UK Biobank (UKB), a population-based cohort study involving over half a million volunteers recruited in the United Kingdom (https://www.ukbiobank.ac.uk/)[11]. (Figure 3) Summary-level statistics for AR (5,527 cases and 212,387 controls), AD (7,024 cases and 198,740 controls), allergic asthma (4,859 cases and 135,449 controls), non-allergic asthma (3,155 cases and 184,148 controls), mixed asthma (724 cases and 135,448 controls) and childhood asthma (age<16 years) (3,025 cases and 135,449 controls) were retrieved from another large-scale biomedical European databases of FinnGen (*https://www.finngen.fi/en*), launched in 2017, unique in its integration of genomic information with digital medical data[12]. (Figure 3) The selection of GWAS summaries for each phenotype in this study followed the following principle: when no data for the phenotype was available in the UKB or no available IVs (the F statistics of SNPs were all <10) could be obtained from the UKB, GWAS data will be obtained from the FinnGen.

The latest and largest GWAS data sets for SARS-CoV-2 infection (159,840 cases and 2,782,977 controls) and severe respiratory confirmed COVID-19 (18,152 cases and 1,145,546 controls) were acquired from the COVID-19 Host Genetics Initiative (HGI) GWAS meta-analysis round 7 without the 23andMe cohort, released on 8 April 2022[13]. Details of the cohorts included in this meta-analysis and the quality control were available at*https://www.covid19hg.org/results/r7/* . The population included was predominantly European.

### 2.3 IVs selection criteria

SNPs associated with the exposures at genome-wide significance ($P < 5.0\times10^{-8}$) were selected as IVs. However, this criterion was too strict for mixed asthma: only one SNP could be used as the IV, so we

set a P value of less than $5.0\times10^{-6}$ for mixed asthma only. Then, independent IVs were identified utilizing the cutoff of the matching linkage disequilibrium (LD) value (threshold set at $r^2 < 0.001$ and clump window > 10,000 kb) to ensure their independence. We further removed SNPs associated with the outcomes ($P<5.0\times10^{-5}$) and SNPs associated with confounders via the PhenoScannerV2 database (http://www.phenoscanner.medschl.cam.ac.uk/). To assess the strength of IVs, the F statistic was calculated for each IV: F statistic = $R^2$ (N-2)/(1-$R^2$), $R^2$: the phenotypic variance explained by each IV in the exposure, N: the sample size[14,15]. IVs with an F statistic < 10 were considered weak and should be deleted[16].

### 2.4 Statistical analysis

The inverse variance-weighted (IVW) mode was applied as the primary approach, which used meta-analysis to combine the SNP-specific Wald ratio estimates for each IV and obtained an overall estimate of the effect[17]. Three other methods, MR-Egger[18], weighted-median[19], and weighted mode[20]approaches were used as supplements.

Heterogeneity was evaluated by Cochrane's Q statistic[21]. The horizontal pleiotropy was accessed by the intercept of MR-Egger regression, which should not be significantly different from 0 (i.e., P > 0.05)[18]. We also used the Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) global test to identify and fix horizontal pleiotropic outliers[22].

The multivariate IVW model with Lasso penalization was further used to evaluate the independent causal effect of related diseases on severe COVID-19. The Lasso penalization could shrink the coefficients of the invalid variables to zero, preventing overfitting[23]. In multivariate MR analysis, phenotypes with comparable traits could be treated as controls for each other to identify the predominant phenotypes[24].

Odds ratios (OR) and 95% confidence intervals (CI) were used to describe the causal impact of exposures on outcomes. To correct for the multiple testing, the Bonferroni adjusted P values of significance were < 0.0167 ($\alpha = 0.05/3$ exposure factors) and < 0.0125 ($\alpha = 0.05/4$ exposure factors) in multivariate MR analyses for the three allergic diseases and the four asthma subtypes, respectively. P<0.0167/0.0125 was regarded as strong evidence of causality, while 0.0167/0.0125<P<0.05 was considered suggestive evidence of causality. In addition, other statistical tests had a two-sided design, with the threshold of statistical significance set at P<0.05. The R language (version 4.2.2) was used to select IVs, perform statistical analyses, and visualize our findings.

