Association of autoimmune diseases with the occurrence and 28-day mortality of sepsis: an observational and Mendelian randomization study

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Abstract

Background

Observational studies have indicated a potential association between autoimmune diseases and the occurrence of sepsis, with an increased risk of mortality among affected patients. However, whether a causal relationship exists between the two remains unknown.

Methods

We accessed genomic data from both the MRC Integrative Epidemiology Unit (MRC-IEU) and the FinnGen consortium, encompassing genome-wide association studies for 10 autoimmune disorders. Genome-wide association study data for sepsis and its 28-day mortality were obtained from MRC-IEU. We employed univariable, multivariable, and reverse Mendelian randomization (MR) analyses to explore potential associations between autoimmune disorders and the occurrence of sepsis. Additionally, a two-step mediation MR analysis was performed to investigate indirect factors possibly influencing the relationship between the two. For 28-day mortality in sepsis, we first analyzed the relationship between autoimmune diseases and 28-day mortality in sepsis by MIMIC-IV database, and further verified the relationship by MR analysis.

Results

In univariable MR analysis, there appeared to be causal relationships between genetically predicted type 1 diabetes (OR = 1.036, 95% CI = 1.023–1.048, p = 9.130E-09), rheumatoid arthritis (OR = 1.077, 95% CI = 1.058–1.097, p = 1.00E-15) and sepsis, while a potential causal link was observed between celiac disease and sepsis (OR = 1.013, 95% CI = 1.002–1.024, p = 0.026). In a subsequent multivariable MR analysis, only rheumatoid arthritis was found to be independently associated with the risk of sepsis. Other autoimmune diseases were not found to have a causal association with sepsis. Furthermore, for all autoimmune diseases no causal link was established between autoimmune disorders and 28-day mortality from sepsis, aligning with the results obtained from the retrospective analysis of the MIMIC database. In reverse MR analysis, sepsis was suggested to potentially trigger the onset of psoriasis (OR = 1.084, 95% CI = 1.040–1.131, p = 1.488E-04), but this result requires further validation.

Conclusion

Apart from rheumatoid arthritis, there is no causal relationship between other autoimmune diseases and sepsis. At the genetic level, we did not find a causal relationship between autoimmune diseases and 28-day sepsis mortality, which is consistent with the results from the observational study from MIMIC-IV. Additionally, sepsis may increase the risk of developing psoriasis.

1. Introduction

Autoimmune diseases are a group of diseases in which the immune system mounts an immune response against its own normal tissue components, often resulting in chronic tissue and organ damage, affecting approximately 7.6–9.4% of the global population[1]. The primary features of autoimmune diseases include the production of self-targeting antibodies and abnormalities in the function of immune cells. Often, the management of these conditions involves the use of immunomodulatory or immunosuppressive medications, which can result in compromised immune function and an elevated risk of infections[2]. Although retrospective analyses of autoimmune diseases have primarily associated patients with respiratory infections, It is important to highlight that the main drivers of ICU admissions and mortality in this group are severe infections[3, 4]. The evolving environmental changes brought about by societal industrialization have contributed to an increasing incidence of autoimmune diseases. Consequently, the associated risk of pathogenic infections is expected to rise as well[5, 6]. Therefore, prioritizing infection risks in individuals with autoimmune diseases is crucial for mitigating the emergence of life-threatening infectious conditions.

Sepsis is a complex, infection-induced systemic inflammatory response disorder characterized by an imbalance, often accompanied by acute organ dysfunction and a high mortality rate [7]. Despite a decline of 37.0% in the age-standardized incidence of sepsis and a 52.8% decrease in mortality, the burden of this severe condition persists, particularly in developing countries[8, 9]. It is noteworthy that the increased overall burden could be attributed to severe infections resulting from autoimmune diseases and their associated treatments, such as the use of corticosteroids[10]. For individuals diagnosed with autoimmune diseases, ICU admissions occur at the time of initial diagnosis. Among these cases, sepsis (severe infection) stands out as the primary cause of ICU mortality, followed by acute disease exacerbations [11].

The relationship between autoimmune diseases and sepsis has long been a subject of interest[2]. However, the assessment of the connection between autoimmune diseases and sepsis is currently lacking in prospective cohort studies. Due to limitations in retrospective research, such as missing patient data and sample size issues, a consistent conclusion regarding the relationship between autoimmune diseases and sepsis has not been reached[12, 13]. To further investigate the relationship between autoimmune diseases and sepsis, we designed a Mendelian randomization (MR) study to overcome the limitations of retrospective research. MR is an epidemiological technique designed to enhance causal inference[14]. It employs genetic variations as instrumental variables to assess the impact of these variations. This approach offers two key advantages: it minimizes confounding factors and reduces the likelihood of reverse causation. Genetic variations are randomly allocated during conception and remain unaffected by the development and progression of the disease[15]. Through the implementation of a MR study, we aim to assess the relationship between autoimmune diseases and sepsis, along with the 28-day mortality rate. This endeavor seeks to further ascertain whether there exists a causal link between genetic variations inherent to distinct autoimmune diseases and the occurrence of sepsis, as well as an elevated risk of mortality within 28 days. Furthermore, we are exploring the relationship between autoimmune

diseases and the 28-day mortality risk associated with sepsis using the MIMIV-IV database. This additional effort aims to further substantiate the findings from the MR analysis. While a direct causal relationship between certain autoimmune diseases and sepsis might not be evident, the presence of indirect causation cannot be entirely ruled out. To explore this, we designed a two-step mediation analysis to investigate whether autoimmune diseases can act as mediators in the development of sepsis. Furthermore, to enhance the reliability of result inferences, we conducted multivariable MR analyses to correct for associations among different diseases. Following the onset of sepsis, there is often a reshaping of the immune system's functionality. However, whether this reshaping involves long-term, chronic changes in immune function remains unclear. Thus, we've also employed reverse MR to evaluate whether the occurrence of sepsis increases the risk of subsequent autoimmune diseases.

2. Methods

2.1 Mendelian Randomization

2.1.1 Study design and genetic instrument selection

Figure 1 shows the study design and the assumptions of MR in our study[16]. We used publicly available summary statistics from GWAS sources of predominantly European origin. All studies had current ethical clearance from their respective institutional review boards, including written informed consent from participants and strict quality control. As all analyses herein are based on publicly available summary data, no ethical approval from institutional review boards was required for this study. Three basic assumptions are required for the genetic variants to qualify as valid IVs: (1) they should be robustly associated with the exposure; (2) they should not be associated with potential confounders of the exposure-outcome association; and (3) they should not influence the outcome by any variable other than the exposure[16]. To validate the initial MR hypothesis, we utilized independent single nucleotide polymorphisms (SNPs) that exhibited a robust association with the exposure, reaching genome-wide significance ($P < 5 \times 10^{-6}$). These SNPs were carefully chosen to ensure minimal linkage disequilibrium ($r2 < 0.01$) within a clump window larger than 5000 kb, thus ensuring their independence. It should be noted that in subsequent reverse MR analyses, the inclusion criteria for the instrumental variable SNP were as follows: $P < 1 \times 10^{-5}$, $r2 < 0.001$ within a clump window larger than 10000 kb. To further refine the first hypothesis, we quantified the proportion of phenotypic variation explained by the entire set of SNPs and assessed the strength of our instrumental variables using the F statistic ($beta^2/se^2$). The effectiveness of the instruments was gauged based on their precision and the magnitude of the associations observed between the instrumental variables and the risk factor under investigation. An F-statistic exceeding 10 was considered indicative of a robust instrument[17]. R2 was calculated as beta2/[beta2 + se2*(N-2)], N being the sample size, and the genetic variability explained by each SNP was calculated[18]. Finally, after eliminating palindromic SNPs, we proceeded to utilize the remaining selected SNPs as our instrumental variables for subsequent analyses.

2.1.2 Data sources for exposures, mediators and outcomes

By searching publicly available GWAS databases, we obtained eligible exposure and outcome datasets, including the UK Biobank consortium, MRC-IEU, and the FinnGen consortium, among others. Recognizing that utilizing diverse populations could potentially lead to biased estimates, we constrained the genetic background of the population in the MR study to individuals of European ancestry[19].

