Causal relationship between COVID-19 and the risk of asthma: A Mendelian Randomisation study

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Abstract

Background

Existing research has focused on new-onset asthma and viral infections, particularly respiratory syncytial virus (RSV). However, studies on whether COVID-19 can induce asthma are limited.

Methods

We performed bidirectional two-sample Mendelian Randomization (MR) to assess the potential causal relationship between COVID-19 and asthma using genome-wide association study (GWAS) summary data obtained from the COVID-19 Host Genetic Initiative GWAS Meta-analysis Round 5 (release date: 18 January 2021). Several methods (random-effects inverse variance weighted, weighted median, MR-Egger regression, and MR-PRESSO) were used to ensure the robustness of the causal effects. Heterogeneity was measured using Cochran's Q value. Horizontal pleiotropy was evaluated using MR-Egger regression and leave-one-out analyses.

Results

We observed a significant causal association between COVID-19 hospitalisation and asthma (odds ratio (OR) = 1.042, 95% Confidence Interval (CI) = 1.004−1.081, p = 0.031), indicating a significantly increased risk of COVID-19 hospitalisation associated with asthma. However, no statistically significant causal relationships were observed for COVID-19 susceptibility (OR = 1.023, 95% CI = 0.931−1.124, p = 0.637), COVID-19 severity (OR = 1.006, 95% CI = 0.978−1.035, p = 0.669), and asthma.

Conclusions

COVID-19 can trigger the onset of asthma. Individuals experiencing prolonged coughing, chest tightness, or difficulty in breathing long after recovery from COVID-19 should remain vigilant about the possibility of developing asthma.

Introduction

Viral infections, including respiratory syncytial virus (RSV), rhinovirus, and human metapneumovirus, have been implicated in elevating the risk of incident asthma in children [1,2]. It is well known that certain patients with coronavirus disease 2019 (COVID-19) have persistent respiratory symptoms (including coughing, dyspnea, or wheezing) even after the viral infection has subsided [3]. However, the development of new-onset asthma after COVID-19 has not been thoroughly evaluated. Kang et al. reported that fractional exhaled nitric oxide (Feno) levels were generally higher in patients with chronic cough after COVID-19 compared to those without a history of COVID-19 infection [4]. Contrastingly, Lee suggested that recent COVID-19 infections rarely cause asthma, which may be linked to eosinophilic inflammation [5]. Leshchenko et al. reported that 13% of 7,497 long-term COVID-19 patients were newly diagnosed with bronchial asthma [6]. Recently, a retrospective cohort study indicated that the COVID-19 cohort exhibited a higher risk of new-onset asthma (adjusted hazard ratio [HR] 2.14; 95% CI 1.88−2.45) than matched controls [7]. Given the limited number of studies indicating an increased incidence of asthma after COVID-19, we designed this research using the latest Mendelian randomization study to investigate whether COVID-19 infection correlates with an elevated risk of asthma. To assess the association between COVID-19 and asthma, as well as the causal relationship between the two,

we conducted a bidirectional Mendelian randomization (MR) study using the latest publicly available genome-wide association studies (GWAS

Materials and methods

Study Design

To assess whether COVID-19 is associated with asthma and determine the causal relationship between the two, we performed a bidirectional two-sample MR study using the most recent publicly available GWAS. (Fig. 1)The MR analysis was based on three hypotheses: (1) instrumental variables (IVs) were associated with exposure; (2) IVs were not associated with any confounding factors; and (3) IVs could only influence outcomes through exposure factors but not through other routes[8].

Data Sources

Two independent GWAS datasets were utilised in this study. COVID-19 data from the COVID-19 Host Genetic Initiative GWAS meta-analyses round 5 (release date: 18 January 2021) [9](https://www.covid19hg.org/results/r5/), including COVID-19 infection data (38,984 infected cases and 1,644,784 controls), COVID-19 hospitalisation data (9,986 inpatients and 1,877,672 controls), and COVID-19 severe respiratory symptoms data (5,101 patients with severe respiratory symptoms and 1,383,241 controls). COVID-19 infection reflects the overall susceptibility to disease, while COVID-19 hospitalisation data, and COVID-19 severe respiratory symptoms data represent the relative severity of the disease, using uninfected individuals as controls. Asthma data were extracted from a GWAS conducted in the UK Biobank including 56,167 patients and 352,255 control subjects[10]. The summary data of GWAS analyses were derived from IEU Open GWAS Project and can be downloaded at https://gwas.mrcieu.ac.uk/. To reduce the impact of ethnicity-related factors on the results, all summary statistics are publicly available, anonymous, de-identified, and no ethical approval was required. (Table 1)