## 3 Results

### 3.1 Bidirectional two-sample MR between the allergic disease and COVID-19

74 and 73 IVs were selected for the two-sample MR analysis of the allergic disease on SARS-CoV-2 infection and severe COVID-19, respectively. In addition, 19 and 31 IVs were selected for MR analysis of SARS-CoV-2 infection and severe COVID-19 on the allergic disease, respectively. (Figure 2) The characteristics of IVs were presented in Supplementary Tables 1 to 4 in the order shown in Figure 2.

The allergic disease was not causally associated with SARS-CoV-2 infection (P=0.545; OR=0.99; 95% CI: 0.97-1.02) but have a causal and protective effect on severe COVID-19 (P=0.028; OR=0.91; 95% CI: 0.83-0.99). In the analysis of the effect of allergic disease on severe COVID-19, the four methods were in the same direction. The heterogeneity test indicated a minor problem (P=0.001) but no significant pleiotropy was observed (P=0.691). In contrast, no significant causal effect was found of SARS-CoV-2 infection/severe COVID-19 on the allergic disease. Incidentally, horizontal pleiotropy was not detected (all P >0.05) in any of the above analyses. (Figures 2 and 4)

### 3.2 Univariate MR between the various allergic diseases and severe COVID-19

The numbers of selected IVs were listed in Figure 3, with specific characteristics (including F values) described in Supplementary Tables 5 to 12 in the order shown in Figure 3. AD showed a clear causal relationship with severe COVID-19 (P=0.019; OR=0.94; 95% CI: 0.88-0.99). No significant pleiotropy or heterogeneity was observed (P=0.343 and 0.617, respectively). (Figures 3 and 4)

Although no causal relationship between asthma and severe COVID-19 was observed in univariate MR analysis (P=0.424; OR=0.97; 95% CI: 0.91-1.04), the analysis of each asthma subtype showed positive results: mixed asthma (P=0.007; OR=0.97; 95% CI: 0.94-0.99) and childhood asthma (age<16 years old) (P=0.017; OR=0.90; 95% CI: 0.83-0.98) were causal protective factors for severe COVID-19. Heterogeneity and horizontal pleiotropy were not observed in the analyses of both mixed asthma (P= 0.559 and 0.718, respectively) and childhood asthma (P= 0.111 and 0.896, respectively). (Figures 3 and 4)

Additionally, the univariate MR analysis of doctor-confirmed hay fever, AR, or eczema exhibited an ambiguous result: a positive protective result (P=0.035; OR=0.935; 95% CI: 0.878-0.995) was obtained using the primary method (IVW), and the directions of MR Egger and weighted median were consistent on the left, but the direction of weighted mode was not. There was small heterogeneity (P=0.008) but no horizontal pleiotropy (P=0.420) in this analysis.

The robustness of these univariate MR results was further proved by the insignificant MR-Egger intercepts (all P>0.05), implying the absence of horizontal pleiotropy. (Figure 3)

### 3.3 Multivariate MR of three allergic diseases and fourasthma subtypes

The results of the multivariate MR analysis between the three allergic diseases (AR, AD, and asthma) and severe COVID-19 were shown in Figure 5. In the multivariate MR analysis with AR, AD, and asthma adjusted for each other, asthma was surprisingly found to be a suggestive major causal protective factor against severe COVID-19 (P=0.024; OR=0.90; 95% CI: 0.83-0.98).

Figure 6 displayed the outcomes of multivariate MR analysis between four types of asthma (allergic, non-allergic, mixed, and childhood asthma) and severe COVID-19. Only childhood asthma remained suggestively causally associated with severe COVID-19 (P=0.048; OR=0.770; 95% CI: 0.594-0.998).

## 4 Discussion

This is the first comprehensive bidirectional and multivariable MR analysis to investigate the potential causal link between allergic disease and COVID-19. Our results revealed that allergic diseases have a protective causal association with severe COVID-19, including self-reported asthma and/or hay fever (or AR) and/or eczema (or AD). Though the heterogeneity test indicated a minor problem, heterogeneity is pervasive across MR analyses[25] and the existence of heterogeneity does not render an MR study inadmissible when horizontal pleiotropy is absent[21]. The expression level of angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2, decreases with the increase of environmental allergens, which may be one of the reasons for protecting allergic patients from severe COVID-19[26].

