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Genetic prediction of asthma increases multiple sepsis risks: A Mendelian randomization study

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ABSTRACT

Background: Observational epidemiological studies have indicated a potential association between asthma and sepsis, although the causal relationship between these 2 conditions remains uncertain. To further investigate this relationship, the present study utilized Mendelian randomization (MR) analysis approach to explore the potential links between asthma and various types of sepsis.

Methods: In a large-scale genome-wide association study, single nucleotide polymorphisms (SNPs) associated with asthma were selected as instrumental variables. Three methods, including inverse-variance weighted (IVW), MR-Egger regression, and weighted median were used to assess the causal relationship between asthma and sepsis. The odds ratio (OR) and 95% confidence interval (CI) were used as the evaluation metrics for causal relationships, and sensitivity analysis was conducted to assess pleiotropy and instrument validity. Finally, a reverse MR analysis was conducted to investigate whether there is a causal relationship between sepsis and asthma.

Results: We found a positive association between asthma and an increased risk of sepsis (*OR=1.18, P < 0.05*), streptococcal sepsis (*OR=1.23, P=0.04*), pneumonia-related sepsis (*OR=1.57, P < 0.05*), pneumococcal sepsis (*OR=1.58, P=0.01*), other sepsis (*OR=1.15, P < 0.05*), and sepsis in intensive care unit (ICU) settings (*OR=1.23, P=0.02*). Sensitivity analysis showed consistent results without heterogeneity or pleiotropy. The reverse MR analysis reveals no causal relationship between various types of sepsis and asthma.

Conclusion: Our study demonstrates a causal relationship between asthma and different types of sepsis. These findings suggest the importance of healthcare providers paying attention to the potential risk of sepsis in asthma patients and implementing appropriate preventive and intervention measures in a timely manner.

Keywords: Asthma, Sepsis, Septicaemia, Streptococcal, Mendelian randomization (MR)

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INTRODUCTION

As a major global health problem, sepsis is a serious infection-related disease that affected more than 40 million people and caused more than 10 million deaths in 2017 alone.[1] The main feature of sepsis is a systemic inflammatory response syndrome, including fever, rapid heart rate, shortness of breath, hypotension, and altered consciousness. Sepsis may lead to multi-organ failure and has a high mortality rate.[2] So far, although some modifiable risk factors associated with sepsis have been identified, active exploration is still underway on how to further mitigate the burden of sepsis.

Asthma is a chronic inflammatory respiratory disease characterized by airway inflammation and heightened airway sensitivity, leading to symptoms such as restricted expiratory airflow, breathing difficulties, coughing, and chest tightness.[3] The prevalence of this condition varies significantly worldwide, with rates ranging from 0.2% to 21.0% among adults and 2.8%–37.6% among children aged 6–7 years.[4] Asthma attacks are typically triggered by various factors, including allergens, air pollutants, infections, and physical exertion.[5] Although asthma and sepsis are 2 different diseases, there are a number of associated and interacting factors. Airway inflammation and hypersensitivity in asthmatics make them more susceptible to respiratory infections that eventually develop into sepsis. A study has revealed that acute exacerbation of asthma is associated with an increased risk of mortality within 28 days, whereas stable asthma is associated with a reduced risk of mortality within 28 days.[6] Due to potential biases such as confounding factors or reverse causality, the association between asthma and sepsis has not been systematically investigated; therefore, the causal role of asthma in the development of sepsis remains elusive.

Mendelian randomization (MR) is an epidemiological approach that utilizes genetic variation as instrumental variables (IVs) to infer causal relationships between exposure and outcomes.[7] Single nucleotide polymorphisms (SNPs) are randomly allocated during conception, independent of confounding factors, enabling MR to resemble randomized controlled trials and overcome limitations of previous observational studies.[8] To date, no research has evaluated the role of asthma in the risk of sepsis (or septicaemia) within the MR framework. Therefore, this study employs a MR method using summary statistics from large-scale genome-wide association studies (GWAS) to investigate the causal relationship between asthma and the risk of sepsis.

METHODS

All data utilized in this study were publicly available, sourced from studies with appropriate participant consent and ethical approvals, thus negating the need for institutional review board approval for this particular study.