Exposures included a total of 10 distinct autoimmune diseases, and we aligned our analysis with data available from the FinnGen consortium (R9) (https://www.finngen.fi/fı.*)* and the MRC-IEU online database (https://gwas.mrcieu.ac.uk/*).* The autoimmune diseases considered for inclusion in our analysis were as follows: systemic lupus erythematosus, ankylosing spondylitis, multiple sclerosis, primary biliary cholangitis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, type 1 diabetes, celiac disease, psoriasis. We systematically reviewed and summarized the general characteristics of each autoimmune disease, and we presented these aggregated data in Supplementary Table S1. It is important to note that the ten autoimmune diseases from the Finngen consortium were defined using the codes of the International Classification of Diseases (ICD-9) and ICD-10. In the FinnGen consortium, individuals with undefined sex, high genotype deletion (> 5%), excess heterozygosity (± 4 standard deviations ((SDs)), and non-Finnish ancestry were excluded. All genetic association effect sizes were calculated by logistic regression, and adjusted for age, sex, and genetic principal components[20]. In the MRC-IEU database, all 10 included diseases have been previously published online. However, due to their diverse origins from different research teams, the analytical methods employed and the controlled confounding factors are not entirely uniform. For a comprehensive understanding, please refer to the cited references for detailed information[21–29].

Mediators On the basis of literature reviews of observational and MR studies, we selected 32 candidate mediators (Supplementary Table S2), including blood cell counts, immunoglobulin levels, infectious diseases, and serum cytokine concentrations that may be altered by autoimmune diseases, according to four criteria[30]. First, on the basis of collective scientific knowledge, candidate mediators might lie on the pathways from autoimmunity to sepsis. Second, candidate mediators were potentially accessible clinical interventions. Third, the GWAS data for candidate mediators should be available in individuals of European ancestry or predominantly European ancestry from large-scale consortia or cohorts with no or merely mild sample overlap with the GWASs of exposures and outcomes. Blood cell counts include: basophil cell count, eosinophil cell count, lymphocyte cell count, monocyte cell count, neutrophil cell count, white blood cell count; serum immunoglobulin levels included IgA, IgM, IgG, IgE; cytokines included IL-1α, IL-6, IL-12, IL-4, IL-10, IL-13, TGF-β1, TGF-β2, TGF-β3, TNF-α, and IFN-γ. We screened for mediators of the causal relationship between autoimmune disease and sepsis based on the following criteria: (1) the mediator should be causally related to sepsis; (2) the mediator should have a direct causal effect on sepsis independent of the autoimmune disease; (3) the autoimmune disease should be causally related to the mediator rather than the other way around; and (4) the association of the autoimmune disease with the mediator and the association of mediators with longevity outcomes should be in the opposite direction[31]. Surprisingly, none of the mediators qualified for inclusion. In the UVMR analyses, the

genetic instruments for each mediator were at a genome-wide significance level ($P < 1.00\times10^{-5}$) independent of each other (LD r2 < 0.001 within 10,000 kb).

Outcomes We acquired summary-level data for genetic association with sepsis and sepsis (28-day death) from the MRC-IEU database. Sepsis (ID: finn-b-AB1_SEPSIS) was built by the FennGen consortium and included 203,824 Europeans (6,164 cases and 197,660 controls) with 16,380,410 SNPs. Sepsis (28-day death, ID: ieu-b-5086) was built by the UK Biobank consortium and contained 486,484 Europeans (1,896 cases and 484,588 controls) with 12,243,487 SNPs. These data performed were analyzed using regenie v2.2.4, adjusted for age, sex, chip, and the first 10 PCAs.

2.1.3 Other factors

To satisfy the second condition of MR, we conducted an exhaustive search within the PhenoScanner database, aiming to identify established links between instrumental SNPs and potential confounding variables. Given our focus on autoimmune diseases as the target exposures, it became evident that the most influential genetic loci associated with these conditions were predominantly situated within the major histocompatibility complex (MHC), a genomic region intricately involved in adaptive immune responses. However, due to the robustness of the associations between variants in the major histocompatibility complex (MHC) region and autoimmune diseases, as well as the intricate structure of linkage disequilibrium (LD) within this region, we took a deliberate step to exclude variants falling within the MHC region [32, 33]. Specifically, we defined this exclusionary region as encompassing base positions 24,000,000 to 35,000,000 on chromosome 6 (GRCh37). This precautionary measure was taken to mitigate the potential impact of strong associations with autoimmune diseases and the intricate LD structure, which could introduce horizontal pleiotropy and undermine the assumptions central to the MR framework. Subsequently, we conducted a fresh round of MR analyses, this time excluding instrumental variables linked to the MHC, with the intention of minimizing the influence of confounding factors. Notably, autoimmune diseases exhibited associations with one another through instrumental variables. To delve into the direct influence of distinct autoimmune diseases on sepsis, we adopted a multivariate MR approach-an extension of the conventional univariate MR. This advanced technique enabled us to simultaneously explore causality across multiple exposures and outcomes. The efficacy of multivariate MR was underscored by its incorporation of the phenotypic spectrum characterizing associations between autoimmune diseases. This approach duly acknowledged the inherent interplay among SNPs used in MR analyses, often manifesting shared associations across different autoimmune conditions. In our study, the SNPs utilized for multivariate MR were formulated as combinations of instrumental variables per exposure, thereby accounting for the intricate web of associations (including those associated with phenotypes of at least two autoimmune diseases).

2.1.4 Statistical analyses

In order to evaluate the third MR assumption, we conducted tests to assess the heterogeneity of independent SNP effects using Cochran Q statistics. Additionally, we employed the MR Egger intercept test to examine directional pleiotropy, and employed various pleiotropic robust MR methods to investigate

potential pleiotropy[34, 35]. The MR-Egger regression technique offers estimated values that are adjusted for pleiotropy, although it may lead to a reduction in statistical power. The P-value of the MR-Egger intercept was utilized to determine the presence or absence of directional pleiotropy. The random effects inverse variance weighted (IVW) method was employed as the primary statistical analysis approach[34]. The IVW values derived from MR analyses of exposure and outcome data, conducted separately in datasets from FinnGen consortium and the MRC-IEU, are employed in a fixed-effects meta-analysis. To account for multiple testing in our analyses, a Bonferroni-corrected threshold of $P < 0.00125$ ($\alpha = 0.05/40$ exposure factors) was applied. Associations with $P < 0.00125$ were considered significant, and associations with $P \geq 0.00125$ and < 0.05 were considered suggestive. We employed the MR-Egger regression method to account for genetic pleiotropy and obtain adjusted estimates, although this approach may result in a reduction of statistical power. The P-value of the MR-Egger intercept was utilized to indicate the presence of directional pleiotropy. We performed MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO), and weighted median as pleiotropy-robust methods[34]. The goal of the MR-PRESSO approach is to detect possible outliers and generate estimates after removal of outliers. The embedded distortion test can discern the differences between estimates before and after the removal of outliers. The weighted median specifies that at least 50% of the weight in the analysis comes from variables that are valid instruments, whereas the weighted mode requires that the largest subset of tools identifying the same causal effect be effective tools [36]. To mitigate potential confounding factors, a multivariable Mendelian Randomization study was conducted on the exposure that was causally associated with the outcome. Otherwise, to adjust for systemic lupus erythematosus in our models, we performed a multivariable IVW MR analysis. The Multivariable IVW considers multiple exposure factors simultaneously[37]. It limits the effects of SNP-exposure on their corresponding effects on the characteristics of other assumed risk factors along an indirect pathway by regaining the summary genetic associations resulting from genetic associations with exposure and risk factors in a weighted regression model. All statistical analyses were conducted using the Mendelian Randomization (0.4.2), TwoSampleMR (0.5.7), MR-PRESSO (1.0), MVMR (0.3) and meta (4.11.0) packages in R, version 4.2.2.

2.2 Real-World Observational Analysis

2.2.1 Data source

This study used the publicly available Multiparameter Intelligent Monitoring in Intensive Care (MIMIC) IV database version 1.0 [MIMIC-IV, a freely accessible electronic health record dataset][38]. A total of 523,740 admissions were recorded in the MIMIC-IV database, of which 76,540 were admitted to the ICU [MIMIC-IV, a freely accessible electronic health record dataset], and was jointly developed by the Massachusetts Institute of Technology, Phillips Healthcare, and Beth Israel Deaconess Medical Center. Any researcher who adheres to the data use requirements is permitted to use the database. To access this database, the first author of this study, Hui Li, completed the Collaborative Institutional Training Initiative (CITI) course and passed both the “Conflicts of Interest” and “Data or Specimens Only Research” exams (ID: 11839105). The research team was finally qualified to use the database and extract data.