However, SARS-CoV-2 infection was not found to be causally associated with allergic diseases, and severe COVID-19 did not in turn lead to an increase or decrease in the risk of the allergic disease. The Korea National Health and Nutrition Examination Survey also did not show a significant reduction in the incidence of each allergic disease (asthma, AD, AR), whether self-reported or physician-diagnosed, in 2020 compared with 2019[27]. Although COVID-19 does not cause allergic diseases, viral infections (not just SARS-CoV-2) may exacerbate the symptoms of allergic diseases, so telemedicine is still advised during the COVID-19 pandemic[28].

Further analysis of various types of allergic diseases and asthma showed that AD and asthma (especially mixed asthma and childhood asthma) were causal protective factors for severe COVID-19. AD, a form of eczema, is an allergic skin disease often related to asthma, food allergy, allergic conjunctivitis, and AR[29]. In observational studies, the relationship between AD and COVID-19 remained murkier: some studies[30-32] suggested that AD was associated with increased risk for COVID-19, while others suggested that it was associated with reduced risk[33-35] or had no effect[36]. Cohort studies have shown a reduced risk of SARS-CoV-2 infection in patients with AD treated with Dupilumab[35]. This may be attributable to the fact that Dupilumab lowered the incidence of severe infections, such as herpes simplex and skin infections[37], and thus SARS-CoV-2. In addition, Dupilumab was also found to reduce the risk of SARS-CoV-2 infection in patients with asthma[38].

A meta-analysis concluded that asthma was not associated with higher SARS-CoV-2 infection or a worse prognosis and that patients with asthma had lower mortality than those without asthma[39]. Previous MR analysis studies have also suggested that asthma was a protective factor for SARS-CoV-2 infection and severe COVID-19[7,8]. Although similar results were obtained only in the multivariate MR analysis with AR and AD as references, the two-sample MR analysis of asthma-severe COVID-19 in this study was negative. After comparing the differences between this study and these two previous studies, three possible reasons for the different results were found. First, limited by research time, the study that suggested asthma was a protective factor for SARS-CoV-2 infection[8] used a relatively old COVID-19 database (the COVID-19 Host Genetic Initiative GWAS meta-analyses round 4, released on October 20, 2020), when the COVID-19 pandemic was just beginning, and the amount of GWAS data for COVID-19 patients was far from enough. Second, "COVID-19 infection" and " COVID-19 hospitalization" were chosen as the outcomes in these two MR studies, instead of "very severe respiratory confirmed COVID-19" as in our study. Differences in the selection of outcomes may have contributed to the differences in results. Thirdly, the choices of LD value in these two studies were more liberal than that in our study, and both of them chose $r^2<0.01$. Our choice ($r^2<0.001$) was 10 times more stringent. These factors are all optional and acceptable. Given the positive result of multivariate MR analysis after adjusting for AD and AR and the further analysis of asthma subtypes, we still consider asthma a protective factor for severe COVID-19.

Both mixed asthma and childhood asthma have causal protective effects against severe COVID-19, with childhood asthma playing a major role. To our knowledge, this study is the first to suggest that mixed asthma is a protective factor against severe COVID-19. Mixed asthma was described in the FinnGen database as the "combination of conditions listed in predominantly allergic asthma and nonallergic asthma". Conditions listed in "predominantly allergic asthma" included allergic (bronchitis, rhinitis with asthma), atopic asthma, extrinsic allergic asthma, and hay fever with asthma. Symptoms of "nonallergic asthma" included idiosyncratic asthma and intrinsic nonallergic asthma. We hypothesized that the development of mixed asthma is involved in the interaction of exogenous anaphylaxis and endogenous infection, leading to a more active asthma-related immune response. However, the specific pathophysiological reasons still need to be further explored.

