Genetic Associations between Autoimmune Diseases and the Risks of Sepsis and 28-day Mortality in critical care: A Two-Sample Mendelian Randomization Study

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Abstract

Background

Sepsis is a prominent reason for admission in the Intensive Care Unit (ICU), where certain autoimmune diseases exhibit dysregulation of cytokines similar in sepsis. Existing research suggests that individuals with autoimmune disorders are more susceptible to developing sepsis and experiencing higher mortality rates. This highlights the need for more precise strategies. However, current observational studies provide conflicting conclusions regarding the relationship between autoimmune conditions and sepsis. Therefore, we utilize the Mendelian randomization (MR) to further investigate this association.

Methods

We conducted a two-sample MR study in European population to assess causal relationships between autoimmune diseases and sepsis, we employed the inverse variance-weighted (IVW) method and used Cochran's Q test for heterogeneity. We performed MR Egger intercept and MR pleiotropy residual sum and outlier (MR-PRESSO) global test to test for potential imbalanced pleiotropy.

Results

Genetically predicted Crohn's disease ($\beta = 0.067, \text{se} = 0.034, p = 0.046, \text{OR} = 1.069, 95\% \text{ CI} = 1.001–1.141$) and idiopathic thrombocytopenic purpura ($\beta = 0.069, \text{se} = 0.031, p = 0.023, \text{OR} = 1.071, 95\% \text{ CI} = 1.009–1.136$) were positively associated with an increased risk of sepsis in critical care. Conversely, rheumatoid arthritis ($\beta = -0.104, \text{se} = 0.047, p = 0.025, \text{OR} = 0.901, 95\% \text{ CI} = 0.823–0.987$), ulcerative colitis ($\beta = -0.208, \text{se} = 0.084, p = 0.013, \text{OR} = 0.812, 95\% \text{ CI} = 0.690–0.957$), and narcolepsy ($\beta = -0.202, \text{se} = 0.092, p = 0.028, \text{OR} = 0.818, 95\% \text{ CI} = 0.684–0.978$) were associated with a reduced risk of sepsis in critical care. Moreover, Crohn's disease ($\beta = 0.234, \text{se} = 0.067, p = 0.001, \text{OR} = 1.263, 95\% \text{ CI} = 1.108–1.440$) and idiopathic thrombocytopenic purpura ($\beta = 0.158, \text{se} = 0.061, p = 0.009, \text{OR} = 1.171, 95\% \text{ CI} = 1.041–1.317$) were also linked to an increased risk of 28-day mortality of sepsis in critical care. In contrast, multiple sclerosis ($\beta = -0.261, \text{se} = 0.112, p = 0.020, \text{OR} = 0.771, 95\% \text{ CI} = 0.619–0.960$) and narcolepsy ($\beta = -0.536, \text{se} = 0.184, p = 0.003, \text{OR} = 0.585, 95\% \text{ CI} = 0.408–0.838$) were linked to a decreased risk of 28-day mortality of sepsis in critical care.

Conclusion

This MR study identified causal associations between certain autoimmune diseases and risks of sepsis in critical care, and 28-day mortality in the European population. These findings provide us with a more refined approach to preventing the incidence of sepsis among individuals afflicted with autoimmune diseases. Additionally, exploring the underlying mechanisms of autoimmune diseases may potentially yield innovative approaches to diagnosing and treating sepsis.

Introduction
Sepsis, a condition characterized by severe systemic inflammation in response to infection, is a prominent reason for admission in the Intensive Care Unit (ICU). It is regarded as one of the "oldest and most elusive syndromes in medicine", which has the potential to cause organ dysfunction and mortality[1, 2, 3]. The annual incidence of sepsis is approximately 437 cases per 100,000 people, with over half of the patients experiencing severe sepsis, resulting in approximately 5.3 million deaths annually [4]. Among the sepsis patients receiving treatment in ICU, approximately 30% of individuals succumb to mortality due to sepsis [3, 5]. The pathogenesis of sepsis is related to dysregulated immune responses triggered by invading pathogens, leading to sustained and excessive inflammation and immunosuppression [6]. This hyperactive inflammatory response is considered a key driving factor behind sepsis-related mortality, thus garnering significant attention in recent years regarding the dysregulation of pro-inflammatory and anti-inflammatory pathways [7, 8, 9].

Autoimmune diseases consist of a wide range of disorders characterized by aberrant immune reactions of hyperactive immune cells against the body's healthy tissues. In certain autoimmune diseases, there exists dysregulation of cytokine expression pathways similar to those seen in sepsis pathophysiology. Changes in cytokine levels can influence the likelihood and consequences of sepsis in autoimmune individuals[10, 11, 12, 13, 14]. Based on speculation, the likelihood of sepsis occurrence and mortality rates after sepsis are higher in patients with autoimmune diseases due to the immune dysfunction they experience. Due to the considerable size of the population of individuals with autoimmune conditions, it is imperative to adopt more precise strategies to proactively prevent the occurrence of sepsis among this group[15, 16]. However, some existing observational studies seem to yield inconsistent conclusions, a cohort study using the MIMIC III database found some autoimmune diseases have a protective association with sepsis occurrence and mortality [17]. In contrast, two retrospective studies investigating the association between rheumatoid arthritis and sepsis yielded markedly disparate conclusions [18, 19]. Given the high heterogeneity of both autoimmune diseases and sepsis, numerous confounding factors have led to contradictory findings in different observational studies. Hence, it is essential to employ an accurate and persuasive method to analyze the relationship between these two conditions [20, 21, 22].