2.2.2 Patient population

The primary study population consists of adult ICU patients with sepsis. All patients were required to have at least 24 h of ICU data, and we selected the last ICU stay meeting these criteria for each patient. We identified 35160 patients in the database meeting the sepsis inclusion criterion. Predictor and outcome variables Throughout this study, autoimmune disease refers to a set of related conditions, defined using ICD-10-CM diagnosis codes and free text analysis of the patient discharge summaries. For each patient in the study, we extracted several confounding factors from data stored in the MIMIC-IV database. They included age, race, sex, Sequential Organ Failure Assessment (SOFA) score, and Charlson-score at ICU admission. SOFA includes information about the condition of a patient's respiratory, renal, and cardiovascular systems, among others, and has been found to be a strong predictor of prognosis for ICU patients with sepsis[39]. The primary outcome of interest in this study is patients' 28-day mortality. The 28-day mortality rate is based on data from the Social Security Death Index, which reflects the number of deaths within the 28-day window after discharge and the number of hospital deaths.

2.2.3 Statistical analysis and modeling

In the analysis, we estimated relative risks with odds ratios (ORs) and 95% confidence intervals (CIs) for patients with autoimmune disease, compared with patients without autoimmune disease using a multivariable logistic regression model[40]. ORs were adjusted for potential confounders using two approaches: (1) all potential confounders were included in the final model and (2) only potential confounders that meaningfully affected model estimates were included in the final model. Factors that were considered as potential confounders included the following: age, race, SOFA score, Charlson-score. In this analysis, we used Cox Proportional-Hazards models[41, 42] with both confounder adjustment approaches (discussed above) and report the odds ratio (OR). We performed all statistical analyses using the SPSS software (IBM Corporation, version 26). $P < 0.05$ was regarded as significant.

3. Result

3.1 Mendelian Randomization

The F statistics for IVs and estimated power for all analyses are shown in Supplemental Table S3-S4. None of these IVs had an F-statistic below the threshold of 10, indicating that there was low evidence of weak instrument bias in this study. No pleiotropy was identified in the analysis of all exposures in the MRC-IEU and FinnGen consortium by the MR-Egger regression. Moderate heterogeneity was found in the analysis of most exposures (P for Cochrane's $Q < 0.001$) (Supplemental Table S5). Using MR-PRESSO to detect outliers, although in some computations Global test $P < 0.05$, but we did not identify any outliers.

In the univariable MR study, there was a causal association between genetically predicted RA (OR = 1.077, 95% CI = 1.058–1.097, p = 1.00E-15) and T1DM (OR = 1.036, 95% CI = 1.023–1.048, p = 9.130E-09) with sepsis. This connection holds true for exposure data from both the FinnGen consortium and the MRC-IEU database. Moreover, this association is nearly consistent across two additional complementary analytical approaches (MR Egger and Weighted Median), as demonstrated in the Supplementary Table S5. The

genetic-level association between celiac disease and sepsis varies between the FinnGen consortium and MRC-IEU databases. However, following the meta-analysis, the P_{IVW} combined effect size < 0.05, suggesting a potential genetic-level connection between celiac disease (OR = 1.013, 95% CI = 1.002–1.024, $p = 0.026$) and sepsis (Fig. 2). Conversely, for CD (OR = 1.018, 95% CI = 0.997–1.039, $p = 0.098$) and UC (OR = 0.992, 95% CI = 0.969–1.015, $p = 0.491$), genetic-level disparities with sepsis are evident in databases from two distinct sources. However, the post meta-analysis yielded P_{IVW} values > 0.05, indicating no significant association with sepsis (Fig. 2). Surprisingly, despite an increasing trend in sepsis for most diseases, we did not identify a significant genetic-level association between several other autoimmune diseases (systemic lupus erythematosus, ankylosing spondylitis, multiple sclerosis, primary biliary cholangitis) and sepsis (Fig. 2). This conclusion is drawn from a meta-analysis of data from MRI-IEU and the FinnGen consortium, particularly for systemic lupus erythematosus. Furthermore, we explored the causal relationship between autoimmune diseases and 28-day sepsis-related mortality. Unexpectedly, our study did not find any significant association between the included autoimmune diseases and 28-day sepsis-related mortality, except for the potential negative correlation between RA and sepsis-related mortality (Fig. 3, Supplemental Table S6).

In the multivariable MR analysis, we conducted analyses on autoimmune diseases potentially associated with sepsis in the FinnGen consortium dataset. Surprisingly, following the multivariable MR analysis, only rheumatoid arthritis (OR = 1.138, 95% CI = 1.044–1.24, $p =$ 3.36E-03) was found to have a causal association with sepsis (Fig. 4, Supplementary Table S7). Using PhenoScanner, we identified associations of instrumental variables (IVs) with systemic lupus erythematosus and other autoimmune diseases. Consequently, we performed a multivariable analysis with other exposure factors and systemic lupus erythematosus to explore more stable exposure factors causally related to sepsis. After multivariable adjustment, we found that rheumatoid arthritis (OR = 1.091, 95% CI = 1.061–1.123, $p =$ 1.66E-09) continues to exhibit a causal association with sepsis by adjusting for systemic lupus erythematosus (Fig. 4). In summary, based on the comprehensive analysis, we can deduce that rheumatoid arthritis is independently associated with the risk of sepsis occurrence.

To assess the potential induction of sepsis by autoimmune diseases through latent mediating factors, we incorporated possible sepsis-related risk factors, including blood cell counts, immunoglobulins, inflammatory cytokines, infectious diseases, and more, based on literature [43]. We screened for eligible mediating factors according to established criteria. Regrettably, we did not discover any mediating factors between autoimmune diseases and sepsis (Fig. 5, Supplementary Table S8). Our mediation analysis results indicated that certain autoimmune diseases could lead to decreased blood cell counts (e.g., systemic lupus erythematosus, celiac disease). However, we did not observe a causal relationship between blood cell counts and sepsis occurrence (Fig. 6, Supplementary Table S9). Therefore, the reduction in blood cell counts induced by autoimmune diseases is not causally linked to sepsis development. Similarly, the levels of immunoglobulins and autoimmune disease-related cytokines also failed to mediate the relationship between the two (Fig. 5–6, Supplementary Table S10-13). Furthermore, we included other infectious diseases, but again, we did not observe definitive mediating effects (Fig. 5–

6, Supplementary Table S14-15). Hence, the mediation analysis further reinforces the absence of a widespread causal relationship between autoimmune diseases, their potential correlates, and the occurrence of sepsis.

Sepsis is a severe infectious disease caused by pathogenic microorganisms, and immune dysfunction stands out as one of its primary characteristics. Previous studies have indicated a correlation between microbial infections and the onset of autoimmune diseases, as well as the significance of immune dysfunction as a triggering factor for autoimmune conditions[44, 45]. Hence, we explored the potential causal relationship between sepsis and autoimmune diseases at the genetic level. Through reverse MR, we discovered a causal association between genetically predicted sepsis and the occurrence of psoriasis (OR = 1.084, 95% CI = 1.040–1.131, p = 1.488E-04), while no associations were observed with other autoimmune diseases (p = 0.05/10) (Fig. 7, Supplementary Table S16-17).

3.2 Observational Study

The study cohort consisted of 34,986 patients with sepsis. Among these, 1,911 (5.48%) had at least one autoimmune disease. To comprehend the distinctions between the autoimmune and non-autoimmune patient populations, we examined the baseline characteristics of each group (Table 1). Generally, individuals with an autoimmune disease were more likely to be of Caucasian ethnicity, younger, and female. They also exhibited lower SOFA scores but higher Charlson scores.