Table 1
Data source

Variable	Cases	Controls	Sample size	Year	Population	PubMed ID
COVID – 19 (hospitalized vs population)	9,986	1,877,672	1,887,658	2020	European	32404885
COVID – 19 (RELEASE 5)	38,984	1,644,784	1,683,768	2020	European	32404885
COVID – 19 (very severe respiratory confirmed vs population)	5,101	1,383,241	1,388,342	2020	European	32404885
asthma	56,167	352,255	408,442	2021	European	34103634

Selection of Instrumental Variables

We used single nucleotide polymorphism (SNP) as a tool variable to extract SNPs by genome-wide significant association level ($P < 5\times10^{-8}$), while linkage disequilibrium treatment was performed with $r^2 = 0.001$, kb = 10,000 to ensure that SNPs were significantly associated with exposure factors while meeting independence. We searched the PhenoScanner website (http://www.phenoscanner.medschl.cam.ac.uk/) and removed SNPs associated with known confounders to guarantee the absence of associations with confounders. Additionally, we estimated F statistics to

assess the intensity of the tool variables selecting SNPs with F statistics > 10 to remove weak tool variables [11] to the greatest extent possible. Finally, we used the remaining SNPs as tool variables for MR analysis.

MR analysis

We performed MR studies using R, version 4.3.1, and R software packages (TwoSampleMR, MR-PRESSO) to analyse the causal relationship between COVID-19 and asthma. Effect sizes were expressed as ORs with their 95% CIs. For MR analysis, we used the inverse variance-weighted (IVW) method as the main approach [12]. We used Cochran 's Q test to assess heterogeneity, with $p > 0.05$ indicating no statistical heterogeneity among SNPs, prompting the use of a fixed-effects model for MR. Conversely, $P \leq 0.05$ indicated statistical heterogeneity among SNPs, leading to the adoption of a random-effects model. Complementary analyses, included the weighted mode (WM), weighted median (WME), simple mode (SM), and MR-Egger regression methods for effect size estimation. Cochran's Q test was used to assess differences between variables for each instrument, with greater differences indicating stronger heterogeneity[13]. MR-Egger intercept method was used as pleiotropic[14] for assessing SNPs. To assess whether causal estimates were driven by a single SNP, we performed a leave-one-out analysis in which each SNP associated with exposure was sequentially removed and the IVW analysis was repeated.

Results

In this study, the selected instrumental variables were carefully selected to ensure that their F statistic exceeded 10, indicating no evidence of weak instrumental bias. (Supplementary Table S1) Following MR analysis to assess the causal relationships between COVID-19 susceptibility, severe respiratory symptoms, hospitalisation, and asthma, we observed a significant causal relationship, between COVID-19 hospitalisation and asthma (odds ratio (OR) = 1.042, 95% Confidence Interval (CI) = 1.004−1.081, $p = 0.031$), indicating a significantly increased risk of COVID-19 hospitalisation associated with asthma. However, no statistically significant causal relationships were detected for COVID-19 susceptibility (OR = 1.023, 95% CI = 0.931−1.124, $p = 0.637$), COVID-19 severity (OR = 1.006, 95% CI = 0.978−1.035, $p = 0.669$), and asthma.(Fig. 2−6) Sensitivity analyses, including Cochran's Q test, MR-Egger intercept, and MR-PRESSO, revealed no significant heterogeneity, horizontal pleiotropy, or outliers (Table 2). Additionally, in the reverse MR analysis using asthma as an exposure, no statistically significant reverse associations were found ($p > 0.05$), confirming the unidirectional nature of all observed associations.

Table 2
Heterogeneity test and horizontal pleiotropy test

Exposure	MR method	Heterogeneity test		Horizontal pleiotropy test	
		Cochran's Q	Q_pval	Egger intercept	pval
COVID – 19 (hospitalized vs population)	IVW	4.340	0.361	-	-
	MR-Egger	3.750	0.28	0.005	0.541
COVID – 19 (RELEASE 5)	IVW	12.051	0.060	-	-
	MR-Egger	9.068	0.106	0.012	0.181
COVID – 19 (very severe respiratory confirmed vs population)	IVW	10.207	0.177	-	-
	MR-Egger	8.395	0.210	0.003	0.446
IVW, inverse-variance weighted; MR, Mendelian randomization. Statistical significance: p < 0.05.					