Childhood asthma was considered a major protective factor against severe COVID-19 in our study, and there have been many reports on childhood asthma and severe COVID-19. In Spain, children were thought to usually develop mild COVID-19[40]. Clinical observations indicated that allergies or asthma were not hazardous conditions in pediatric patients with COVID-19[41]. A meta-analysis of COVID-19 patients in children and young people found that patients with asthma were less likely to be admitted to critical care and less likely to die[42]. Data from a pediatric referral hospital indicated that the prevalence of asthma in pediatric patients with COVID-19 was low, with varied clinical manifestations and laboratory findings[40]. New confirmed cases of childhood asthma in Japan dropped significantly after the COVID-19 pandemic began, and 15 months later they have not recovered[43]. The impact was particularly strong for younger children. New diagnoses of atopic dermatitis also fell slightly[43]. As mentioned above, no significant decrease was shown in the incidence rates of allergic diseases (asthma, AD, AR) in Korea[27]. However, data from the nationally representative Korean Adolescent Risk Behavior Survey presented that the prevalence of allergy among Korean adolescents increased before 2019, but decreased significantly in 2020[44]. Regardless of prior trends, the prevalence of three allergic diseases, asthma, AD, and AR, all decreased in adolescents in 2020[44]. All of these studies showed an association between COVID-19 and asthma in children.

Our study has several strengths. Firstly, large datasets covering multidimensional phenotypes were used, and the F-statistics were also large enough to prevent any weak instrumental bias. Second, compared with traditional observational studies, MR analysis is usually less affected by confounding factors and reverse causality, leading to a higher level of evidence. Third, the sample used was largely derived from populations of European ancestry, which minimized stratification bias. In addition, the pleiotropy that IVs do not have also illustrates the robustness of this study. Our study also has certain limitations, such as uneven weighting among phenotypes and a relatively small number of cases in some phenotypes. Moreover, most of the included populations were of European ancestry, which does not represent the general population, and

verification of the results in populations with different ancestries is required.

In summary, this study, based on the population genetic variation model, pointed out the protective effect of allergic diseases against severe COVID-19. More specifically, AD and asthma (both mixed and childhood asthma) were protective, but childhood asthma played a major role. This protective effect may come from the persistent inflammatory response and ACE2. More research is still needed to figure out why the protective effect is stronger in children than in adults.

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### Data availability statement

The datasets of hay fever, allergic rhinitis, or eczema and the datasets of asthma diagnosed by the doctor were acquired from the UK Biobank (UKB) (https://www.ukbiobank.ac.uk/). The datasets of allergic rhinitis, atopic dermatitis, allergic asthma, non-allergic asthma, mixed asthma, and childhood asthma were retrieved from FinnGen (https://www.finngen.fi/en). The datasets of COVID-19 are available from the COVID-19 Host Genetics Initiative (Round 7, released April 8, 2022,*https://www.covid19hg.org/results/r7/*).

### Conflict of interest disclosure

The authors have declared that no competing interests exist.

## AUTHOR CONTRIBUTION STATEMENT

Yangyiyi Yu analyzed the data and wrote the manuscript. Qianjin Lu supervised the study and revised the manuscript. All authors critically reviewed and revised the manuscript and agreed to the published version of the manuscript.

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**Figure Legends**

**Figure 1. Study design.**

The solid line indicates a causal relationship. Direct causal relationships between variables that go against the MR assumptions are shown by dashed lines. Assumption 1: The genetic instruments used as instrumental variables (IVs) are associated with exposure. Assumption 2: The IVs are not associated with any confounders. Assumption 3: IVs are not directly related to the outcome, and they influence the outcome only through exposure, not through any alternative pathways. Abbreviation: MR, mendelian randomization; IVW, inverse variance-weighted.

**Figure 2. Bidirectional two-sample MR analysis between the allergic disease and COVID-19.**

Cases: The number of cases in the database of exposure; Controls: The number of controls in the database of exposure; IVs: the number of SNPs used as instrumental variables; P: P-value of the causal estimate; OR: odds ratio; CI: confidence interval.