Table 1
Baseline characteristics of sepsis patients

	Autoimmune disease	No autoimmune disease	P-value
Number of patients	1911	32985	
28-day mortality	13.6%	18.7%	0.008
Age (mean ± SD)	61.27 ± 15.48	66.98 ± 15.99	< 0.001
Sex (% female)	54.8%	41.7%	< 0.001
Race			< 0.001
Asian	2.6%	3.2%	
Black	14.3%	10%	
Hispanic	2.4%	3.7%	
White	69.8%	67.5%	
Other	3.9%	4.6%	
Unknow	7.1%	10.9%	
SOFA at admission (mean ± SD)	6.45 ± 3.63	6.88 ± 3.82	< 0.001
Charlson score	7.30 ± 2.89	6.86 ± 3.23	< 0.001

A total of 1911 (5.48%) patients with autoimmune diseases and 32985 (94.52%) patients without autoimmune diseases died either during their hospital stay or within 28-days after hospital discharge. In our analysis, we employed a multivariate logistic regression model to adjust for various potential confounding factors, such as age, SOFA score, ethnicity, Charlson score, etc., to explore the relationship between autoimmune diseases and 28-day mortality in sepsis in a more robust manner. After adjusting for multiple potential confounders, the presence of autoimmune diseases did not increase the risk of 28-day mortality in sepsis for the patients included in the analysis (Table 2). This finding aligns with conclusions drawn from prior retrospective studies, indicating that autoimmune diseases do not increase the 28-day mortality rate in sepsis[30, 46].

Table 2
The relationship between autoimmune diseases and 28-day mortality rate in sepsis

Autoimmune disease	Sepsis 28-day mortality risk	
	OR (95% CI)	P-value
Systemic lupus erythematosus	0.71(0.46–1.1)	0.20
Rheumatoid arthritis	0.55(0.23–1.2)	0.55
Crohn's disease	0.72(0.10–0.88)	0.29
Psoriasis	0.80 (0.50–1.40)	0.60
Type 1 diabetes mellitus	0.50(0.40–0.70)	0.34
Ankylosing spondylitis	0.40(0.30–1.10)	0.70
Celiac disease	0.40(0.20–1.10)	0.10
Multiple sclerosis	0.34(0.10–0.80)	0.23
Ulcerative colitis	0.62(0.30–1.30)	0.20

4. Discussion

In this study, we conducted a comprehensive investigation into the relationship between autoimmune diseases and sepsis, along with their 28-day mortality, employing both MR and real-world observational analyses. The results from the MR study indicate that only genetically predicted rheumatoid arthritis is causally associated with the occurrence of sepsis. Additionally, we conducted a thorough analysis of sepsis-related risk factors associated with autoimmune diseases, yet no mediating factors capable of explaining the causal relationship between autoimmune diseases and sepsis were identified. In subsequent reverse MR analyses, a potential causal relationship between psoriasis and sepsis occurrence was detected. Subsequently, we conducted a comprehensive analysis of the relationship between autoimmune diseases and 28-day mortality in sepsis. After adjusting for factors such as age, gender, SOFA score, Charlson score, and others, retrospective analysis indicated that there was no association between autoimmune diseases and 28-day mortality in sepsis. This finding was consistent in the MR analysis as well, meaning that we did not identify a causal relationship between autoimmune diseases and 28-day mortality in sepsis.

Over the past two decades, systemic lupus erythematosus has become one of the most prevalent autoimmune diseases in the intensive care unit (ICU) setting[11]. Among these cases, severe infections stand out as the most common cause of ICU admission and mortality[47]. While several retrospective studies have found a strong association between systemic lupus erythematosus and severe infections, this relationship is often multifactorial, and influenced by factors such as the use of moderate to high-dose corticosteroids, disease activity, and coexisting organ dysfunctions [48, 49]. Julia et al.

demonstrated that the occurrence of infections, including severe infections, among systemic lupus erythematosus patients is correlated with immunosuppressive or immune-modulating medications [50]. In the context of other autoimmune diseases, such as RA, Bella et al.'s research revealed a significant increase in the incidence of sepsis when compared to non-inflammatory rheumatic and musculoskeletal diseases. This association persisted even after adjusting for other risk factors[51]. Likewise, studies by Ashwin et al. highlighted an elevated risk of sepsis among inflammatory bowel disease patients. However, this risk is intertwined with various factors such as age, comorbidities, and the use of immunosuppressive medications[52]. Similarly, Gary et al. identified independent factors associated with severe infections in Crohn's disease, which included the use of prednisone, anesthesia pain relief medications, and moderate to severe disease activity[53]. In a retrospective study on multiple sclerosis, Richard et al. found a significant association between multiple sclerosis and severe infections[12]. However, the occurrence of these infections was also strongly correlated with disease-related organ dysfunctions, such as decreased respiratory clearance capacity and bladder dysfunction[12]. Research by Iain et al. found that individuals with type 1 diabetes face a higher risk of severe infections compared to the general population. However, this outcome is influenced to varying extents by other contributing factors such as blood glucose levels, obesity, and age[54]. In the study conducted by Junko et al., revealed that the risk of severe infections among individuals with psoriasis is primarily linked to the severity of the disease itself. Moderate to severe psoriasis increases the risk of sepsis. However, this study did not specifically investigate the impact of biologic therapies[55]. In an observational study on ankylosing spondylitis, no significant correlation was found between ankylosing spondylitis and severe infections. This study concluded that ankylosing spondylitis does not have a significant relationship with severe infections, especially when considering the use of TNF blockers[56]. From the collective results of the mentioned studies, it becomes evident that a certain degree of association exists between most autoimmune diseases and sepsis. However, this association is often intertwined with factors such as the use of immunosuppressive medications, disease-related comorbidities, and age. Therefore, we conducted a two-sample MR analysis to investigate the relationship between autoimmune diseases and sepsis, aiming to explore the intrinsic nature of these diseases and their association with sepsis in comparison to retrospective studies. Our study findings indicate that genetically predicted risk of systemic lupus erythematosus, Crohn's disease, ulcerative colitis, multiple sclerosis, primary biliary cirrhosis, and psoriasis showed no causal relationship with sepsis. The occurrence of severe infections in these autoimmune diseases is likely more influenced by other contributing factors, such as the use of immunosuppressive/immunomodulatory medications, disease activity, comorbid organ dysfunctions, advanced age, and more. However, while rheumatoid arthritis, type 1 diabetes, celiac disease, and others showed causal associations with sepsis in univariable MR analysis, after conducting multivariable analysis, only rheumatoid arthritis remained causally associated with the occurrence of sepsis. This may be related to the existence of a common genetic basis for rheumatoid arthritis and sepsis. It has been found that abnormalities in PAD4 (Peptidyl arginine deiminase 4) structure and function lead to a significantly increased risk of developing rheumatoid arthritis, and that dysregulation of PAD4-mediated citrullination of extracellular proteins is a driver of the autoimmune response in RA, as 75% of patients develop anticitrullinated protein antibodies (ACPA) [57]. It is well known that Neutrophil extracellular traps

(NETs) are one of the major factors contributing to the severity of septic disease, and that in the early stages of sepsis, depletion of NETs does not help to prevent or contain systemic infections, and even exacerbates pathological changes [58–61]. The citrullination of nuclear histones by PAD4 leads to chromatin depolymerization, which is a key step in the formation of NETs[62]. Therefore, the abnormal structure and function of PAD4 make rheumatoid arthritis patients more susceptible to sepsis.

In order to further explore the potential mediation of autoimmune diseases in the occurrence of sepsis through underlying intermediary factors, we included risk factors related to autoimmune diseases associated with sepsis [30]. We found that not all autoimmune diseases lead to a decrease in blood cell counts; only systemic lupus erythematosus, celiac disease, type 1 diabetes, and reduced blood cell count showed a causal association, whereas conditions such as rheumatoid arthritis and primary biliary cholangitis had less pronounced effects. Despite an inverse causal trend between blood cell counts and sepsis, statistical significance was lacking. While some observational studies suggest a predictive relationship between changes in blood cell counts and the risk of severe infection in autoimmune diseases[63, 64], these studies are often limited in their sensitivity and specificity. The cytokine storm is a prominent feature of sepsis, and autoimmune diseases frequently lead to alterations in cellular cytokine levels [65]. However, it remains unclear whether autoimmune diseases impact sepsis progression through cytokine modulation[66]. Through MR studies, we did not identify any potential associations, indicating that autoimmune diseases do not causally influence the occurrence of sepsis via changes in inflammatory cytokines. Similarly, we did not find a mediating role of immunoglobulin levels between the two conditions. As observed in previous studies, autoimmune diseases often increase the risk of infections in the respiratory and urinary tracts[11]. We conducted mediation analyses using GWAS data for infections in common sites but did not identify infections that met the criteria for mediation, where exposure, mediator, and outcome are causally linked. Notably, no causal relationship was found between autoimmune diseases and severe pneumonia. Based on comprehensive mediation analyses, we concluded that factors such as blood cell counts, plasma inflammatory cytokines, immunoglobulin levels, and infectious diseases do not mediate the causal relationship between autoimmune diseases and sepsis.