Research procedure and data sources

This study followed the key principles of the STROBE-MR[7] guidelines, with the STrengthening the REporting of Genetic Association Studies (STREGA) list[9] as its extended statement, to ensure methodological transparency and scientific credibility. We utilized the MR study approach to examine the causal association between asthma and sepsis. The study methodology is depicted in Fig. 1. Publicly accessible summary statistics from the Integrative Epidemiology Unit (IEU) Open GWAS (https://gwas.mrcieu.ac.uk/)[10] project are used for the MR analysis here. To mitigate the impact of population stratification bias, both the exposure (asthma) and outcome (sepsis or septicaemia) cohorts were restricted to individuals of European descent. GWAS summary-level data for asthma were obtained from the IEU Open database[11] involving a total of 408,422 participants (including 56,167 case and 352,255 controls). In this study, asthma was defined based on a set of criteria developed by experts. These criteria included information from hospital records, death records, primary care records, and self-reported data. Asthma cases were identified using diagnosis codes from hospital records (ICD-9 or ICD-10 codes) or primary care medical records, as well as self-reported asthma status.[11] The GWAS summary-level data for sepsis were sourced from the IEU Open database[12,13] and a FinnGen database.[14] The identification of sepsis aligns with recent literature through the utilization of

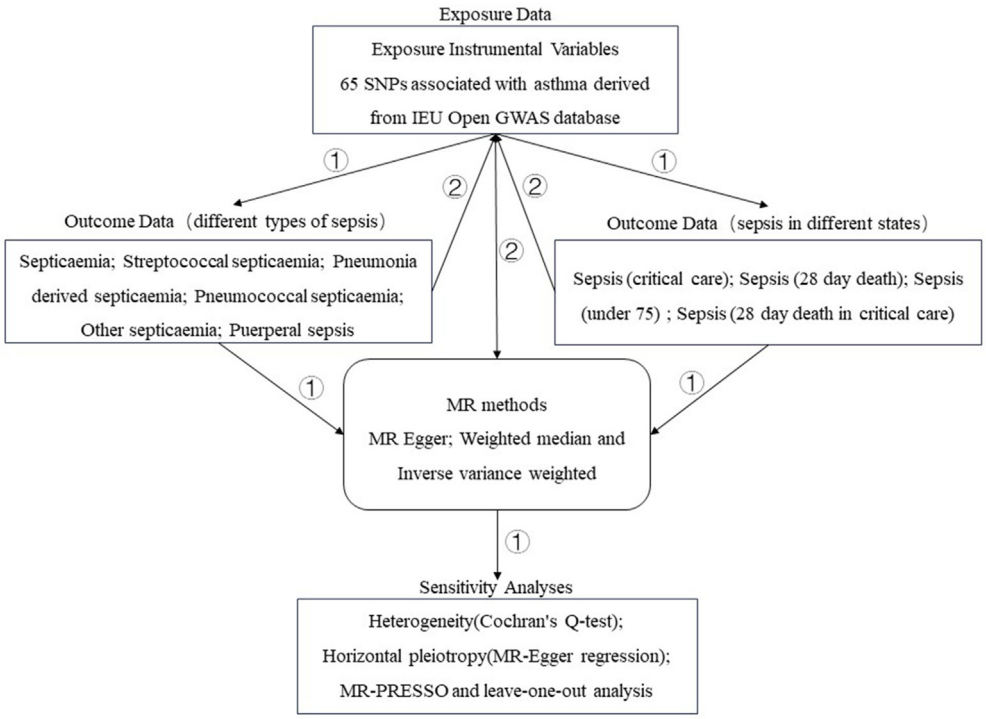


Fig. 1 The research process. MR, Mendelian randomization; SNP, single-nucleotide polymorphisms; MR-PRESSO, MR Pleiotropy Residual Sum and Outlier; ①: The first step is to analyze the relationship between asthma and sepsis; ②: The second step is to analyze the relationship between sepsis and asthma

either ICD-9 or ICD-10 codes.[15] Inpatient duration and related information are extracted using the Hospital Episode Statistics coding system.[16] Detailed data of all GWAS can be found in Table 1.