Discussion

Prior studies have frequently analysed the relationship between a history of underlying asthma and the severity of COVID-19. This study, for the first time, employed Mendelian randomisation to investigate whether COVID-19 can induce asthma. This conclusion clearly indicates that COVID-19 infection can exacerbate asthma, but is not associated with susceptibility to COVID-19 or severe respiratory symptoms of COVID-19. At the same time, reverse MR analysis revealed no significant correlation.

Currently, there are limited clinical studies on COVID-19 and asthma; however, some studies have identified an association between the infection and exacerbation of COVID-19 and an increased risk of asthma, which is supported by this MR study. Bloom et al. presented data from January to August 2020 for all patients admitted with COVID-19 disease in England, Scotland, and Wales obtained from the World Health Organization Clinical Characterization Protocol UK study of the International Alliance for Serious Acute Respiratory and Emerging Infections[15]. The data included patients diagnosed with asthma and/or chronic lung disease and measured mortality by adjusting for demographics, comorbidities, and medications. Patients with asthma were more likely to require intensive care than those without asthma; patients with severe asthma alone had increased mortality compared to those without asthma (hazard ratio (HR) = 1.96 [95% CI = 1.25–3.08] for patients 16–49 years and 1.24 [95% CI = 1.04–1.49] for patients over 50 years). In elderly asthmatics, inhaled corticosteroids during the first 2 weeks of admission reduced mortality compared to patients not using asthma medication. These data suggest that severe asthma (but not the use of inhaled corticosteroids) may be a risk factor for adverse outcomes in this infection. Bo-Guen Kim et al[7] conducted a retrospective cohort study using the Korean National Health Insurance Claims dataset to collect COVID-19 data (561,009 infected cases and 7,902,703 controls) from October 2020 to December 2021. Their study found that the risk of new asthma (HR = 2.14 [95% CI 1.88–2.45]) was higher in the COVID-19 cohort than in matched controls, consistent with the results of this current study. Taken together, the above findings collectively suggest that the risk of COVID-19 hospitalisation is associated with an increased risk of asthma development and progression.

Theoretical mechanisms include the participation of respiratory viruses as enablers of asthma exacerbation. Respiratory viruses can alter the composition of the airway microbiota, promoting the growth of pathogens, which

may lead to asthma attacks[16]. Additionally, viral infection of epithelial cells produces cytokines such as IL-25 and IL-33, which interact with allergic inflammation to induce the TH2 pathway (including innate and antigen-specific TH2 cell-related pathways), resulting in increased TH2-related inflammation, eosinophilia, and increased IL-4, IL-5, IL-13, and mucin production[17]. The process of airway remodelling in virus-induced asthma is as follows: (1) First, the epithelial inflammatory response to viral elimination includes the production of cytokines such as IL-13 and GM-CSF. (2) Second, activation of leukocytes, including lymphocytes, neutrophils, eosinophils, mastocytes, and monocytes/macrophages, and the production of cytokines and inflammatory factors derived from them. (3) Third, fibroblast and smooth muscle cell proliferation were initiated by previous processes. Airway remodelling is generally induced by respiratory virus infections involving chemokines, cytokines, and cellular immunity[18,19].