In this context, MR using single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) provides an effective means to explore causal relationships between exposures and outcomes. The fundamental assumption of MR study is that traits determined by genes are less susceptible to measurement errors or confounding influences. Compared to traditional observational studies, MR study is less affected by measurement errors or confounding and are less prone to reverse causality; thus, it is recommended for research on sepsis [22, 23, 24].

In this study, we harnessed the amalgamated dataset originating from publicly accessible genome-wide association studies (GWASs). Employs two-sample MR analysis to assess the association between genetically predicted autoimmune diseases and the risk of sepsis in critical care and 28-day mortality. The purpose is to provide the population of individuals with autoimmune diseases with more accurate approaches for preventing sepsis and to further investigate the causal relationship between autoimmune diseases and sepsis.

**Method**

Study Design
This study follows the reporting guidelines of STROBE-MR (Supplementary Table S1) [25]. MR analysis must satisfy three key assumptions (Fig. 1a): 1. Genetic variables are significantly associated with exposure; 2. Genetic variation serving as IVs for exposure is unrelated to other confounding factors; 3. Genetic variation affects the outcome solely through its impact on the exposure (without pleiotropic effects). Figure 1b illustrates a summary of the study design.

First, we searched published genome-wide association study (GWAS) data in the European population, encompassing all available autoimmune diseases as exposure factors and sepsis in critical care and sepsis 28-day mortality in critical care as outcomes. Based on publicly available GWAS data, we selected 30 autoimmune diseases eligible for the study. All disease criteria were defined according to the International Classification of Diseases, Tenth Revision (ICD-10). For each autoimmune disease, single-nucleotide polymorphisms were selected as IVs, followed with two-sample MR analysis using genetic data of sepsis to estimate the causal effects of different autoimmune diseases on the risk of sepsis in critical care and the risk of sepsis 28-day death in critical care this study did not establish a prospective plan or disclose an analysis plan.

Genetic Data Sources and Instruments

Sepsis GWAS Data

We identified sepsis in critical care and sepsis 28-day mortality in critical care as outcomes, utilizing data from the UK Biobank, a substantial cohort of adult volunteers in the UK with all participants providing written informed consent for research participation, detailed descriptions of which are available in the references [26]. The UK Biobank has established a direct connection between genetic and physical information and the dataset of the National Health Service, which can be directly accessed and downloaded from the IEU OpenGWAS Project website (https://gwas.mrcieu.ac.uk/). In the ICU-treated sepsis cohort, it combined a total of 1,380 cases and 429,985 controls. In the cohort of 28-day mortality in ICU-treated sepsis patients, there were 347 cases and 431,018 controls. More detailed information is provided in Supplementary Tables S2 and S3.

Autoimmune Disease GWAS Data:

We searched published data related to autoimmune diseases in individuals of European descent in GWAS catalogs and PubMed. After reviewing recruitment procedures and diagnostic criteria, we excluded trials with potential significant overlap between GWAS populations and selected 7 groups of system/organ(tissue)-specific autoimmune diseases, consisting of 30 different autoimmune diseases as exposures. Their diagnostic criteria and detailed information are available in Supplementary Tables S2 and S3 [27, 28, 29, 30, 31, 32, 33].

Selection of Genetic IVs:

In the selection of genetic IVs, we employed two strategies to ensure the accuracy of the experiment. First, we extracted IVs for the exposure factors (30 autoimmune diseases) from SNPs that reached genome-wide significance (p < 5×10^-8). In this step, if the number of SNPs extracted for a particular autoimmune disease was less than 5, we adjusted the significance level to p < 5×10^-6 to include more SNPs as IVs to reduce
potential errors caused by insufficient IVs. Second, to ensure the independence between SNPs, we pruned the SNPs in the exposure factors using a threshold of \( r^2 > 0.001 \) and a data distance of 10,000 kb to eliminate the impact of linkage disequilibrium (LD). Among the remaining SNPs in the exposure factors, we set an allele frequency threshold (MAF) of 0.3 and allowed for the presence of palindromic SNPs. Finally, we harmonized the genetic data to ensure the causal effects of SNPs on the exposure factors matched the same alleles affecting each outcome.