Genetic association datasets for asthma and sepsis

Using the TwoSampleMR R package, we performed the selection of genetic instrumental variables. From the GWAS summary data of asthma, we identified SNPs strongly associated with asthma based on a threshold of $P < 5 \times 10^{-8}$. Subsequently, we conducted screening of these SNPs within a 10000 kb window with an $R^2 < 0.001$ to ensure the removal of SNPs in linkage disequilibrium (LD). Additionally, we excluded SNPs with incompatible alleles, such as rs35320232, and removed palindromic SNPs with intermediate allele frequencies, such as rs13099273, to avoid ambiguity in allele coordination between exposure and outcome datasets. Furthermore, we used the PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/)[17] to exclude 6 SNPs that could potentially confound the results (Supplementary Table S1). The remaining SNPs were chosen as instrumental variables (IVs). To assess the presence of weak bias in the selected IVs, indicating weak associations between the chosen genetic variations as IVs and the exposure factor, we calculated the F-statistic [$F = R2(n-k-1)/k(1-R2)$].[18] Here, R2 represents the proportion of exposure variance explained by the selected IVs, n is the sample size, and k is the number of IVs. If the F-statistic for the instrument-exposure association is greater than 10, it indicates a low likelihood of weak bias in the instrumental variables.[19] In order to comprehensively evaluate the relationship between asthma and different types of sepsis, we utilized the outcome data from the FinnGen database including Septicaemia, Streptococcal septicaemia, Puerperal sepsis, Pneumonia derived septichemia, Pneumococcal septichemia, and Other septicaemia, as well as the IEU Open database including Sepsis (28 day death), Sepsis (under 75), Sepsis (critical care), and Sepsis (28 day death in critical care). In these data we extracted SNPs consistent with the above analysis.

Mendelian randomization analysis

After harmonizing the effect alleles in GWAS of asthma and sepsis, we employed three distinct methodologies, namely inverse variance weighting

Traits	Sample size (cases/controls)	SNPs	Gender	Year	Data sources
Asthma (ebi-a-GCST90014325)	408,442 (56,167/352,255)	34,551,291	Males and Females	2021	EBI database
Sepsis (critical care) (ieu-b-4982)	431,365 (1380/429,985)	12,243,372	Males and Females	2021	IEU Open
Sepsis (28 day death) (ieu-b-5086)	486,484 (1896/484,588)	12,243,487	Males and Females	2021	IEU Open
Sepsis (28 day death in critical care) (ieu-b-4981)	431,365 (347/431,018)	12,243,324	Males and Females	2021	IEU Open
Sepsis (under 75) (ieu-b-5088)	462,869 (11,568/451,301)	12,243,540	Males and Females	2021	IEU Open
Septicaemia (finn-b-AB1_SEPSIS)	203,824 (6164/197,660)	16,380,410	Males and Females	2021	FinnGen
Streptococcal septicaemia (finn-b-AB1_STREPTO_SEPSIS)	198,750 (1090/197,660)	16,380,403	Males and Females	2021	FinnGen
Pneumonia derived septicaemia (finn-b-SEPTICHE_PNEUMONIA)	208,794 (470/208,324)	16,380,447	Males and Females	2021	FinnGen
Pneumococcal septicaemia (finn-b-PNEUMO_SEPTHICHE)	218,769 (447/218,322)	16,380,466	Males and Females	2021	FinnGen
Other septicaemia (finn-b-AB1_OTHER_SEPSIS)	203,033 (5373/197,660)	16,380,409	Males and Females	2021	FinnGen
Puerperal sepsis (finn-b-O15_PUERP_SEPSIS)	121,441 (2286/119,155)	16,379,757	Males and Females	2021	FinnGen

Table 1. Data sources

(IVW), MR-Egger regression, and weighted median to estimate the MR effects between asthma and different types of sepsis. The IVW method is the most widely used approach in Mendelian randomization. It involves estimating causal effects using multiple IVs, where the inverse of the variance for each locus is used as weights for the causal effect estimates at each locus. These weighted estimates are then summed, yielding the final estimate of causal effect via the IVW method. This approach possesses strong capabilities in detecting causal relationships.[20] The biggest difference between MR-Egger and IVW lies in considering the presence of intercept terms in regression and using them to assess pleiotropy. When IVs exhibit pleiotropy, rendering IVW inapplicable, MR-Egger can be employed as a supplementary method to IVW.[21] The principle of the weighted median method is to sort the effect estimates of all SNPs from small to large and then take the effect estimate at 50% position as the final causal effect estimate. This method will effectively avoid the influence of outliers. For these three methods, when IVs exhibit no heterogeneity or pleiotropy, the estimate results from the IVW method are preferred. When only heterogeneity is present without pleiotropy, the results from the weighted median method are prioritized. In cases of pleiotropy, the results calculated by the MR-Egger method are given priority. Because weighted median and MR-Egger can provide estimates in a wider range of scenarios, their statistical efficiency will be lower than IVW and have wider confidence intervals.[22,23] Then, we also performed reverse Mendelian randomization analysis for asthma and corresponding sepsis that had a causal relationship.