Studies with long-term follow-up reported that patients who presented with respiratory infections caused by RSV continued to have hyper-responsiveness and persistent airway obstruction up to 30 years later[20]. A recent study indicated that the approximately 15%of 5-year current asthma cases could be prevented by avoiding RSV infection during infancy[21]. Additionally, recurrent infections with other viruses, such as rhinovirus, influenza virus, adenovirus, and can lead to the occurrence of asthma[22]. For the infection of the novel coronavirus, the initial focus has been on Long COVID syndrome. However, the relationship between allergic diseases and Long COVID, as well as the increased asthma incidence of post-COVID-19, has not been extensively studied. Wolff's research suggests that pre-existing asthma, measured in hospital-based populations, may be associated with an increased risk of Long COVID (Odds Ratio 1.94, 95% CI 1.08, 3.50). Similar associations were observed for pre-existing rhinitis (Odds Ratio 1.96, 95% CI 1.61, 2.39), with both pieces of evidence characterised as very low certainty[23]. Gerce's study revealed that eight weeks post-COVID-19 infection, some individuals still experienced symptoms such as cough and breathing difficulties. Among the patients, 40 (26.5%) showed an increase in Forced Expiratory Volume in 1 second (FEV1) of ≥ 200 ml, while 14 (9.3%) were diagnosed with asthma. During the 1-year follow-up, the post−COVID−19 cohort experienced increased healthcare utilisation for asthma, with a risk ratio of 1.95 (95% CI 1.86−2.03), compared with the non−COVID−19 cohort[24]. Kim et al. found that the risk of new-onset asthma development after COVID-19 is high, especially in older subjects[7]. Additionally, viral infection has been reported to be one of the triggers of asthma in elderly[25].

Our study had several limitations. Patients in the GWAS-pooled data used in our study were of European ancestry, possibly leading to biased estimates, and we must be cautious when extrapolating our findings to other ethnic groups. Second, increasing the sample size is essential to estimate the link between COVID-19 and asthma more precisely. Third, due to a lack of personal data, the COVID-19-affected population was only assessed using summary statistics. Additional population-stratified analyses (e.g. by sex, age, and BMI) may be performed to account for potential differences between investigation teams. Finally, as the MR analysis was based on untestable hypotheses, further clinical validation studies are warranted to determine the clinical significance of COVID-19 in contributing to the risk of asthma development.

Conclusion

COVID-19 has been identified as a potential trigger for the development of asthma. Individuals experiencing prolonged coughing, chest tightness, or difficulty breathing long after recovering from COVID-19 should be vigilant about the possibility of developing asthma.

Declarations

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

Author Contributions

XXC, JLL, and SS: conceptualization. XXC and JLL: methodology. XXC: software. XXC and SS : validation. XXC: formal analysis. XXC, JLL, and SS: writing – original draft preparation. XXC, JLL and HC: writing – original and editing. JLL and HC: supervision. HC: funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Availability of data and material

All data generated or analysed during this study are included in this published article and its supplementary information files.

Ethics approval and consent to participate

All summary statistics are publicly available, anonymous, de-identified, the authorization from Institutional Review Board was not necessary for this study. **Consent for publication**

Not applicable.

Competing interests

The authors declare no competing interests.