**Statistical Analysis**

The reliable interpretation of causal estimation in MR analysis depends on meeting the three key assumptions mentioned earlier. Heterogeneity in causal estimates among IVs indicates potential violations of the MR analysis assumptions[34]. The research utilized two-sample Mendelian randomization analysis. In order to confirm assumption 1, we computed the F value, which measures the strength of the association between SNPs and the exposure (\( F = \beta^2 / s.e^2 \)) [35]. To avoid weak instrument bias, we kept SNPs with an F statistic exceeding 10. The retained SNPs were then used as IVs in subsequent analyses to address the causal analysis regarding whether the exposure factors influence the outcomes. In the study, we utilized the inverse variance-weighted (IVW) method (fixed/random effects) as the primary analysis. The IVW method precisely meta-analyzes the specific effects of exposure on each SNP [36]. We performed Cochran's Q test to identify potential heterogeneity in the retained SNPs [37]. If a set of SNPs exhibited heterogeneity, subsequent analyses employed the random-effects IVW method, while SNPs without heterogeneity were analyzed using the fixed-effects IVW method. We also performed MR Egger intercept and MR pleiotropy residual sum and outlier (MR-PRESSO) global test to test for potential imbalanced pleiotropy. As the exchangeability and exclusion restriction assumptions cannot be formally tested, we conducted extensive sensitivity analyses using the MR Egger method [38], the weighted median method [39], the weighted mode method [40], and the MR-PRESSO outlier correction test [37], comparing their results with the IVW (fixed/random effects) to estimate the causal relationship of the core assumption.

All effect size and standard error calculations for all results and the calculation of the odds ratio (OR) with 95% confidence intervals for binary outcomes were performed using the "TwoSampleMR","mendelianrandomization" and "MR-PRESSO" packages in R (version 4.2.1).

**Results**

This study included 30 autoimmune diseases and 2 outcomes (sepsis in critical care, sepsis 28-day mortality in critical care), providing specific information and diagnostic codes in Supplementary Table S2. Supplementary Table S3 summarizes detailed information on the included genome-wide analysis studies, and additional information about each disease can be found on the website (IEU OpenGWAS project at mrcieu.ac.uk) using the GWAS ID. We applied strict selection criteria and ultimately included 20 autoimmune diseases, with a genome-wide significance threshold of \( p < 5 \times 10^{-6} \), while the remaining 10 autoimmune diseases had an even stricter genome-wide significance threshold of \( p < 5 \times 10^{-8} \). All IVs had an F statistic greater than 10, indicating no evidence of weak instrument bias (Supplementary Table S4).
Risk of Autoimmune Diseases for Sepsis in Critical Care

Among the 30 autoimmune diseases considered as exposure factors, 5 of them showed statistically significant associations with an increased or decreased risk of sepsis in critical care (Table 1, Fig. 2−1). There was no apparent causal relationship between the remaining 25 autoimmune diseases and sepsis in critical care. IVW analysis revealed that Crohn's disease (β = 0.067, se = 0.034, p = 0.046, OR = 1.069, 95% CI = 1.001−1.141) and idiopathic thrombocytopenic purpura (β = 0.069, se = 0.031, p = 0.023, OR = 1.071, 95% CI = 1.009−1.136) were associated with an increased risk of sepsis in critical care. On the other hand, rheumatoid arthritis (β =−0.104, se = 0.047, p = 0.025, OR = 0.901, 95% CI = 0.823−0.987), ulcerative colitis (β =−0.208, se = 0.084, p = 0.013, OR = 0.812, 95% CI = 0.690−0.957), and narcolepsy (β =−0.202, se = 0.092, p = 0.028, OR = 0.818, 95% CI = 0.684−0.978) were associated with a reduced risk of sepsis in critical care. No heterogeneity was observed in the above analysis. The MR-PRESSO global test and MR Egger intercept indicated no evidence of pleiotropic effects in any of the MR analyses (p > 0.05), suggesting that there is no pleiotropy in any of the autoimmune diseases considered. Scatter plots, forest plots, leave-one-out plots, and funnel plots were generated to illustrate the specific effects and influences of SNPs on exposure and outcomes (Supplementary Figs. 1−5).