Sensitivity analysis

To address potential horizontal pleiotropy, we employed heterogeneity markers derived from the IVW approach, where a significance threshold of Cochran's Q-derived $P < 0.05$ was utilized. Additionally, the intercept obtained from MR-Egger regression served as an indicator for directional pleiotropy, with directional pleiotropy being considered present when the *P-value* was below 0.05. To evaluate and mitigate the influence of horizontal pleiotropy, we employed the MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) methods. Additionally, a leave-one-out analysis was conducted to assess whether the MR estimate was influenced or biased by individual SNPs.

The aforementioned analyses were performed using the TwoSampleMR package (version 0.5.6) in R (version 4.1.3).

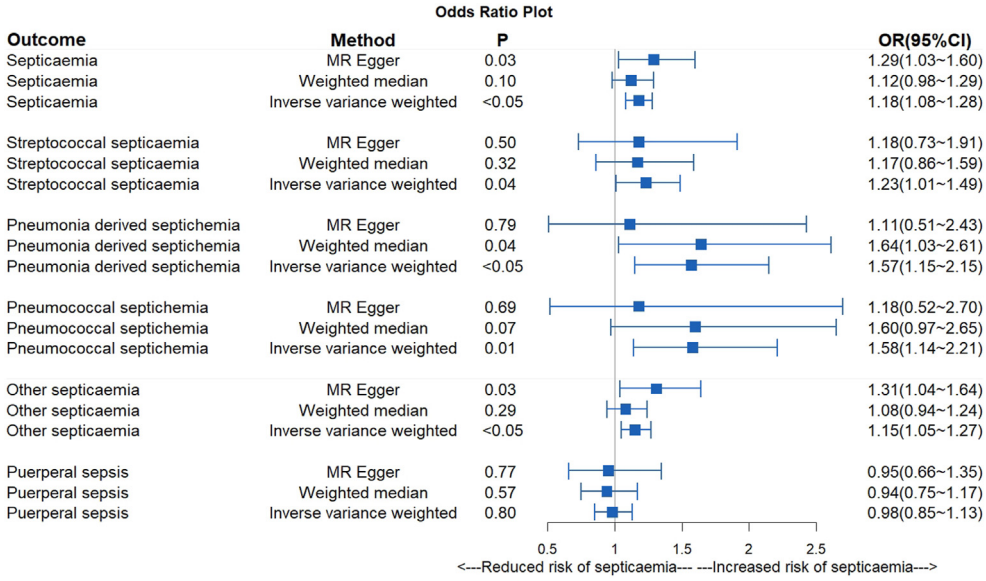


Fig. 2 Mendelian randomization analysis on the association between asthma and different types of sepsis

RESULTS

IV Selection for asthma

Detailed information on the SNPs associated with asthma can be found in Supplementary Table S2. All analyzed SNPs were strong IVs, with F values ranging from 29.8 to 251.4, exceeding the recommended threshold of 10, indicating the absence of bias caused by weak IVs in the study. After screening, a total of 65 SNPs were included in the analysis of the causal relationship between asthma and sepsis (Supplementary Table S3).

Mendelian randomization between asthma and different types of sepsis (FinnGen database)

Since there were no weak instrumental variables, the causal analysis was mainly performed using the IVW method, and the results supported that asthma may increase the risk of septicaemia (*OR=1.18, P<0.05*). Asthma was found to be associated with an increased risk of Streptococcal septicaemia (*OR=1.23, P=0.04*), Pneumonia derived septicaemia (*OR=1.57,P < 0.05*), Pneumococcal septicaemia (*OR=1.58, P=0.01*), and Other septicaemia (*OR=1.15,P < 0.05*). However, there