**Figure 3. Univariate MR analysis between the various allergic diseases and severe COVID-19.**

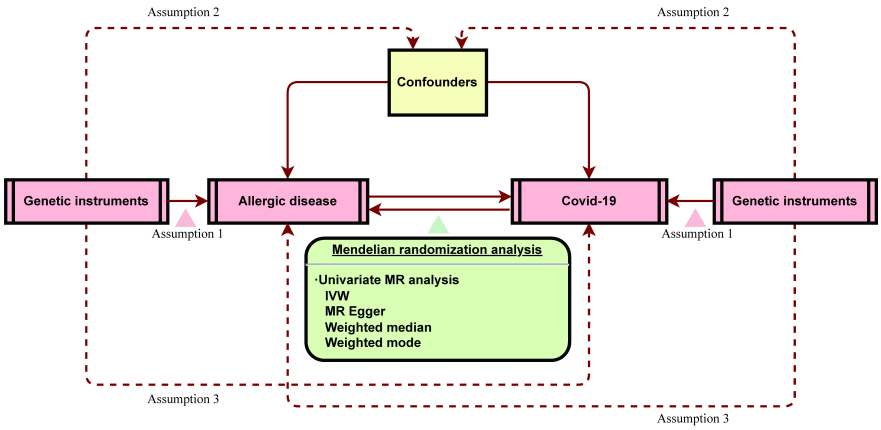
P: P-value of the causal estimate; Cases: The number of cases in the database of exposure; Controls: The number of controls in the database of exposure; IVs: the number of SNPs used as instrumental variables; OR: odds ratio; CI: confidence interval.

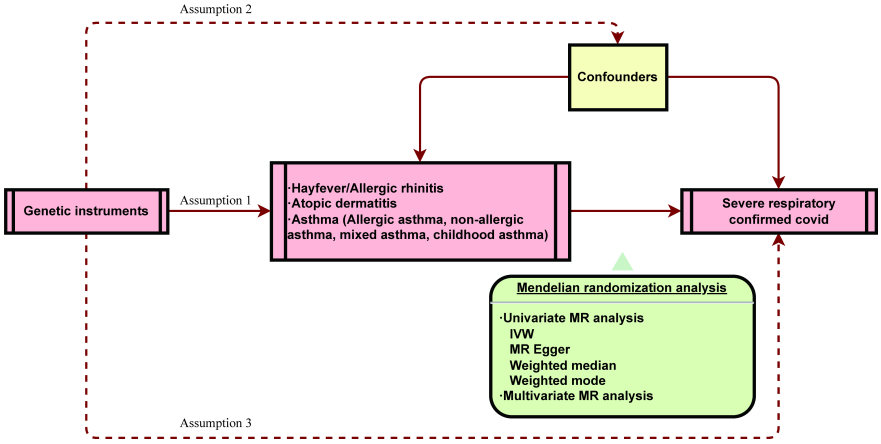
**Figure 4. Scatterplots of potential effects of SNPs on allergic disease, atopic dermatitis, mixedasthma, and childhood asthma versus severe COVID-19.**

(A) allergic disease (asthma, hay fever, or eczema); (B) atopic dermatitis; (C) mixed asthma; (D) childhood asthma. Analyses were conducted using inverse variance-weighted (IVW) mode, MR-Egger, weighted-median, and weighted mode. The slope of each line represents the estimated MR effect for each approach.

**Figure 5. Multivariate MR analysis of the three allergic diseases versus severe COVID-19.**
P: P-value of the causal estimate; OR: odds ratio; CI: confidence interval.

**Figure 6. Multivariate MR analysis of the four asthma subtypes versus severe COVID-19.**
P: P-value of the causal estimate; OR: odds ratio; CI: confidence interval.