In the sensitivity analysis, among the autoimmune diseases that showed statistically significant associations in the IVW analysis, the results of MR−Egger analysis, weighted median method analysis, and weighted mode method analysis were consistent with the main analysis direction, demonstrating the robustness of the results (Supplementary Table 5−1).
Table 1
1: An overview of the genetic instruments used in the MR study and the causal relationship between Autoimmune disease and Sepsis in critical care estimated by the inverse-variance weighted method.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Used SNPs</th>
<th>Sample</th>
<th>(b/se)</th>
<th>IVW P</th>
<th>IVW het P</th>
<th>Intercept P</th>
<th>MPO P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Connective tissue disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis&amp;</td>
<td>25/26</td>
<td>22647</td>
<td>0.112/0.214</td>
<td>0.602</td>
<td>0.038#</td>
<td>0.552</td>
<td>0.059</td>
</tr>
<tr>
<td>Hypersensitivity angiitis*</td>
<td>5/5</td>
<td>213230</td>
<td>-0.012/0.021</td>
<td>0.588</td>
<td>0.819</td>
<td>0.570</td>
<td>0.776</td>
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<tr>
<td>Polymyositis*&amp;</td>
<td>7/7</td>
<td>213264</td>
<td>0.025/0.026</td>
<td>0.328</td>
<td>0.027#</td>
<td>0.086</td>
<td>0.069</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>10/10</td>
<td>153457</td>
<td>-0.104/0.047</td>
<td>0.025#</td>
<td>0.521</td>
<td>0.900</td>
<td>0.579</td>
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<td>Sjogren syndrome*</td>
<td>12/13</td>
<td>214435</td>
<td>-0.036/0.053</td>
<td>0.492</td>
<td>0.230</td>
<td>0.118</td>
<td>0.286</td>
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<td>Systemic lupus erythematosus</td>
<td>36/43</td>
<td>14,267</td>
<td>0.016/0.028</td>
<td>0.572</td>
<td>0.110</td>
<td>0.748</td>
<td>0.110</td>
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<td>Systemic sclerosis*</td>
<td>6/7</td>
<td>218606</td>
<td>-0.002/0.013</td>
<td>0.929</td>
<td>0.464</td>
<td>0.830</td>
<td>0.630</td>
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<tr>
<td>Wegener granulomatosis*</td>
<td>8/9</td>
<td>213388</td>
<td>-0.026/0.02</td>
<td>0.177</td>
<td>0.510</td>
<td>0.725</td>
<td>0.595</td>
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<td>2. Endocrine system</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adrenocortical insufficiency*</td>
<td>9/10</td>
<td>211526</td>
<td>0.011/0.038</td>
<td>0.785</td>
<td>0.188</td>
<td>0.986</td>
<td>0.226</td>
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<tr>
<td>Autoimmune hyperthyroidism</td>
<td>5/5</td>
<td>173938</td>
<td>-0.046/0.069</td>
<td>0.501</td>
<td>0.062</td>
<td>0.926</td>
<td>0.168</td>
</tr>
<tr>
<td>Autoimmune thyroiditis*</td>
<td>9/11</td>
<td>187928</td>
<td>-0.02/0.02</td>
<td>0.319</td>
<td>0.333</td>
<td>0.598</td>
<td>0.417</td>
</tr>
<tr>
<td>Hypothyroidism, strict autoimmune</td>
<td>41/56</td>
<td>198472</td>
<td>-0.032/0.061</td>
<td>0.595</td>
<td>0.403</td>
<td>0.593</td>
<td>0.372</td>
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<tr>
<td>Type 1 diabetes</td>
<td>7/8</td>
<td>185115</td>
<td>0.015/0.028</td>
<td>0.599</td>
<td>0.052</td>
<td>0.552</td>
<td>0.148</td>
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<td>3. Nervous system</td>
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<tr>
<td>Guillain-Barre syndrome*</td>
<td>6/6</td>
<td>215931</td>
<td>0.03/0.027</td>
<td>0.262</td>
<td>0.884</td>
<td>0.879</td>
<td>0.934</td>
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<td>Multiple sclerosis</td>
<td>25/26</td>
<td>27098</td>
<td>-0.048/0.051</td>
<td>0.339</td>
<td>0.444</td>
<td>0.651</td>
<td>0.505</td>
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<tr>
<td>Myasthenia gravis*</td>
<td>8/8</td>
<td>217288</td>
<td>-0.03/0.027</td>
<td>0.273</td>
<td>0.954</td>
<td>0.928</td>
<td>0.966</td>
</tr>
<tr>
<td>Narcolepsy *</td>
<td>5/5</td>
<td>12307</td>
<td>-0.202/0.092</td>
<td>0.028#</td>
<td>0.970</td>
<td>0.627</td>
<td>0.971</td>
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<tr>
<td>4. Digestive system</td>
<td></td>
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<tr>
<td>Biliary cirrhosis, primary*</td>
<td>12/12</td>
<td>176861</td>
<td>0.006/0.021</td>
<td>0.783</td>
<td>0.378</td>
<td>0.194</td>
<td>0.374</td>
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<td>Coeliac disease</td>
<td>8/8</td>
<td>212937</td>
<td>-0.01/0.027</td>
<td>0.711</td>
<td>0.558</td>
<td>0.408</td>
<td>0.626</td>
</tr>
<tr>
<td>Risk factor</td>
<td>Used SNPs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Sample</td>
<td>(b/se)</td>
<td>IVW P</td>
<td>IVW het P</td>
<td>Intercept P</td>
<td>MPO P</td>
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<td><strong>1. Connective tissue disease</strong></td>
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<tr>
<td>Crohn's disease*</td>
<td>104/115</td>
<td>51874</td>
<td>0.067/0.034</td>
<td>0.046#</td>
<td>0.807</td>
<td>0.701</td>
<td>0.813</td>
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<td>Ulcerative colitis*</td>
<td>5/6</td>
<td>212551</td>
<td>-0.208/0.084</td>
<td>0.013#</td>
<td>0.833</td>
<td>0.683</td>
<td>0.866</td>
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<tr>
<td><strong>5. Hematologic disease</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Allergic purpura*</td>
<td>12/12</td>
<td>216569</td>
<td>-0.024/0.032</td>
<td>0.463</td>
<td>0.339</td>
<td>0.235</td>
<td>0.388</td>
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<tr>
<td>Idiopathic thrombocytopenic purpura*</td>
<td>11/11</td>
<td>216493</td>
<td>0.069/0.031</td>
<td>0.023#</td>
<td>0.966</td>
<td>0.999</td>
<td>0.984</td>
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<tr>
<td><strong>6. Dermatology</strong></td>
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</tr>
<tr>
<td>Alopecia areata*</td>
<td>8/12</td>
<td>211428</td>
<td>-0.033/0.03</td>
<td>0.272</td>
<td>0.831</td>
<td>0.798</td>
<td>0.862</td>
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<tr>
<td>Bullous pemphigoid*</td>
<td>12/14</td>
<td>218285</td>
<td>0.013/0.016</td>
<td>0.422</td>
<td>0.515</td>
<td>0.187</td>
<td>0.511</td>
</tr>
<tr>
<td>Dermatitis herpetiformis*</td>
<td>12/14</td>
<td>218344</td>
<td>0.008/0.021</td>
<td>0.722</td>
<td>0.158</td>
<td>0.993</td>
<td>0.253</td>
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<tr>
<td>Localized scleroderma*</td>
<td>4/4</td>
<td>207662</td>
<td>-0.015/0.019</td>
<td>0.440</td>
<td>0.735</td>
<td>0.830</td>
<td>0.766</td>
</tr>
<tr>
<td>Pemphigoid*</td>
<td>9/12</td>
<td>218348</td>
<td>0.023/0.021</td>
<td>0.267</td>
<td>0.480</td>
<td>0.987</td>
<td>0.447</td>
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<tr>
<td>Psoriasis</td>
<td>11/13</td>
<td>216752</td>
<td>0.037/0.056</td>
<td>0.511</td>
<td>0.358</td>
<td>0.168</td>
<td>0.412</td>
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<td><strong>7. Urologic disease</strong></td>
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<tr>
<td>IgA nephropathy*</td>
<td>4/4</td>
<td>5957</td>
<td>-0.063/0.067</td>
<td>0.353</td>
<td>0.081</td>
<td>0.191</td>
<td>0.176</td>
</tr>
</tbody>
</table>