Considering the results from both univariate and mediation MR analyses, the relationship between autoimmune diseases and sepsis is likely the result of multiple overlapping factors. Therefore, the focus should extend beyond autoimmune diseases themselves, encompassing aspects like the use of immunomodulatory/suppressive drugs and comprehensive evaluation of organ function. Numerous studies on the use of biologics (such as Rituximab) in autoimmune diseases have shown an increased risk of severe infections[67–70]. Hydroxychloroquine reduces the risk of severe infections in systemic lupus erythematosus patients, while the use of glucocorticoids, especially in high doses, is closely related to severe infections[71]. Montgomery et al. found functional impairment to be a significant risk factor for severe infections in multiple sclerosis patients[13]. Therefore, patients with autoimmune diseases require closer monitoring of organ function, comorbidities, medication usage, and other factors to reduce the risk of sepsis. It is worth noting that rheumatoid arthritis is associated with an increased risk of sepsis, which can occur early in the course of the disease.

The 28-day mortality risk in sepsis is a crucial measure of disease severity, and whether autoimmune diseases increase this risk remains inconclusive. A retrospective study by Antón et al. found that autoimmune diseases often lead to a higher mortality rate in critically ill patients[4]. However, this study primarily predicted high mortality risk without correcting for concurrent confounding factors such as SOFA score, age, underlying diseases, and had a relatively small sample size. In our analysis using two-sample MR analysis, we inferred causal relationships between autoimmune diseases and sepsis at the genetic level. We did not find a causal association between autoimmune diseases and the 28-day mortality rate in sepsis. Similarly, in the retrospective analysis from MIMIC-IV, there was no observed relationship between autoimmune diseases and the 28-day mortality rate in sepsis. Therefore, we believe that autoimmune diseases do not increase the 28-day mortality rate in sepsis. This might be related to the immune dysregulation caused by autoimmune diseases, leading to imbalanced cytokines in the sepsis inflammatory cascade [72], making it difficult to form a cascading reaction. The early mortality in sepsis is closely associated with this inflammation storm. Jorge et al.'s observational study found that the risk of death in autoimmune diseases may be related to factors such as experiencing shock upon admission to the intensive care unit, having hemoglobin levels below 8 g/dL, using immunosuppressive agents before ICU admission, and having low complement C3 levels[73]. Additionally, the quality of care provided by hospitals is a key factor influencing patient mortality risk, with more experienced hospitals often having lower mortality rates[3]. Therefore, for autoimmune disease patients admitted to the ICU, it is crucial to focus on the management of complications while enhancing diagnostic and treatment capabilities specific to autoimmune diseases to reduce the risk of mortality.

A key feature of sepsis is the immune dysfunction triggered by infections, leading to prolonged alterations in immune function such as changes in immune cell functionality and numbers. Similarly, the immunopathological mechanisms of autoimmune diseases are accompanied by disruptions in immune function [32, 74]. Furthermore, infections caused by pathogenic microorganisms can act as triggering factors for autoimmune diseases[75]. However, it remains uncertain whether the immune dysfunction triggered by severe infections caused by pathogenic microorganisms could lead to the development of autoimmune diseases. Through reverse MR analysis, we identified a causal relationship between sepsis and psoriasis, but no associations with other autoimmune diseases, and current research has also found that infection is an important trigger for the occurrence of psoriasis [76]. The specific mechanisms underlying this relationship require further investigation. MR provides a novel method to discover associations between different diseases at the genetic level, offering a new perspective for future observational studies.

This study has several limitations in the MR analysis. First, potential horizontal pleiotropy is a concern in any MR study. In our research, we did not observe significant evidence of pleiotropic effects in all exposure analyses using the MR-Egger intercept test. Additionally, the MR-PRESSO analysis detected few outliers, and associations remained consistent after removing outlier SNPs. However, the possibility of undetected outliers still exists. Second, sample overlap might be a concern as we selected a subset of autoimmune diseases from the FinnGen consortium. Nonetheless, sample overlap is unlikely to bias our results significantly, given that our instrumental variables (IVs) were selected from large-scale GWAS.

Third, due to the limited number of SNPs meeting the inclusion criteria for certain autoimmune diseases (P value < 5e-08, R2 = 0.001with kb = 10000), we slightly relaxed the selection criteria, which may introduce a certain level of false positives. Fourth, genetic factors are not the sole determinants of autoimmune disease onset; environmental factors also play a role in triggering disease processes. Therefore, our MR analysis lacks associations between genetically predicted autoimmune diseases and sepsis risk, but this does not exclude the potential impact of autoimmune diseases on the pathophysiology of sepsis [32]. Fifth, the genetic associations of blood cell counts, inflammatory cytokines, and infectious diseases are based on relatively small global genomic studies, potentially leading to issues of statistical power. Sixth, univariate MR analysis may not capture the direct impact of specific biomarkers on disease outcomes, as the effect of a biomarker might be mediated by other biomarkers within a complex network. Seventh, all our analyses are based on individuals of European ancestry; generalizability to other populations requires further investigation. In real-world retrospective studies, there are also limitations. First, our results could be influenced by diagnostic bias, where the severity of autoimmune diseases and the immunocompromised state of autoimmune disease patients might lead them to be admitted to ICUs earlier than other populations, potentially resulting in better survival rates. This selection process could lead to a higher incidence of autoimmune diseases in the ICU population. In our analysis, we observed that the SOFA scores of autoimmune disease patients were significantly lower than those of non-autoimmune disease patients, suggesting that autoimmune disease patients had better conditions upon ICU admission (6.45 ± 3.63 vs. 6.88 ± 3.82, P < 0.001). To account for this difference, we statistically adjusted for SOFA scores in all analyses, thus mitigating this bias. Additionally, we controlled for other potential influencing factors, yet the overall confounding factors included in our analysis might not be exhaustive, such as other clinical scores that were not incorporated. We believe that further research with more diverse pre-ICU admission data from intensive care units would help fully eliminate diagnostic bias. Second, the MIMIC database is derived from a single-center research institution, which may limit the generalizability of the study outcomes.

5. Conclusion

In this study, our aim was mainly to assess the association of autoimmune diseases with the development of sepsis and 28-day mortality through a MR and observational study. In our findings, genetically predicted rheumatoid arthritis was independently associated with the development of sepsis, which may be related to the reduced formation of NETs due to rheumatoid arthritis. We did not find that none of the other autoimmune diseases predicted by genes were independently associated with the development of sepsis, including subsequent mediation analyses. In addition, neither observational studies nor MR analyses found autoimmune diseases to be associated with 28-day mortality from sepsis., Surprisingly, there was a causal relationship between genetically predicted sepsis and the development of psoriasis.

Declarations

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Authors' contributions

Author Hui Li, Xiaojun Pan and Wan Li collected and processed the data, as well as wrote this article. Xuan Shen, Zhenliang Wen and Sheng Zhang provided language help and writing assistance. Sisi Huang and Weifeng Shang and Limin Chen proof readed the article. Jiao Liu and Dechang Chen designed the study. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed in this study are publicly available summary statistics. Data used can be obtained upon a reasonable request to the corresponding author.

All studies had been approved by a relevant ethical review board and participants had given informed consent. Ethical approval was not required because of the public characteristics of the data of GWAS.

Consent for publication

Not applicable.

Competing interests

The authors have stated that they have no conflict of interest.