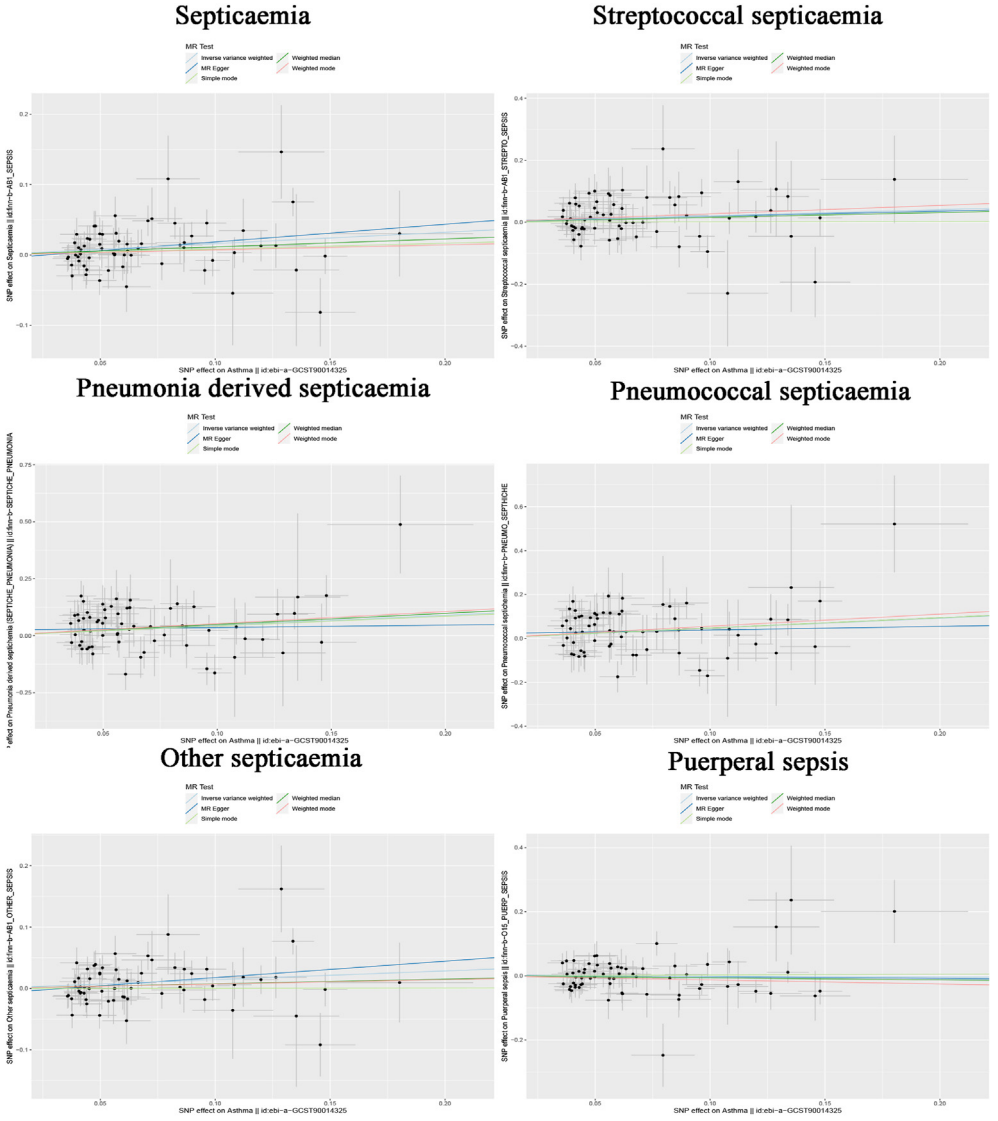
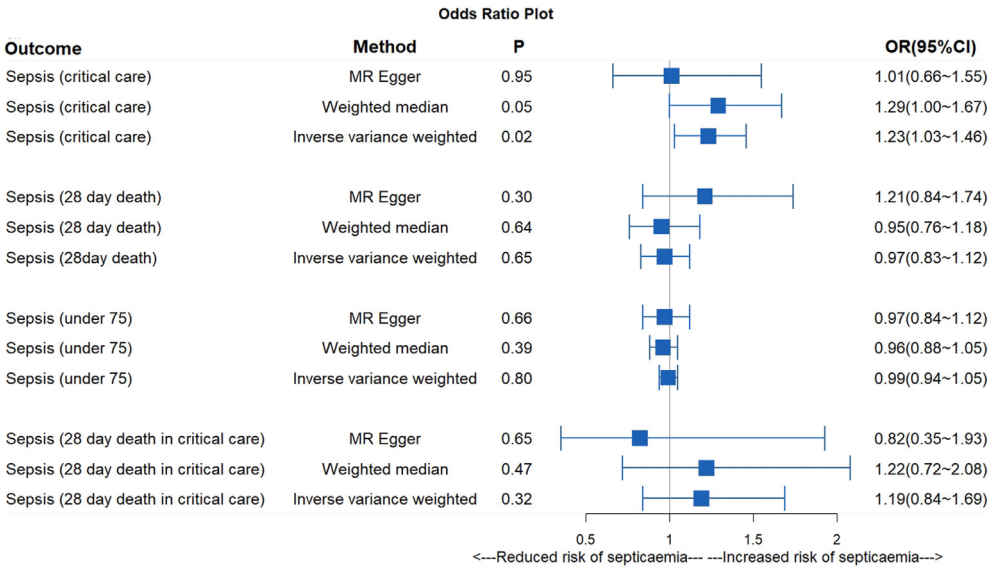