*: Genome-wide significance of the selected SNPs associated with the factors is less than 5×10^-8, factors with * is less than 5×10^-6.

<sup>a</sup>: SNPs used in the present MR analysis

#: p < 0.05

&: Used IVW random effect model
Table 1
2: An overview of the genetic instruments used in the MR study and the causal relationship between Autoimmune disease and 28 day death in critical care estimated by the inverse-variance weighted method

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Used SNPs</th>
<th>Sample</th>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>25/26</td>
<td>22647</td>
<td>0.461/0.342</td>
<td>0.178</td>
<td>0.742</td>
<td>0.444</td>
<td>0.773</td>
</tr>
<tr>
<td>Hypersensitivity angiitis*</td>
<td>5/5</td>
<td>213230</td>
<td>-0.014/0.042</td>
<td>0.743</td>
<td>0.912</td>
<td>0.559</td>
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<td>7/7</td>
<td>213264</td>
<td>0.042/0.033</td>
<td>0.207</td>
<td>0.478</td>
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<td>Rheumatoid arthritis</td>
<td>10/10</td>
<td>153457</td>
<td>-0.169/0.101</td>
<td>0.092</td>
<td>0.311</td>
<td>0.375</td>
<td>0.370</td>
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<tr>
<td>Sjogren syndrome*</td>
<td>12/13</td>
<td>214435</td>
<td>0.113/0.114</td>
<td>0.321</td>
<td>0.129</td>
<td>0.069</td>
<td>0.163</td>
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<td>Systemic lupus erythematosus</td>
<td>36/43</td>
<td>14,267</td>
<td>0.032/0.055</td>
<td>0.561</td>
<td>0.117</td>
<td>0.466</td>
<td>0.132</td>
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<td>Systemic sclerosis*</td>
<td>6/7</td>
<td>218606</td>
<td>-0.003/0.025</td>
<td>0.909</td>
<td>0.675</td>
<td>0.369</td>
<td>0.671</td>
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<td>Wegener granulomatosis*</td>
<td>8/9</td>
<td>213388</td>
<td>-0.033/0.047</td>
<td>0.488</td>
<td>0.169</td>
<td>0.052</td>
<td>0.217</td>
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<tr>
<td>Adrenocortical insufficiency*</td>
<td>9/10</td>
<td>211526</td>
<td>-0.106/0.084</td>
<td>0.205</td>
<td>0.090</td>
<td>0.249</td>
<td>0.114</td>
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<td>Autoimmune hyperthyroidism</td>
<td>5/5</td>
<td>173938</td>
<td>0.045/0.118</td>
<td>0.706</td>
<td>0.157</td>
<td>0.807</td>
<td>0.338</td>
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<td>Autoimmune thyroiditis*</td>
<td>9/11</td>
<td>187928</td>
<td>-0.046/0.037</td>
<td>0.221</td>
<td>0.863</td>
<td>0.681</td>
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<td>Hypothyroidism, strict autoimmune</td>
<td>41/56</td>
<td>198472</td>
<td>0.026/0.119</td>
<td>0.827</td>
<td>0.785</td>
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<td>Type 1 diabetes</td>
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<td>0.767</td>
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<tr>
<td>Guillain-Barre syndrome*</td>
<td>6/6</td>
<td>215931</td>
<td>-0.051/0.054</td>
<td>0.339</td>
<td>0.409</td>
<td>0.329</td>
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<tr>
<td>Multiple sclerosis</td>
<td>25/26</td>
<td>27098</td>
<td>-0.261/0.112</td>
<td>0.020#</td>
<td>0.180</td>
<td>0.563</td>
<td>0.228</td>
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<tr>
<td>Myasthenia gravis*</td>
<td>8/8</td>
<td>217288</td>
<td>-0.026/0.053</td>
<td>0.633</td>
<td>0.700</td>
<td>0.960</td>
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<td>Narcolepsy *</td>
<td>5/5</td>
<td>12307</td>
<td>-0.536/0.184</td>
<td>0.003#</td>
<td>0.757</td>
<td>0.455</td>
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<td></td>
</tr>
<tr>
<td>Biliary chirrosis, primary*</td>
<td>12/12</td>
<td>176861</td>
<td>0.029/0.04</td>
<td>0.472</td>
<td>0.627</td>
<td>0.203</td>
<td>0.601</td>
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<tr>
<td>Coeliac disease</td>
<td>8/8</td>
<td>212937</td>
<td>0.015/0.053</td>
<td>0.787</td>
<td>0.904</td>
<td>0.631</td>
<td>0.904</td>
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<td>Crohn's disease</td>
<td>104/115</td>
<td>51874</td>
<td>0.234/0.067</td>
<td>0.001#</td>
<td>0.809</td>
<td>0.436</td>
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Next, we conducted an analysis on potential causal effect of autoimmune diseases on the risk of sepsis 28-day mortality in critical care. The results revealed that 4 autoimmune diseases showed statistically significant protective/risk effect on sepsis 28-day death in critical care (Table 1–2, Fig. <link rid="g2">2</link>). IVW analysis indicated that Crohn's disease (β = 0.234, se = 0.067, p = 0.001, OR = 1.263, 95% CI = 1.108–1.440) and idiopathic thrombocytopenic purpura (β = 0.158, se = 0.061, p = 0.009, OR = 1.171, 95% CI = 1.041–1.317) were
associated with an increased risk of sepsis 28-day mortality in critical care. On the other hand, systemic sclerosis ($\beta=-0.261$, $se=0.112$, $p=0.020$, $OR=0.771$, 95% CI = 0.619–0.960) and narcolepsy ($\beta=-0.536$, $se=0.184$, $p=0.003$, $OR=0.585$, 95% CI = 0.408–0.838) were associated with a reduced risk of sepsis 28-day mortality in critical care. Scatter plots, forest plots, leave-one-out plots, and funnel plots were generated to illustrate the specific effects and influences of SNPs on exposure and outcomes (Supplementary Figs. 6–9).