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Figures
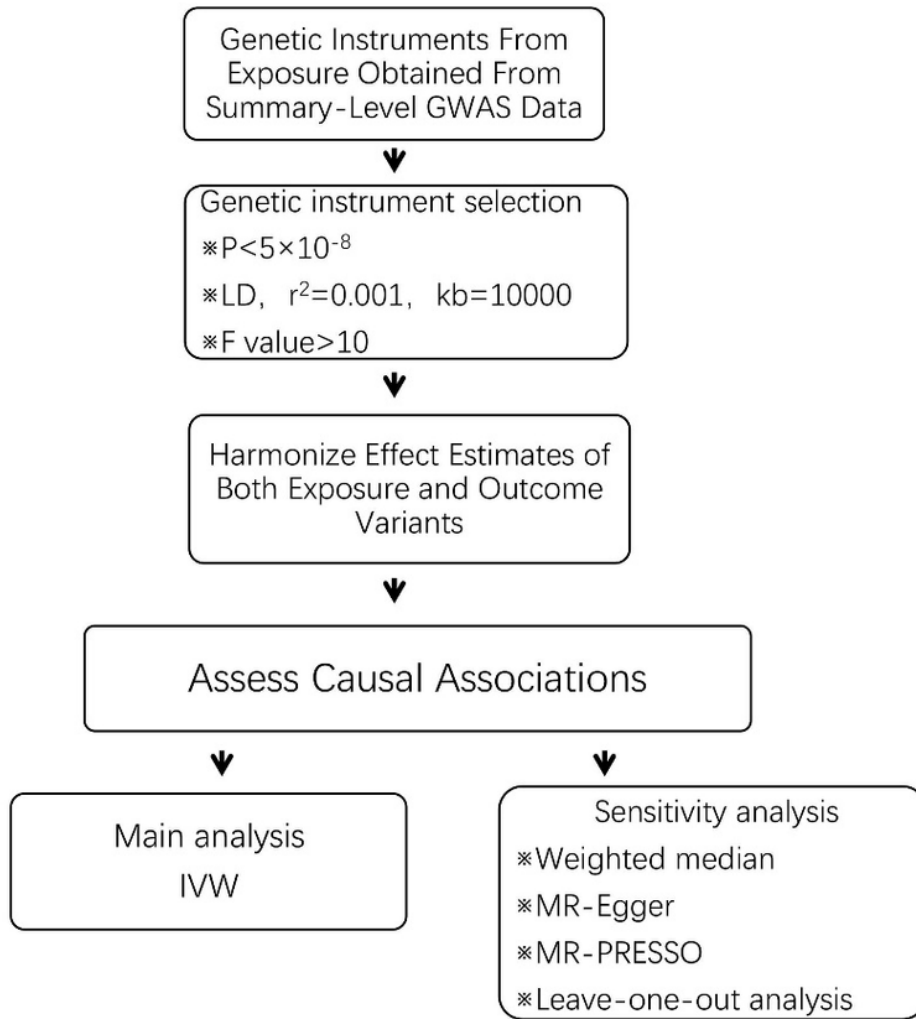
GWAS: Genome-wide association study;LD: Linkage disequilibrium; IVW: Inverse variance weighted; PRESSO: pleiotropy residual sum and outlier; MR: Mendelian randomization
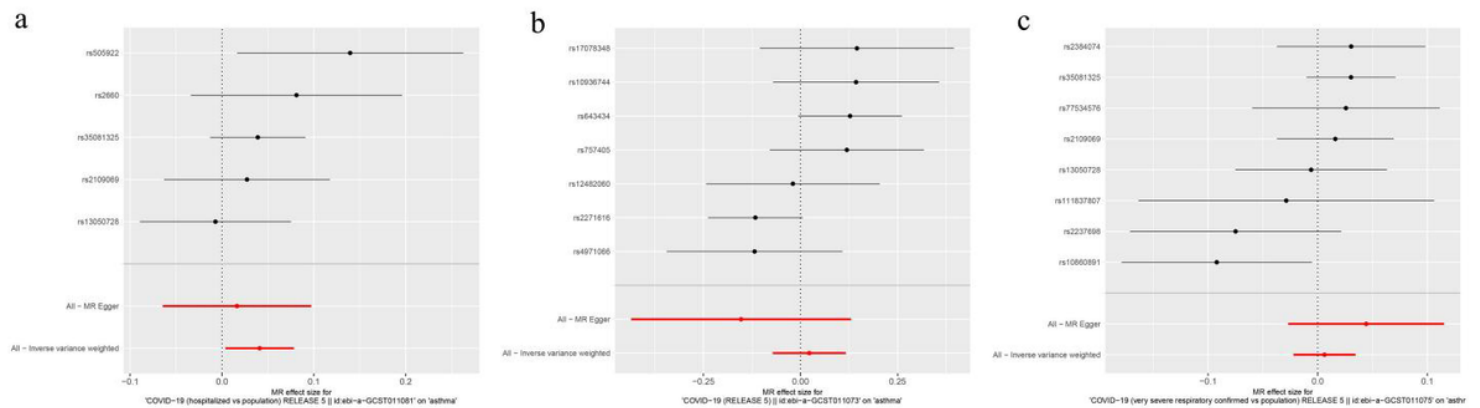
Figure 1

Design of the Mendelian Randomization Study

exposure	nsnp	method	pval		OR(95% CI)
COVID−19 (hospitalized vs population)	5	Weighted median	0.118		1.036 (0.991 to 1.083)
COVID−19 (hospitalized vs population)	5	Inverse variance weighted	**0.031**		1.042 (1.004 to 1.081)
COVID−19 (hospitalized vs population)	5	Weighted mode	0.247		1.033 (0.986 to 1.082)
COVID−19 (RELEASE 5)	7	Weighted median	0.138		1.080 (0.976 to 1.195)
COVID−19 (RELEASE 5)	7	Inverse variance weighted	0.637		1.023 (0.931 to 1.124)
COVID−19 (RELEASE 5)	7	Weighted mode	0.330		1.140 (0.895 to 1.453)
COVID−19 (very severe respiratory confirmed vs population)	8	Weighted median	0.107		1.026 (0.995 to 1.058)
COVID−19 (very severe respiratory confirmed vs population)	8	Inverse variance weighted	0.669		1.006 (0.978 to 1.035)
COVID−19 (very severe respiratory confirmed vs population)	8	Weighted mode	0.186		1.025 (0.992 to 1.058)