Fig. 3 Scatter plots of single nucleotide polymorphism effect on asthma and single nucleotide polymorphism effect on different types of sepsis

was no causal association observed between asthma and Puerperal sepsis ($P > 0.05$). Results including IVW, MR Egger, Weighted median are displayed in Fig. 2. Sensitivity analysis showed no evidence of heterogeneity for any of the analyzed associations based on Cochran's Q-test ($P > 0.05$), and the MR-Egger regression analysis indicated no presence of pleiotropy ($P > 0.05$) (Supplementary Table S4). Scatter plots in Fig. 3 illustrate the causal relationships between asthma and different sepsis risks. Leave-one-out analysis demonstrated that no individual SNPs had a significant impact on the estimates (Supplementary Fig. S1). The funnel plot and forest plot illustrating the associated SNPs with asthma and their risk for various types of sepsis can be found in Supplementary Fig. S3 and Supplementary Fig. S4. Regarding the above results that asthma can increase the risk of different types of sepsis, we conducted a reverse MR analysis in which the 2 were interchanged. The results showed that various septicaemia will not have an impact on asthma ($P > 0.05$) (Supplementary Table S5).

Mendelian randomization between asthma and sepsis in different states (IEU Open database)

In order to explore the causal relationship between asthma and various sepsis phenotypes, we conducted a comprehensive analysis utilizing the IEU Open dataset. Our findings revealed a statistically significant positive association between asthma and Sepsis (critical care), with an odds ratio of 1.23 ($P = 0.02$). However, no significant causal relationship was observed between asthma and Sepsis (28 day death), Sepsis (under 75), or Sepsis (28 day death in critical care), as indicated by non-significant *P-values* > 0.05. The corresponding results are illustrated in Fig. 4. Through the implementation of sensitivity analysis, employing Cochran's Q-test, we found no substantial evidence of heterogeneity in the association between asthma and Sepsis (critical care) ($P > 0.05$). Furthermore, the MR-Egger regression analysis indicated the absence of pleiotropy in this relationship ($P > 0.05$), as presented in Supplementary Table S4. Moreover, Fig. 5 visually depicts scatter plots that illustrate the causal associations between asthma and distinct sepsis phenotypes. Finally, the leave-one-out analysis revealed that no individual single nucleotide polymorphisms (SNPs) significantly influenced the estimates (Supplementary Fig. S2). Supplementary Figs. S5 and S6 present funnel plots and forest plots demonstrating the relationship between asthma-associated SNPs and the risk of sepsis across various conditions. Similarly, when we performed a reverse MR analysis between Sepsis (critical care) and asthma, we found that there was no causal relationship between the 2 ($P > 0.05$) (Supplementary Table S5).