In the sensitivity analysis, no evidence of heterogeneity or pleiotropy was found. Among the 4 autoimmune diseases that showed statistically significant associations in the IVW analysis, the results of MR-Egger analysis, weighted median method analysis, and weighted mode method analysis were consistent with the main analysis direction (Supplementary Table 5–2).

**Discussion**

In this study, we conducted a two-sample MR research aimed at exploring the relationship between 30 autoimmune diseases and the risk of sepsis leading to ICU admission, as well as the 28-day mortality rate among those admitted to the ICU with sepsis. We revealed causal associations between three autoimmune diseases and the two aforementioned outcomes, while another three autoimmune diseases exhibited causal links with individual outcomes. Specifically, Crohn's disease and idiopathic thrombocytopenia were established as risk factors for sepsis in critical care and sepsis 28-day mortality in critical care, respectively. Conversely, narcolepsy demonstrated a protective association with both sepsis in critical care and sepsis 28-day mortality in critical care. Rheumatoid arthritis and ulcerative colitis were identified as protective factors against sepsis in critical care. Additionally, systemic sclerosis exhibited a protective effect on sepsis 28-day mortality in critical care. In comparison to previous observational studies, our MR findings presented both congruent and distinctive conclusions, which were meticulously elucidated through in-depth analysis.

According to our knowledge, this study first utilize Mendelian randomization to comprehensively examine the interrelationships between autoimmune diseases, the risk of sepsis and mortality risk. Our results underscore the significance of targeted interventions for sepsis prevention, particularly among distinct subpopulations of patients with autoimmune disorders, such as Idiopathic thrombocytopenic purpura and Crohn's disease. This approach not only provides a more precise strategy for mitigating sepsis in individuals with autoimmune diseases but also contributes to the alleviation of healthcare resource burden. Concurrently, this study also offers an indication that when managing sepsis in patients with autoimmune diseases, the decision to simultaneously address the underlying autoimmune condition should be contingent upon the individual's disease status. These findings further enrich our comprehension of the interplay between autoimmune diseases and severe sepsis while also facilitating a deeper exploration of the intricate interrelationships between inflammation and septic conditions[41].