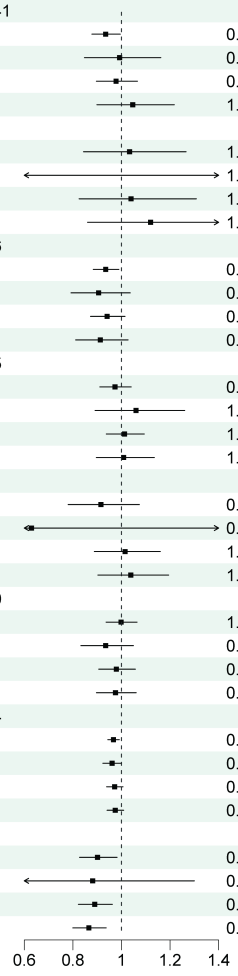


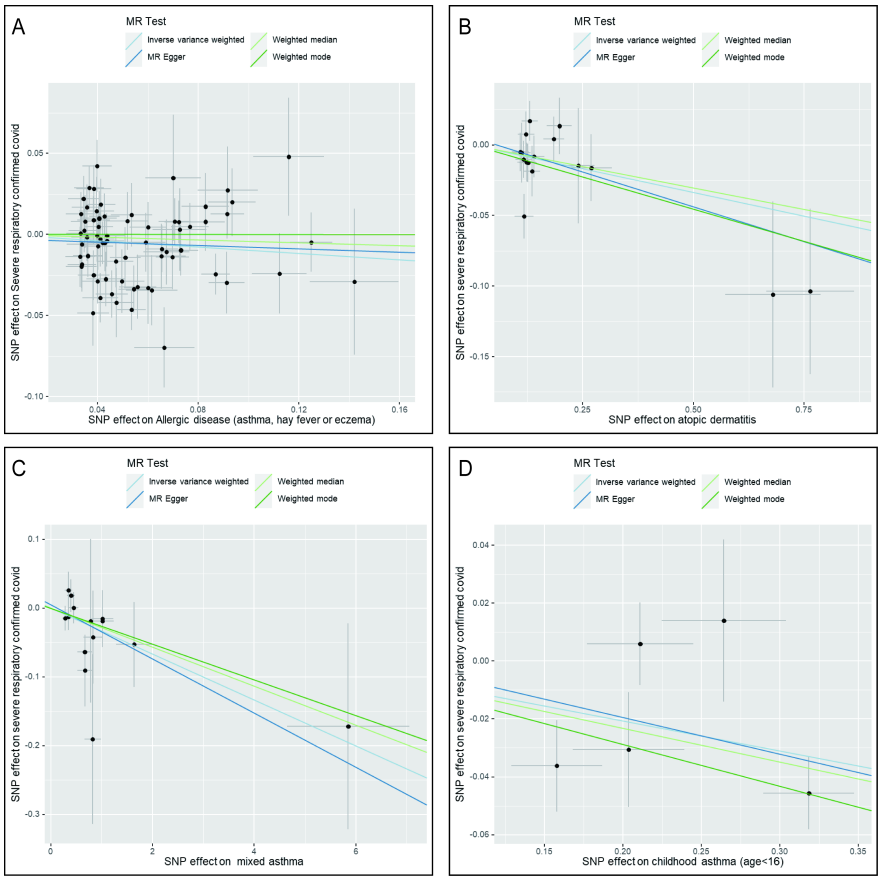




| Exposure | Outcome | Cases | Controls | IVs | P | OR (95% CI) |
|---|---|---|---|---|---|---|
| Allergic disease | SARS−CoV−2 infection | 180129 | 180709 | 74 | | |
| IVW | | | | | 0.545 | 0.99 (0.97 to 1.02) |
| MR Egger | | | | | 0.922 | 1.00 (0.93 to 1.08) |
| Weighted median | | | | | 0.982 | 1.00 (0.97 to 1.03) |
| Weighted mode | | | | | 0.905 | 1.00 (0.95 to 1.06) |
| Allergic disease | Severe respiratory confirmed covid | | | 73 | | |
| IVW | | | | | 0.028 | 0.91 (0.83 to 0.99) |
| MR Egger | | | | | 0.679 | 0.95 (0.74 to 1.21) |
| Weighted median | | | | | 0.432 | 0.96 (0.86 to 1.07) |
| Weighted mode | | | | | 0.983 | 1.00 (0.84 to 1.18) |
| SARS−CoV−2 infection | Allergic disease | 159840 | 2782977 | 19 | | |
| IVW | | | | | 0.359 | 0.97 (0.90 to 1.04) |
| MR Egger | | | | | 0.265 | 0.93 (0.82 to 1.05) |
| Weighted median | | | | | 0.561 | 0.97 (0.86 to 1.08) |
| Weighted mode | | | | | 0.127 | 0.86 (0.72 to 1.03) |
| Severe respiratory confirmed covid | Allergic disease | 18152 | 1145546 | 31 | | |
| IVW | | | | | 0.450 | 1.01 (0.99 to 1.03) |
| MR Egger | | | | | 0.248 | 1.02 (0.99 to 1.06) |
| Weighted median | | | | | 0.466 | 1.01 (0.98 to 1.04) |
| Weighted mode | | | | | 0.392 | 1.01 (0.99 to 1.04) |