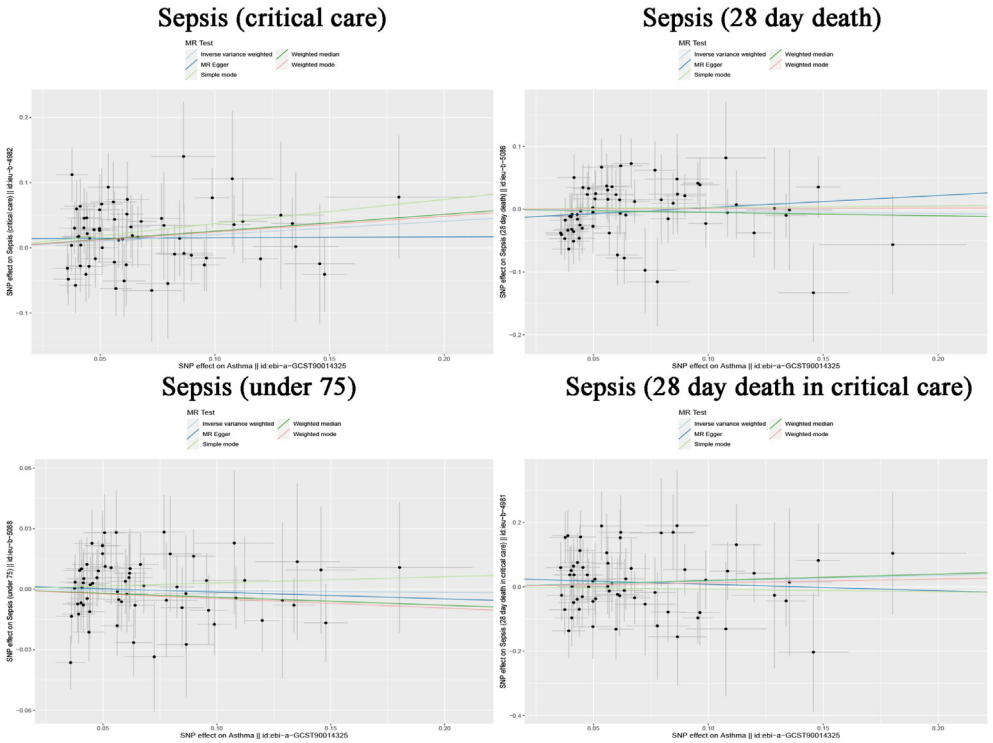


Fig. 5 Scatter plots of single nucleotide polymorphism effect on asthma and single nucleotide polymorphism effect on sepsis in different states

DISCUSSION

Sepsis is a serious infectious disease caused by bacteria or other pathogens that can lead to a systemic inflammatory response and multiple organ dysfunction. Asthma immunopathology involves multiple inflammatory pathways including Th2 responses, IL-17-mediated inflammation, and Toll-like receptors.[24–26] Innate responses due to Toll-like receptors may improve pathogen clearance. In patients with previously intact immune function who develop community-acquired severe sepsis, there is a significant upregulation of Th2/Th1 response, with a predominant Th2 bias. The sustained dynamic increase in Th2 response is associated with ICU-acquired infections and 28-day mortality. IL-17 receptor-deficient mice show reduced neutrophil recruitment, increased inflammation, and increased mortality after cecum ligation and puncture compared to wild-type mice.[27–29] A study utilizing the MIMIC-III intensive care database revealed that among patients with acute exacerbation of asthma, the highest 28-day mortality rate was observed in those with sepsis (35.29%). In comparison, stable asthma patients had the lowest 28-day mortality rate (21.60%), while non-asthmatic patients had a mortality rate of 34.42%.[6] Based on the aforementioned study, we identified limited clinical research evidence specifically investigating the potential impact of asthma on sepsis, with inconsistent reported outcomes. Therefore, we aim to ascertain the causal relationship between asthma and sepsis, aiming to alleviate the burden for this patient population.

Our study results indicate that asthma may be positively associated with septicaemia (*IVW-OR: 1.18, MR Egger-OR: 1.29, $P < 0.05$*), streptococcal septicaemia (*IVW-OR: 1.18, $P < 0.05$*), pneumonia-associated septicaemia (*IVW-OR: 1.57, weighted median-OR: 1.64, $P < 0.05$*), pneumococcal septicaemia (*IVW-OR: 1.58, $P < 0.05$*), other septicaemia (*IVW-OR: 1.15, MR Egger-OR: 1.31, $P < 0.05$*), and sepsis requiring intensive care (*IVW-OR: 1.23, weighted median-OR: 1.29, $P < 0.05$*). Additionally, we observed that all three methods consistently yielded results with an OR value greater than 1 across all analyses, which enhances the credibility of the study findings. The sensitivity analysis results further confirmed the robustness of the study findings, excluding the influence of heterogeneity and pleiotropy on the results, thereby increasing the credibility of the study. Finally, the results of

the reverse MR analysis showed that the occurrence of sepsis does not influence the occurrence of asthma, thus ruling out the possibility of a reverse causal relationship. This further supports the notion that asthma may increase the risk of sepsis while also emphasizing the one-way association between asthma and sepsis.