In previous studies, it has been observed that platelets are the primary effectors of inflammation and hemostasis and may exacerbate the dysregulated host response during sepsis and consequently increasing the risk of severe sepsis and mortality [42, 43, 44]. Consistent with our findings, our study corroborates that idiopathic thrombocytopenic purpura is a risk factor for sepsis in critical care and sepsis 28-day mortality in critical care. Immunothrombosis is a protective response that occurs when pathogens infiltrate the human body, triggering the activation of the coagulation system and causing microvascular thrombosis in the vicinity.
This defense mechanism confines the infection to the specific region. However, when idiopathic thrombocytopenia purpura is present, this defensive mechanism is weakened, thereby elevating the risk of severe sepsis occurrence[45].

Surprisingly, our study revealed opposing effects of Crohn's disease and ulcerative colitis on sepsis. Crohn's disease emerged as a risk factor for sepsis in critical care and 28-day mortality, while ulcerative colitis exhibited a protective association with sepsis in critical care. This conclusion aligns with a previous sepsis and autoimmune disease cohort study using the MIMIC III database but differs from that study in terms of the statistically insignificant reduction in 30-day mortality risk associated with ulcerative colitis (OR = 0.87, 95% CI = 0.52–1.43, P = 0.594)[17]. A similar study using the US national inpatient data arrived at opposing conclusions, showing a statistically significant decrease in the risk of death associated with Crohn's disease (OR = 0.78, 95% CI = 0.63–0.97) and a statistically significant increase in mortality risk associated with ulcerative colitis (OR = 1.61, 95% CI = 1.35–1.93)[19]. However, these observational studies did not account for the potential impact of treatment differences between the two diseases. In fact, Crohn's disease patients are 5 to 10 times more likely to receive anti-tumor necrosis factor-α (TNF-α) treatment than ulcerative colitis patients, which could be a key influencing factor leading to differing results between previous studies and our findings[46, 47]. The opposing effects of Crohn's disease and ulcerative colitis on outcomes can be explained by the primary sites of inflammation in the two diseases: inflammation in ulcerative colitis is predominantly limited to the intestinal mucosa, while transmural inflammation occurs primarily in Crohn's disease[48, 49]. Moreover, these two diseases exhibit significant differences in other aspects as well. Further research into the mechanisms of inflammation between Crohn's disease and ulcerative colitis may provide new insights into the inflammatory response to sepsis[18, 50].

Several studies have presented conflicting results regarding the influence of rheumatoid arthritis on sepsis, thereby generating controversy within this domain. In Germany, a retrospective study conducted suggested an independent correlation between rheumatoid arthritis and increased sepsis mortality[52]. Another retrospective study found that rheumatoid arthritis was a significant independent risk factor for increased long-term mortality in sepsis patients (OR 1.63, 95% CI: 1.03–1.63, p = 0.04), but it did not have an independent effect on short-term mortality risk after admission[18]. Conversely, two other studies considered rheumatoid arthritis as a protective factor against short-term mortality in sepsis patients[17, 19]. In our MR study, we concluded that rheumatoid arthritis is a protective factor for sepsis in critical care, but it is not associated with changes in short-term mortality risk. The underlying reason for this phenomenon might be the overexpression of cytokines IL-12 and IFN-γ in rheumatoid arthritis patients, with relative deficiencies of IL-4 and IL-10[53]. Studies have suggested that therapies increasing the expression of IL-12 and IFN-γ can improve sepsis survival rates[54]. We hypothesize that the overexpression of certain cytokines in rheumatoid arthritis patients may reduce the likelihood of immune dysfunction, thereby decreasing the risk of severe sepsis occurrence[17, 55].

Among the remaining autoimmune diseases with causal relationships to sepsis, only a few retrospective studies are available for reference. As mentioned earlier, a cohort study on sepsis and autoimmune diseases using the MIMIC III database found that multiple sclerosis is a protective factor for sepsis mortality (HR: 0.45, 95% CI: 0.22–0.89, p = 0.023), which aligns with our conclusion[17]. This study proposed that multiple sclerosis patients with specific cytokine overexpression or deficiencies before sepsis may be more likely to survive when immune function is compromised[56, 57, 58]. Narcolepsy, a chronic sleep disorder, is caused by
the depletion of a small number of hypothalamic neurons responsible for generating neuropeptides that promote wakefulness[59]. We found that narcolepsy is a protective factor for sepsis in critical care and 28-day mortality in ICU, but this result has not been confirmed by existing observational studies. According to previous research, narcolepsy patients tend to secrete higher levels of cytokines, including IL-2, tumor necrosis factor, IL-4, and IL-13, which could be the reason for narcolepsy being a protective factor against severe sepsis and 28-day mortality in sepsis patients, but more experiments are needed to verify this[60, 61].

In this study, we conducted two-sample MR analyses to comprehensively assess the causal relationships between 30 autoimmune diseases and the risk of sepsis in critical care and sepsis 28-day mortality in critical care. In previous observational studies, both sepsis and autoimmune diseases are highly heterogeneous, making it challenging to avoid confounding factors[22]. Due to the uniqueness of autoimmune diseases and sepsis, conducting randomized controlled trials would be prohibitively time consuming and costly. Therefore, our MR study is less susceptible to measurement errors, confounding, and reverse causation compared to traditional observational studies, enabling us to better reveal causal relationships. These findings are crucial for a deeper understanding of the association between autoimmune diseases and severe sepsis, as well as for further exploring the interplay between inflammation and sepsis[62].

