Causal effect of negative emotions and insomnia on sepsis and its associated clinical indicators: A Mendelian randomisation and mediation analysis

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Research Article

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Abstract

Background

Negative emotions and insomnia (NEI) are associated with changes in inflammatory factors, which play a role in sepsis.

Methods

We performed Mendelian randomisation (MR) analysis of genome-wide association study (GWAS) data of NEI and sepsis to investigate the causal effect of NEI on sepsis. We employed linkage disequilibrium score regression (LDSC) to calculate the genetic correlation between NEI and sepsis. Inverse variance weighting (IVW) was primarily used for investigating causality, while the weighted median and MR-Egger methods ensured the reliability of the findings. To assess heterogeneity, we employed RadialMR and Cochran's Q test, and we used MR-Egger regression and Mendelian randomisation pleiotropy residual sum and outlier analyses to evaluate the bias of gene polymorphism. Mendelian mediation analysis was conducted to quantify the intermediate effect of inflammatory factors in mediating the relationship between NEI and sepsis, including the percentage of this mediating effect.

Results

LDSC analysis revealed a genetic correlation between NEI and sepsis. Two-sample MR analysis revealed a causal relationship between NEI and sepsis (odds ratio = 1.21, 95% confidence interval: 1.08–1.36, p = 1.07×10^{−3}), with no significant heterogeneity and pleiotropy bias. Mendelian mediation analysis revealed an intermediate effect of NEI on sepsis mediated by chitinase 3-like 1 (CHI3L1) (0.12, 10.31%).

Conclusions

Our findings prove the causal relationship between NEI and sepsis. We identified CHI3L1 as a potential mediator, offering insight into the pathogenesis of sepsis.

1 Introduction

Sepsis is a multiorgan disorder caused by infection, and many patients die from sepsis every year [1, 2]. Sepsis markedly impacts physical and mental health, and reports show that cognitive and emotional disorders are common among sepsis survivors [3, 4]. Interestingly, scholars have found an increase in inflammation-related biomarkers in individuals with negative emotions and insomnia (NEI), and the levels of these markers are directly related to the severity of negative emotions [5–7]. Previous studies have reported the important role of the imbalance of inflammatory biomarkers in sepsis [8, 9]. However, very
little research has explored whether changes in inflammatory biomarkers caused by NEI also induce sepsis.

Negative emotions are closely related to insomnia [10, 11], and the impact of both on infection risk has been a continual focus of scientists. Research shows that depression may increase the risk of multiple infections [12]. Severe depression and anxiety can increase the risk of bloodstream infection, but their correlation with sepsis cannot be confirmed because of various confounding factors [13]. However, some reports show that depression can serve as a defensive instinct and lead to the storage of metabolic resources and adjustment of the immune system to combat the adverse effects of diseases such as infections on the body [14]. Therefore, reasonably avoiding confounding factors during assessment can more truly reflect the correlation between NEI and sepsis.

Mendelian randomisation (MR) is a method that uses genetic mutations to study the causal relationship between exposures and outcomes, such as health and social factors. It offers reduced confounding and bias compared with traditional epidemiological methods [15]. We therefore used MR to investigate the causal relationship between NEI and sepsis. We additionally used linkage disequilibrium score regression (LDSC) and two-sample MR to evaluate the genetic correlation between NEI and sepsis. The latter was combined with inflammation-related biomarkers to perform Mendelian mediation calculations to verify whether inflammation-related biomarkers can mediate the effects of NEI on sepsis.

2 Methods

2.1 Data source for NEI

Relevant data on depression were obtained from a previous study on the main pathogenic genes of depression by the Psychic Genetics Consortium; this study included a meta-analysis of the whole genome data of 135,458 patients with depression and 344,901 controls [16]. Anxiety data were extracted from a genome-wide association study (GWAS) of 30,731 patients and 278,423 controls from the FinnGen project. Insomnia data were retrieved from a GWAS of 2,704 patients and 30,547 controls from the FinnGen project. Stress data were obtained from a GWAS of 10,851 patients and 278,818 controls (Supplementary Table 1).