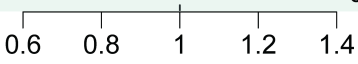
The cases and controls in the header refer to the corresponding exposure data, e.g., 180129 and 180709 in the first row refer to the data of the allergic disease database

| Exposure | P | Cases | Controls | IVs | OR (95% CI) |
|---|---|---|---|---|---|
| Hayfever, allergic rhinitis or eczema | | 104559 | 350890 | 141 | |
| IVW | 0.035 | | | | 0.93 (0.88 to 1.00) |
| MR Egger | 0.925 | | | | 0.99 (0.85 to 1.16) |
| Weighted median | 0.608 | | | | 0.98 (0.90 to 1.07) |
| Weighted mode | 0.560 | | | | 1.05 (0.90 to 1.22) |
| Allergic rhinitis | | 5527 | 212387 | 4 | |
| IVW | 0.749 | | | | 1.03 (0.84 to 1.27) |
| MR Egger | 0.562 | | | | 1.95 (0.40 to 9.65) |
| Weighted median | 0.743 | | | | 1.04 (0.83 to 1.31) |
| Weighted mode | 0.488 | | | | 1.12 (0.86 to 1.46) |
| Atopic dermatitis | | 7024 | 198740 | 16 | |
| IVW | 0.019 | | | | 0.94 (0.88 to 0.99) |
| MR Egger | 0.171 | | | | 0.91 (0.79 to 1.04) |
| Weighted median | 0.114 | | | | 0.94 (0.87 to 1.01) |
| Weighted mode | 0.151 | | | | 0.91 (0.81 to 1.03) |
| Asthma | | 52504 | 402945 | 95 | |
| IVW | 0.424 | | | | 0.97 (0.91 to 1.04) |
| MR Egger | 0.511 | | | | 1.06 (0.89 to 1.26) |
| Weighted median | 0.747 | | | | 1.01 (0.94 to 1.09) |
| Weighted mode | 0.883 | | | | 1.01 (0.90 to 1.14) |
| Allergic asthma | | 4859 | 135449 | 7 | |
| IVW | 0.278 | | | | 0.92 (0.78 to 1.07) |
| MR Egger | 0.746 | | | | 0.63 (0.05 to 8.62) |
| Weighted median | 0.828 | | | | 1.01 (0.89 to 1.16) |
| Weighted mode | 0.619 | | | | 1.04 (0.90 to 1.19) |
| Non−allergic asthma | | 3155 | 184148 | 10 | |
| IVW | 0.963 | | | | 1.00 (0.94 to 1.06) |
| MR Egger | 0.285 | | | | 0.93 (0.83 to 1.05) |
| Weighted median | 0.587 | | | | 0.98 (0.91 to 1.06) |
| Weighted mode | 0.574 | | | | 0.98 (0.90 to 1.06) |
| Mixed asthma | | 724 | 135449 | 14 | |
| IVW | 0.007 | | | | 0.97 (0.94 to 0.99) |
| MR Egger | 0.078 | | | | 0.96 (0.92 to 1.00) |
| Weighted median | 0.108 | | | | 0.97 (0.94 to 1.01) |
| Weighted mode | 0.168 | | | | 0.97 (0.94 to 1.01) |
| Childhood asthma | | 3025 | 135449 | 5 | |
| IVW | 0.017 | | | | 0.90 (0.83 to 0.98) |
| MR Egger | 0.569 | | | | 0.88 (0.60 to 1.30) |
| Weighted median | 0.003 | | | | 0.89 (0.82 to 0.96) |
| Weighted mode | 0.023 | | | | 0.87 (0.80 to 0.94) |






| Exposure | P | OR (95% CI) |
|---|---|---|
| Allergic rhinitis | 0.142 | 1.14 (0.96 to 1.36) |
| Atopic dermatitis | 0.812 | 1.01 (0.91 to 1.13) |
| Asthma | 0.024 | 0.87 (0.76 to 0.98) |




| Exposure | P | OR (95% CI) |
|---|---|---|
| Allergic asthma | 0.378 | 1.197 (0.802 to 1.785) |
| Non−allergic asthma | 0.415 | 1.150 (0.822 to 1.610) |
| Mixed asthma | 0.611 | 1.053 (0.863 to 1.285) |
| Childhood asthma | 0.048 | 0.770 (0.594 to 0.998) |