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Figures

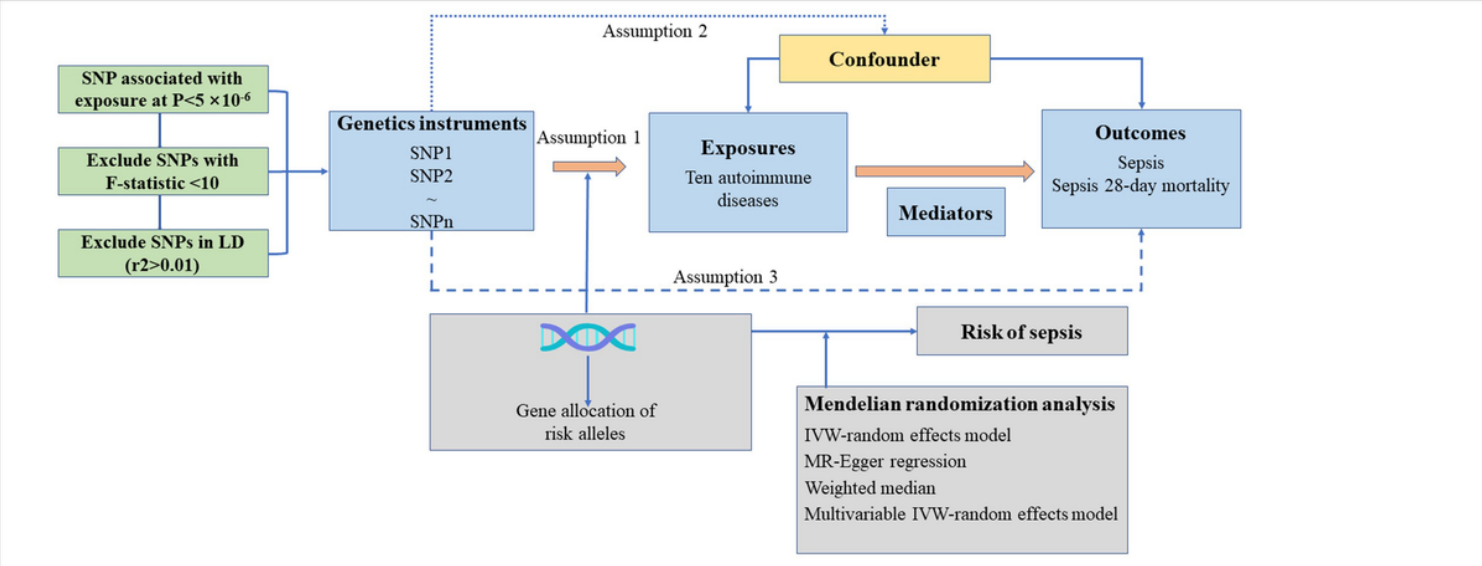

Figure 1

Overview and assumptions of the Mendelian randomization study design

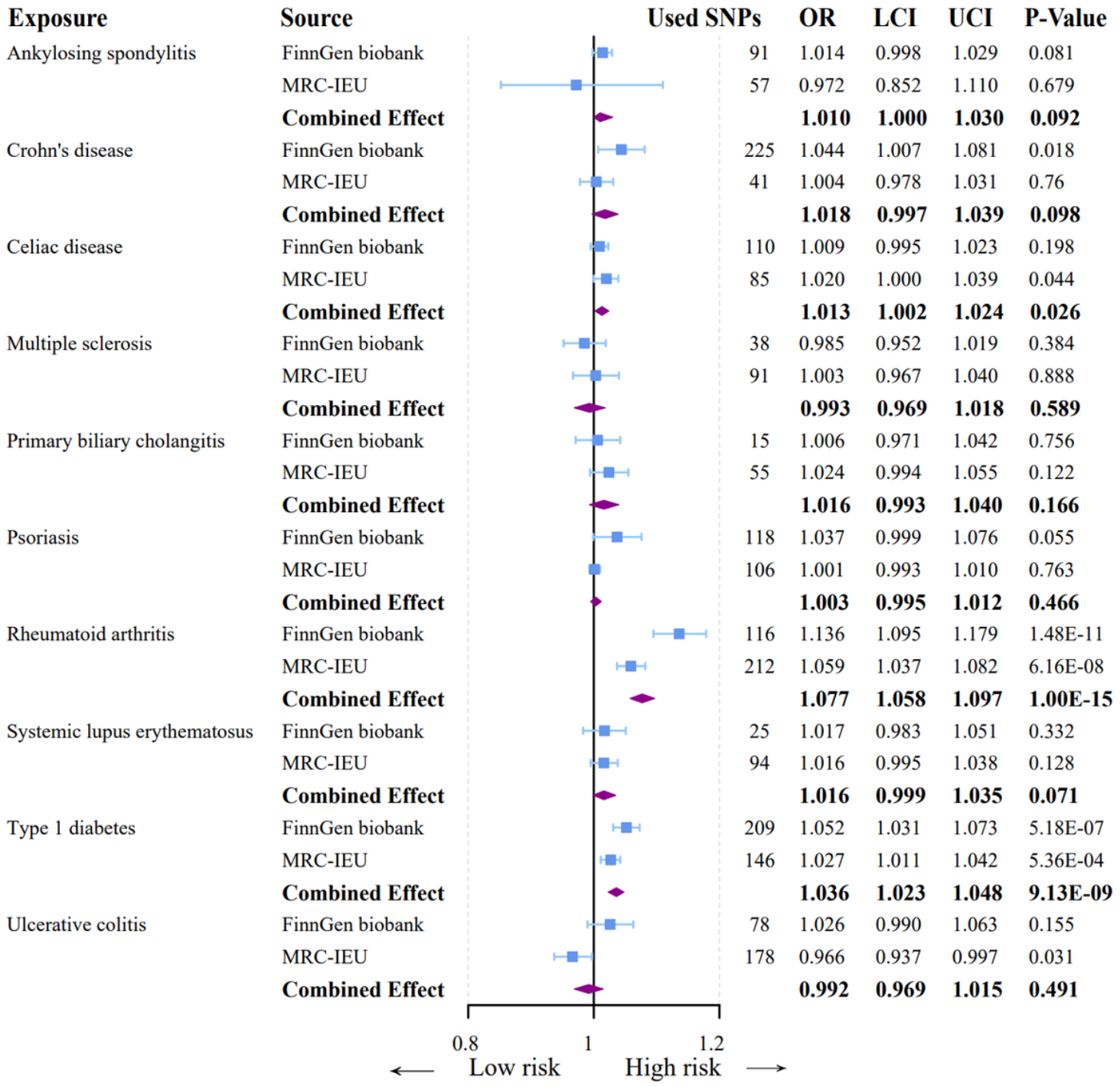

Figure 2

Forest plot to visualize the causal effect of autoimmune diseases on sepsis using the inverse variance-weighted method and meta-analysis. CI: 95% confidence interval. OR, odds ratio.