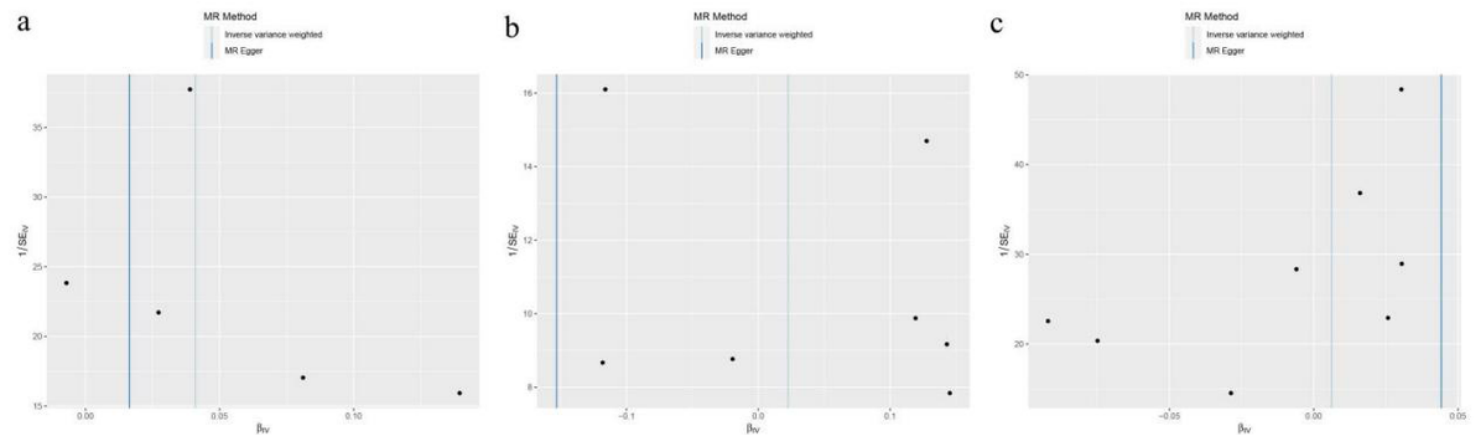## Figure 2

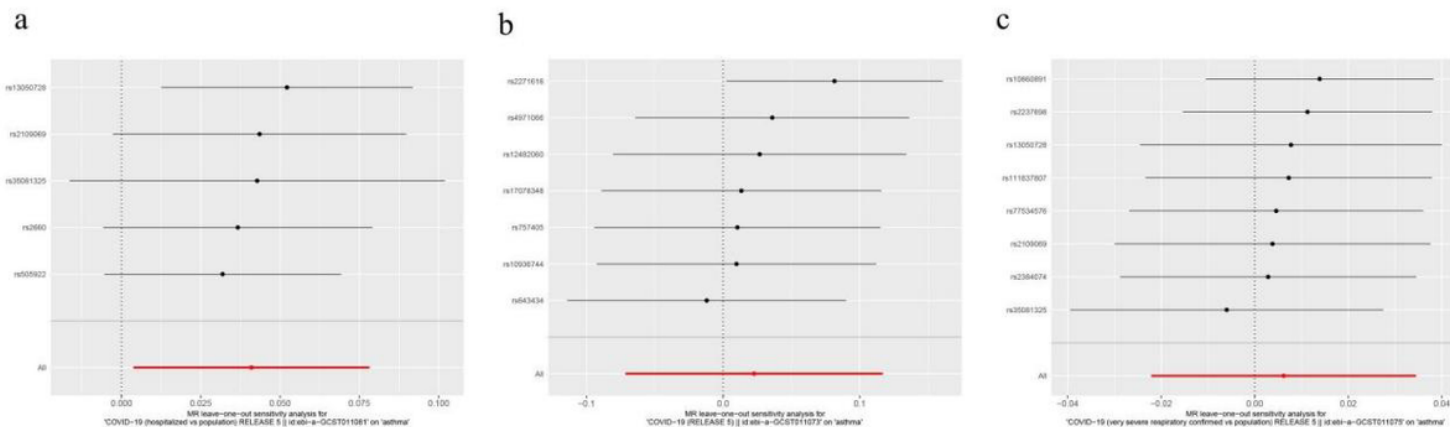Causal effects of COVID-19 on asthma outcomes