There are certain limitations in our research. First, the focus of this research was on European populations, and the restriction to a specific ethnicity may impact the generalizability of the results to other ethnic groups. Second, due to the limited availability of open-access genetic data on autoimmune diseases, we slightly relaxed the genome-wide significance threshold (p < 5×10^-6) in some exposure factors, which might influence our interpretation of causal relationships between certain genes and autoimmune diseases. Additionally, the accuracy of interpreting causal relationships using genetic instruments is limited and cannot completely eliminate the influence of all confounding factors. Hence, cautious interpretation of the results is necessary to avoid overinterpretation. Last, our study results provide genetic evidence for the causal impact of autoimmune diseases on the risk of severe sepsis and 28-day mortality, but it does not delve into detailed mechanistic explanations. Therefore, in future research, further exploration of the specific biological mechanisms between autoimmune diseases and sepsis is needed. This includes studying the differences in inflammation and immune pathways among autoimmune disease patients and how these differences influence the onset and prognosis of sepsis. Through such research, we may discover new therapeutic strategies and novel insights into the prevention and treatment of sepsis.

In conclusion, this MR study identified causal associations between certain autoimmune diseases and risks of sepsis in critical care and 28-day mortality in the European population. The findings contribute robust evidence, advancing our comprehension of the intricate relationship between autoimmune diseases and severe sepsis. The identification of these causal associations suggests that delving into autoimmune disease-related mechanisms could potentially unveil novel therapeutic strategies for the prevention and treatment of sepsis. Moreover, this study sheds light on the interplay between inflammation and sepsis, prompting further investigations in this area. Nonetheless, to enhance the credibility of these findings and acquire a more profound understanding of the underlying processes, it is crucial to conduct further research.

Abbreviations
Declarations

Acknowledgements

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Authors’ contributions

TX and ZYJ contributed equally to this work, they conceived and designed the study. TX supervised the study and data analysis. TX, ZYJ, SJ and LX performed the data analysis with help from ZTJ and YWH. TX and ZYJ wrote the manuscript. All authors revised and approved the final manuscript.

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Availability of data and materials

The data for sepsis and autoimmune diseases can be downloaded from the IEU OpenGWAS Project website (https://gwas.mrcieu.ac.uk/) using the provided GWAS ID.

Ethics approval and consent to participate
The analysis was conducted using publicly accessible data that have obtained approval from appropriate review boards. The utilization of the UK Biobank dataset was granted approval by the Research Ethics Committee (REC reference: 21/NW/0157). All summary data were derived from publicly accessible data sources. No personal information was included in this study.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interests to declare.

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Figures
We searched published GWAS data in European populations to explore autoimmune diseases as exposure factors and their association with Sepsis in critical care and Sepsis 28-day death in critical care.

Identify 30 autoimmune diseases with proposed SNPs as exposure factors

\[ p < 5 \times 10^{-8}, r^2 = 0.001, \text{window size} = 10000\text{kb} \]

Outcome: Sepsis in critical care

Two-sample Mendelian randomization analysis

Outcome: Sepsis 28 day death in critical care

IF SNP<5, setting \( p < 5 \times 10^{-6}, r^2 = 0.001, \text{window size} = 10000\text{kb} \)

Harmonize exposure and outcome data, exclude pleiotropic SNPs, retain SNPs with F-statistics >10

Two-sample Mendelian randomization analysis and sensitivity analyses

**Figure 1**

Flow-chart of study design: Illustrates the step-by-step process of conducting the MR analysis.
Figure 2

The MR analysis presents the causal estimations of 30 autoimmune diseases on the sepsis in critical care and sepsis 28-day mortality in critical care. Figure A exhibits the causal effects between the 30 autoimmune diseases and sepsis in critical care. Figure B illustrates the causal effects between the 30 autoimmune diseases and sepsis 28-day mortality in critical care. The ORs were estimated using the IVW method, with the horizontal bars denoting the 95% confidence intervals (CI).

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

- Supplementaryfigure1RheumatoidarthritisSepsiscriticalcare.png
- Supplementaryfigure2NarcolepsySepsiscriticalcare.png
- Supplementaryfigure3CrohnSepsiscriticalcare.png
- Supplementaryfigure4UlcerativecolitisSepsiscriticalcare.png
- Supplementaryfigure5IdiopathicthrombocytopenicpurpuraSepsiscriticalcare.png
- Supplementaryfigure6MultiplesclerosisSepsis28daydeathincriticalcare.png
- Supplementaryfigure7NarcolepsySepsis28daydeathincriticalcare.png
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- Supplementaryfigure9IdiopathicthrombocytopenicpurpuraSepsis28daydeathincriticalcare.png
- SupplementarytableS1checklist.docx
- SupplementarytableS2Overviewofdiagnosticcriteriarafordisease related exposuresandoutcomes.docx
- SupplementarytableS3ThesourcesandinformationoftheGWASdataforallexposuresandoutcomes.docx
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