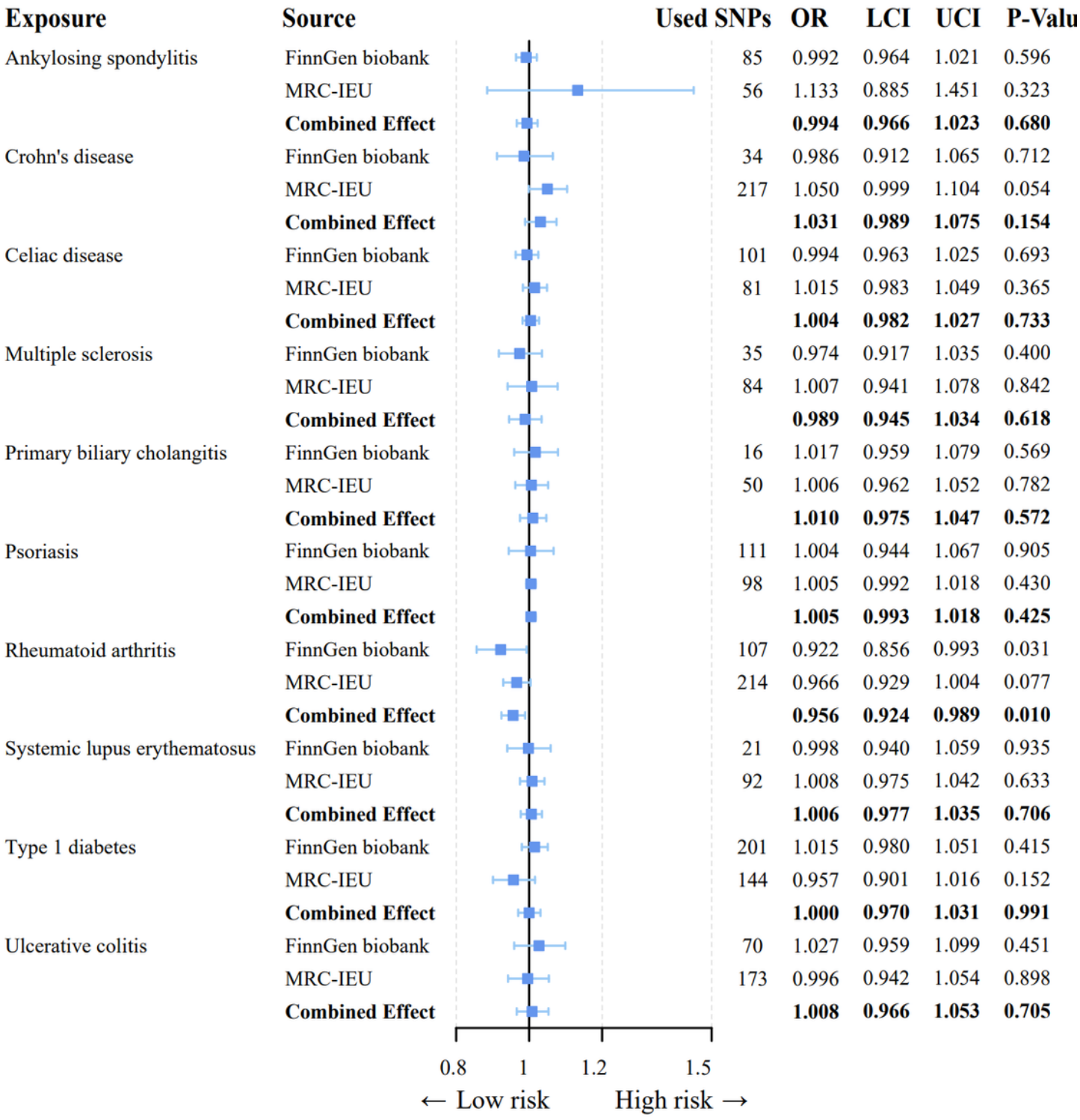

Figure 3

Forest plot to visualize the causal effect of autoimmune diseases on sepsis 28-day mortality using the inverse variance-weighted method and meta-analysis. CI: 95% confidence interval. OR, odds ratio.

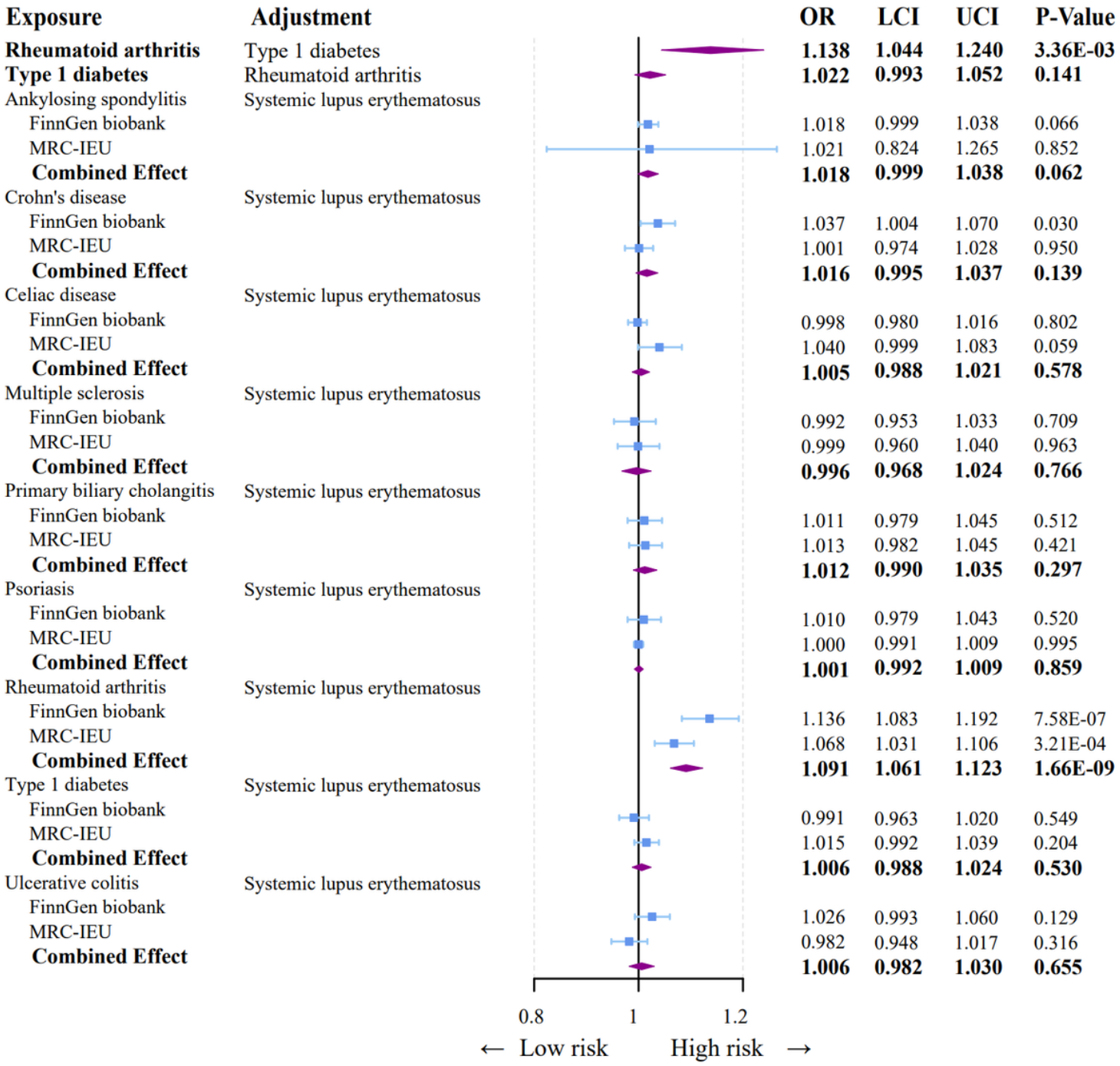

Figure 4

Forest plot to visualize the associations of genetically predicted autoimmune diseases with sepsis using multivariable MR analyses and meta-analysis. CI: 95% confidence interval. OR, odds ratio.

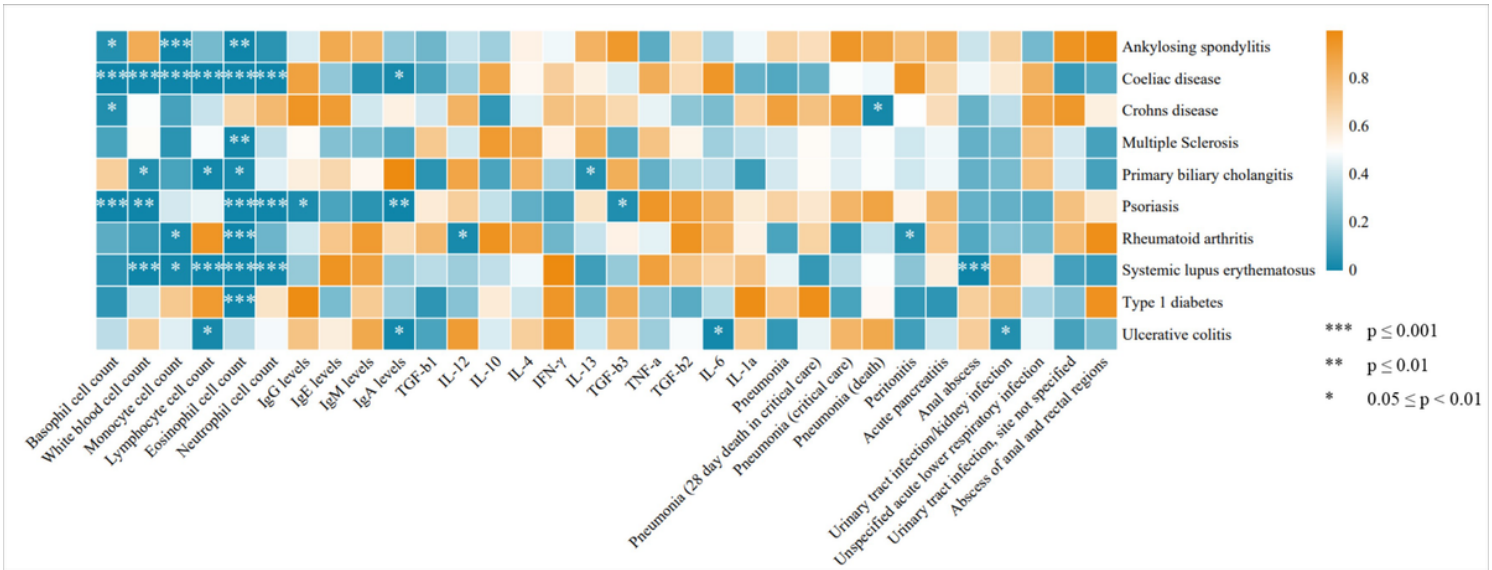

Figure 5

The heat map displays the MR analysis results of autoimmune diseases and mediators.