Previously conducted studies have indicated a lower risk association between asthma and mortality in sepsis, severe sepsis, and septic shock.[30] There is also evidence from research that suggests a higher mortality rate when asthma exacerbation is combined with sepsis.[6] However, previous studies are susceptible to confounding by unmeasured risk factors. In our study, we employed the MR method to mitigate such confounding. These findings provide crucial evidence for the causal relationship between asthma and different types of sepsis. Thomas et al conducted a case-control study to investigate the relationship between asthma and invasive pneumococcal disease. They observed an increased risk of invasive pneumococcal disease in asthmatic patients compared with controls (adjusted odds ratio: 2.4; 95% confidence interval: 1.9 to 3.1). Among those without comorbidities, the annual incidence of invasive pneumococcal disease was 4.2 per 10,000 high-risk asthmatics and 2.3 per 10,000 low-risk asthmatics, compared with 1.2 per 10,000 non-asthma patients.[31] Furthermore, studies have also demonstrated that asthma patients not only have an increased risk of airway-related infections but also a correlation with severe non-airway-related infections such as bloodstream infections (BSI) caused by *Escherichia coli*. This suggests that the influence of asthma on the risk of microbial infections may extend beyond the airways.[32] The above studies are consistent with our results. Therefore, our study findings may offer a new perspective for clinical practice to improve the management and treatment of asthma patients. Firstly, understanding the association between asthma and various types of sepsis can assist physicians in better assessing the health status of asthma patients. Physicians can closely monitor patients' infection status while treating asthma, especially for those with a history of severe asthma or frequent exacerbations. Regular screening for bacterial infections, including testing for streptococcal and pneumococcal infections, can help in early detection and timely treatment of potential infections, thus reducing the occurrence of sepsis. Secondly, asthma patients should strengthen preventive measures against infections to reduce the risk of sepsis resulting from related infections. This includes receiving relevant vaccinations such as pneumococcal and influenza vaccines, as well as avoiding environments that may lead to infections. Additionally, for asthma patients who have already developed sepsis, timely diagnosis and treatment are crucial. Physicians should closely monitor changes in the patient's condition, conduct bacterial cultures and sensitivity tests promptly to determine the most effective antibiotic treatment regimen. During treatment, close attention should also be paid to asthma control to prevent exacerbations triggered by infections. Meanwhile, a retrospective analysis of 28,033 Taiwanese asthma patients showed that overuse of short-acting beta-agonists (SABA) may be associated with an increased risk of sepsis and septic shock.[33] Therefore, for patients with asthma, regular health monitoring and education on the proper use of SABA medications are necessary. This helps to maintain asthma stability and reduce the risk of severe infections such as sepsis.

We also found no significant association between asthma and puerperal sepsis, sepsis with 28-day mortality, sepsis in individuals below the age of 75, and sepsis with 28-day mortality in critically ill patients. This suggests that asthma may not have a substantial impact on the occurrence of these specific types of sepsis in certain circumstances. However, further research may help to provide a more comprehensive understanding of the absence of these associations.

Our study also has certain limitations. Firstly, despite our efforts to identify asthma cases through various methods and employing appropriate statistical techniques to address potential heterogeneity and pleiotropy, we are aware that such heterogeneity may still exist. In future research, we will strive to minimize this heterogeneity as much as possible and carefully consider the impact of different definitions to enhance the accuracy and reliability of our study. Secondly, all the GWAS data used in our study were derived from European populations. Given the variation in body types between European, North American, and Asian populations, the generalizability of our findings to other populations is subject to certain limitations.

Overall, the results of this study provide some evidence for asthma potentially increasing the risk of sepsis. These findings suggest that clinicians should be mindful of the risk of sepsis in asthma patients and take appropriate preventive and treatment measures to mitigate adverse outcomes. Further research may contribute to a deeper understanding of the underlying biological mechanisms between asthma and sepsis, thereby offering more insights into personalized prevention and treatment strategies.

Abbreviations
BSI - bloodstream infections: CI - confidence interval: GWAS - genome-wide association studies: ICU - intensive care unit: IVs - instrumental variables: IVW - inverse-variance weighted: LD - linkage disequilibrium: MR - Mendelian randomization: OR - odds ratio: SM - simple mode: SNPs - single nucleotide polymorphisms.

Funding
Not applicable.

Availability of data and materials
The datasets provided in this study can be found in the GWAS Summary Data repository at https://gwas.mrcieu.ac.uk/. The repository contains the following datasets with their respective names and IDs: Asthma (ebi-a-GCST90014325), Sepsis (critical care)(ieu-b-4982), Sepsis (28 day death)(ieu-b-5086), Sepsis (28 day death in critical care)(ieu-b-4981), Sepsis (under 75)(ieu-b-5088), Septicaemia (finn-b-AB1_SEPSIS), Streptococcal septicaemia (finn-b-AB1_STREPTO_SEPSIS), Pneumonia derived septicaemia (finn-b-SEPTICHE_PNEUMONIA), Pneumococcal septicaemia (finn-b-PNEUMO_SEPTHICHE), Other septicaemia (finn-b-AB1_OTHER_SEPSIS), Puerperal sepsis (finn-b-O15_PUERP_SEPSIS).

Ethics approval and consent to participate
All data utilized in this study were publicly available, sourced from studies with appropriate participant consent and ethical approvals, thus negating the need for institutional review board approval for this particular study.

Consent for publication
Authors consent for publication in WAO Journal.

Declaration of competing interest
The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100937.

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