Figure 3

Forest Plots of Two-Sample MR Analysis. (a) forest plot of the primary MR analysis of the effect of COVID-19 (hospitalized vs population) on asthma;(b) forest plot of the primary MR analysis of the effect of COVID-19 (RELEASE 5) on asthma; (c) forest plot of the primary MR analysis of the effect of COVID-19 (very severe respiratory confirmed vs population) on asthma.
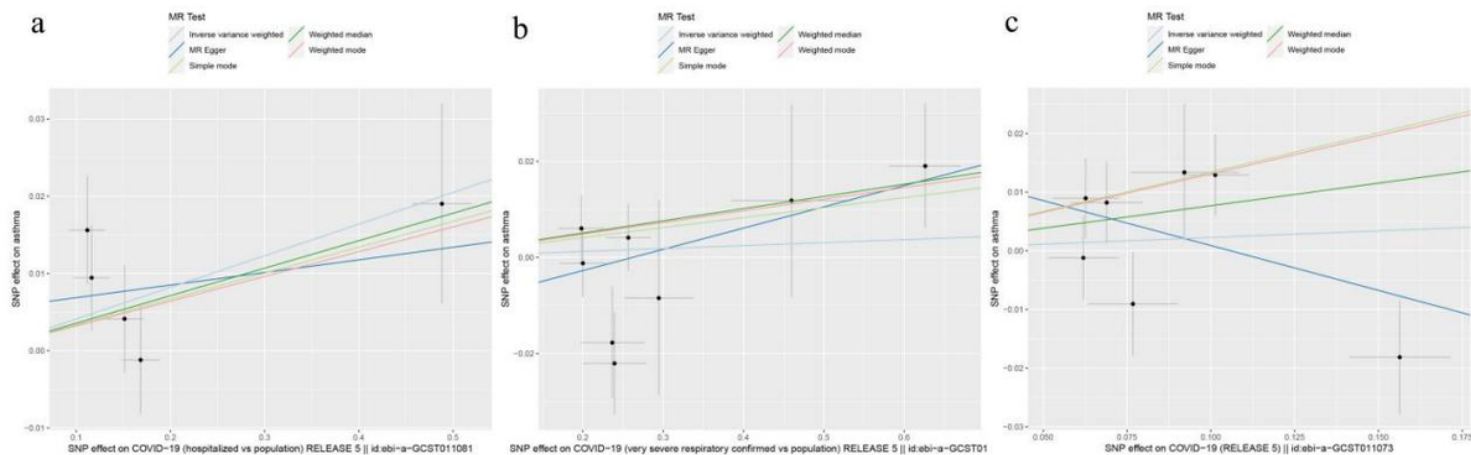

Figure 4

Funnel plot of Two-Sample MR Analysis. (a) funnel plot of the primary MR analysis of the effect of COVID-19 (hospitalized vs population) on asthma;(b) funnel plot of the primary MR analysis of the effect of COVID-19 (RELEASE

5) on asthma; (c) funnel plot of the primary MR analysis of the effect of COVID-19 (very severe respiratory confirmed vs population) on asthma.

Figure 5

Leave-one-out of Two-Sample MR Analysis. (a) leave-one-out of the primary MR analysis of the effect of COVID-19 (hospitalized vs population) on asthma;(b) leave-one-out of the primary MR analysis of the effect of COVID-19 (RELEASE 5) on asthma; (c) leave-one-out of the primary MR analysis of the effect of COVID-19 (very severe respiratory confirmed vs population) on asthma.

Figure 6

Scatter plot of Two-Sample MR Analysis. (a) scatter plot of the primary MR analysis of the effect of COVID-19 (hospitalized vs population) on asthma;(b) scatter plot of the primary MR analysis of the effect of COVID-19 (RELEASE 5) on asthma; (c) scatter plot of the primary MR analysis of the effect of COVID-19 (very severe respiratory confirmed vs population) on asthma.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTableS1CharacteristicsoftheinstrumentalvariablesforCOVID19andtheirrelationshipwithasthma.xlsx