2.2 Data sources for sepsis and inflammatory factors

Data on sepsis were retrieved from a UK Biobank study that included data from 486,484 European individuals (Supplementary Table 2). In addition, because lactic acid levels are closely associated with death in patients with sepsis [17], we included lactic acid levels in the outcome study. Data on lactate levels were extracted from a study involving a European population sample of 114,802 individuals (Supplementary Table 2). Simultaneously, because of the advantages of the Sequential Organ Failure Assessment (SOFA) score in evaluating the organs of patients with sepsis [18], we also included the SOFA score for each organ in the outcome analysis. The data on creatinine levels in the SOFA score were
obtained from the Chronic Kidney Disease Genetics study on the glomerular filtration rate of 133,413 individual samples [19]. Data on bilirubin levels were obtained from a study on the genetic map of human blood metabolites, including two European populations with 7,824 adults [20].

Similarly, data on platelet counts were obtained from a genome-wide analysis of blood cell trait variations by the British Biological Bank and the INTERVAL trial, including 173,480 samples [21]. We did not find relevant data on mean arterial pressure; therefore, we replaced it with systolic and diastolic blood pressure. These data were retrieved from a genetic association study on the blood pressure characteristics of more than one million European people [22]. The GWAS data regarding inflammatory cytokines were derived from 21,758 patients from 13 European ancestry cohorts [23].

2.3 Genetic correlation

Genetic correlation is a key population parameter used to describe the shared genetic structure of complex traits and diseases [24]. Genetic correlations can be assessed using LDSC. The principle uses regression of the correlation test statistics of single nucleotide polymorphisms (SNPs) on their linkage disequilibrium (LD) scores. The LD score is the sum of LD $r^2$ values measured by all SNPs. We analysed the genetic correlation between NEI and sepsis using the LDSC software (https://github.com/bulik/ldsc).

2.4 Selection of genetic tools

In this study, negative emotions, including depression, anxiety, and stress, were examined to determine the causal relationship between NEI and sepsis. We included insomnia in the analysis because it is closely related to negative emotions [11]. The genetic tools were selected based on the following criteria: (1) p-value of depression < $5 \times 10^{-7}$ in genome-wide association studies and p-value of anxiety, insomnia, and stress < $5 \times 10^{-6}$; these values were used because no suitable tool enabled the filtration of variables with p-values < $5 \times 10^{-8}$ and (2) an LD $r^2 < 0.001$ at a 10,000-kb window. We removed the threshold for sepsis and SNP of its related clinical index data before each MR analysis. After this, we used RadialMR to eliminate potential abnormal values. F statistics were calculated according to the method described by Pierce et al. to ensure the validity of tool variables [25]. When the F statistic was > 10, we determined that no weak tool bias was present.

2.5 MR analyses

The inverse variance weighting (IVW) method was the main method used for causal effect evaluation, as it is an ideal evaluation with strong causality and can increase the robustness of the causal assessment. We used two other methods, weighted median and MR-Egger, to ensure the reliability and stability of the results [26]. The MR may be heterogeneous because of differences in the analysis platform and experimental conditions. We also used Cochran’s Q test to identify heterogeneity; the test results (p < 0.05)
were considered heterogeneous. We used the MR-Egger regression intercept test and Mendelian
randomisation pleiotropy residual sum and outlier (MRPRESSO) to evaluate gene pleiotropy bias. A
smaller regression intercept indicated a smaller pleiotropy. Bonferroni corrections were utilised for
multiple corrections to avoid type I errors. A p-value of < $1.79 \times 10^{-3}$ (0.05/28) was considered
statistically significant. The results were considered nominally significant from $p = 1.79 \times 10^{-3}$ to 0.05.
This study was conducted using TwoSampleMR (version 0.4.25), RadialMR (version 1.0), and
MRPRESSO (version 1.0) in R (version 4.1.2).

2.6 Effects of inflammatory factors as mediators of sepsis

The product of coefficients method was used to analyse the role of inflammatory factors as mediators in
the relationship between NEI and sepsis [27]. We selected NEI that showed causal relationships with
sepsis as the exposures. Two-sample MR was used to determine the causal relationship between NEI and
inflammatory factors. Subsequently, we selected NEI and inflammatory factors that showed a causal
relationship as exposures and used Mendelian mediation to evaluate the causal relationship between
these and sepsis; we also calculated the percentage of the mesomeric effect according to the method
described by Liu et al. [28] A flow chart of this study is shown in Fig. 1.

2.7 Ethics approval

This study involved the re-analysis of data from a previous study, and no further ethical approval or
consent was required.