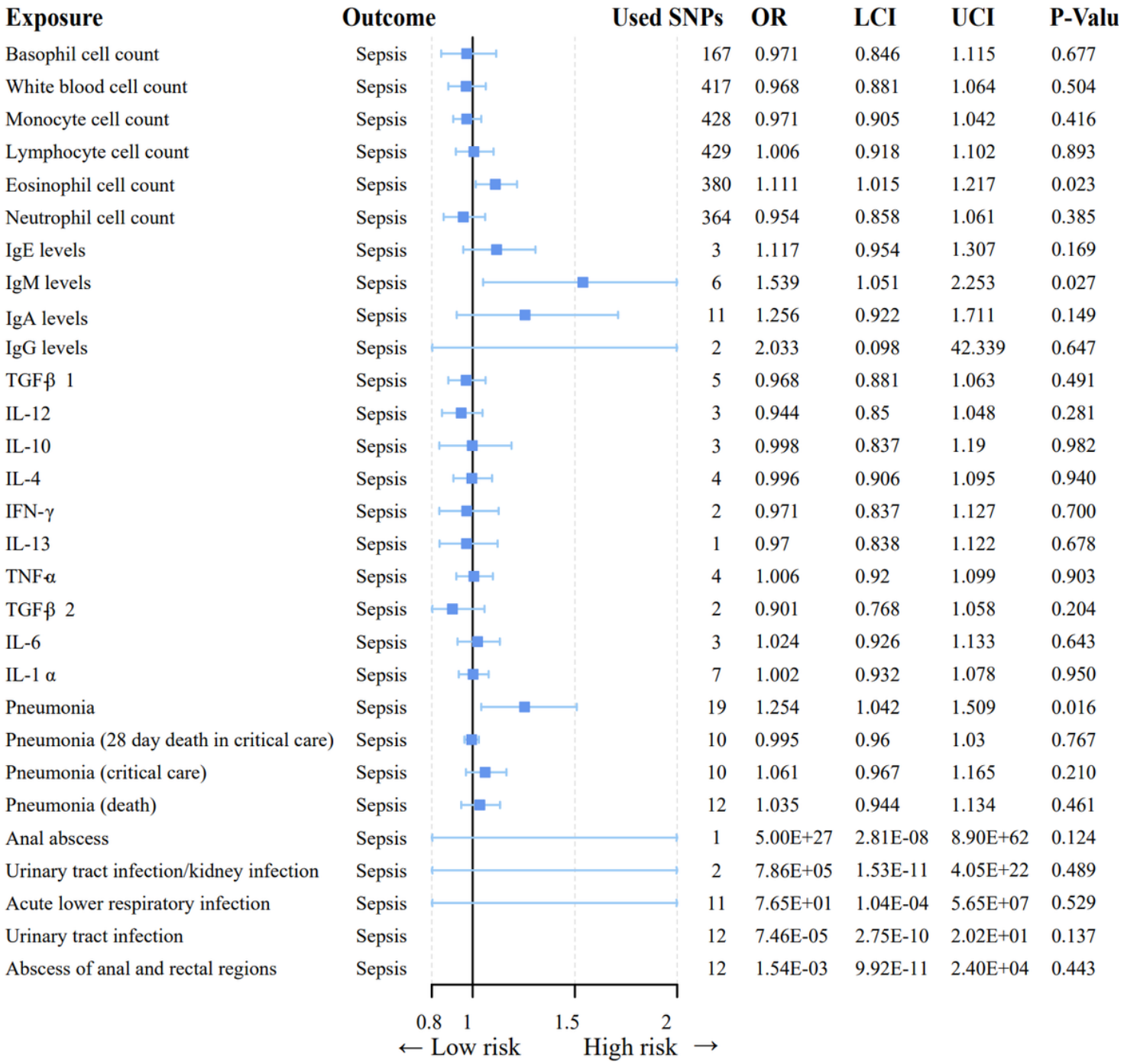

Figure 6

Forest plot to visualize the causal effect of mediators on sepsis using the inverse variance-weighted method. CI: 95% confidence interval. OR, odds ratio.

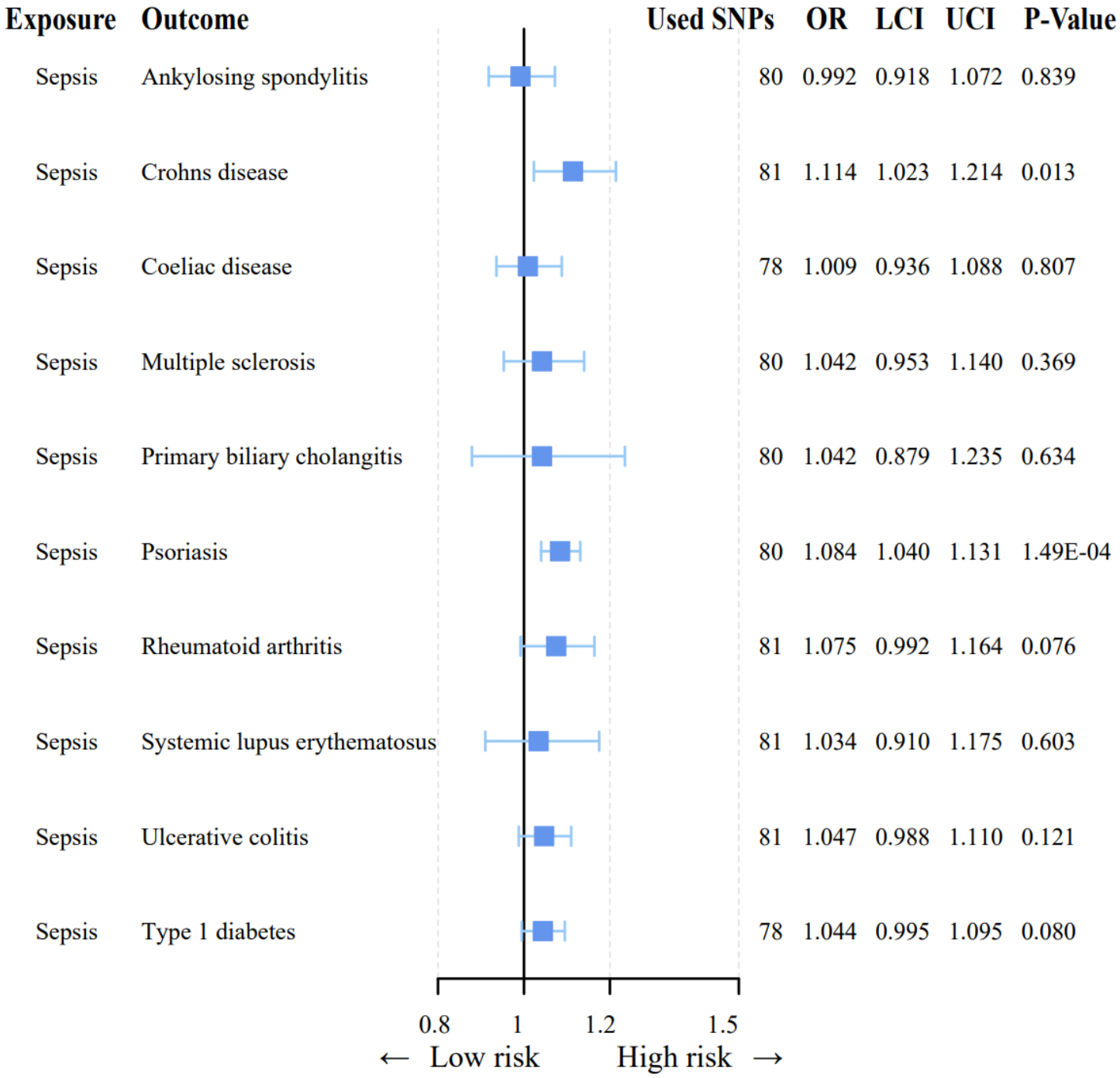

Figure 7

Forest plot to visualize the causal effect of sepsis and autoimmune diseases using the inverse variance-weighted method. CI: 95% confidence interval. OR, odds ratio.

Supplementary Files

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

- SupplementaryTable.xlsx