3 Results

3.1 Genetic correlation analysis

Using LDSC, we found a genetic correlation between depression and sepsis (genetic correlation = 0.31, $p$
$= 6.70 \times 10^{-3}$). Anxiety was genetically correlated with sepsis (genetic correlation = -0.22, $p = 3.88 \times 10^{-2}$),
diastolic blood pressure (genetic correlation = -0.08, $p = 3.00 \times 10^{-3}$), and systolic blood pressure
(genetic correlation = -0.05, $p = 3.83 \times 10^{-2}$), and stress was genetically correlated with diastolic blood
pressure (genetic correlation = -0.09, $p = 4.48 \times 10^{-2}$).

3.2 Causal relationship between NEI and sepsis

Figure 2 shows the causal relationship between NEI and several indicators of sepsis. A strong causal
relationship was identified between depression and sepsis on IVW (odds ratio [OR] = 1.21, 95% confidence
interval [CI]: 1.08 to 1.36, $p = 1.07 \times 10^{-3}$), MR-Egger (OR = 1.05, 95% CI: 0.61 to 1.81, $p = 8.53 \times 10^{-1}$), and
weighted median (OR = 1.17, 95% CI: 1.00 to 1.37, p = 5.43×10^-2) analyses. Other positive results of causation are shown in Table 1.

### Table 1
Significant and nominally significant Mendelian randomisation estimates for the relationship between negative emotions and sepsis

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>IVW-derived p-value</th>
<th>B (95% CI)</th>
<th>Cochran’s Q test-derived p-value</th>
<th>MR-Egger intercept-derived p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant estimates***</td>
<td>Depression</td>
<td>Sepsis</td>
<td>1.07 × 10^{-3}</td>
<td>1.21 (1.08 to 1.36)</td>
<td>1.00</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Systolic blood pressure</td>
<td>6.85× 10^{-6}</td>
<td>1.84 (1.41 to 2.41)</td>
<td>0.41</td>
<td>0.39</td>
</tr>
<tr>
<td>Lactate level</td>
<td></td>
<td>1.47 × 10^{-3}</td>
<td>0.95 (0.92 to 0.98)</td>
<td>0.91</td>
<td>0.68</td>
</tr>
<tr>
<td>Nominally significant estimates*</td>
<td>Insomnia</td>
<td>Systolic blood pressure</td>
<td>2.50 × 10^{-2}</td>
<td>0.83 (0.70 to 0.98)</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>Diastolic blood pressure</td>
<td>2.09 × 10^{-2}</td>
<td>0.90 (0.83 to 0.98)</td>
<td>0.43</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>Stress</td>
<td>Platelet count</td>
<td>4.06 × 10^{-2}</td>
<td>1.04 (0.98 to 1.10)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

***IVW-derived p < 1.79 × 10^{-3}; *IVW-derived p < 0.05. Cochran’s Q test- and MR-Egger intercept-derived p-values < 0.05 were considered significant. IVW, inverse variance weighting; CI, confidence interval; MR, Mendelian randomisation

The p-value was > 0.05 using Cochran’s Q test, indicating no heterogeneity and confirming the reliability and stability of the results. The p-value of the MR-Egger intercept was > 0.05, indicating the absence of pleiotropy (Table 1). The funnel plot method was used to verify the symmetry of the results. The sensitivity evaluation was performed using the leave-one-out method (Supplementary Fig. 1).

### 3.3 Mediators of the effects of depression on sepsis
We found that selectin E (SELE), tissue plasminogen activator (t-PA), tumour necrosis factor (TNF)-related apoptosis inducing ligand receptor 2 (TRAIL-R2), matrix metalloproteinase-12 (MMP-12), chitinase 3-like 1 (CHI3L1), leptin (LEP), lectin-like oxidized low-density lipoprotein receptor 1 (LOX-1), interleukin (IL)-16, IL-6 receptor alpha (RA), IL-1RA, and C-C motif chemokine ligand (CCL)-20 were significantly associated with depression. Among them, only CHI3L1 mediated the effects of depression on sepsis (Table 2). We defined the causal effect of depression on sepsis as $\beta_1 = 1.21$, representing the total effect. The causal impact of depression on CHI3L1 was $\beta_2 = 0.12$, and the causal impact of CHI3L1 on sepsis was $\beta_3 = 1.04$. Thus, the intermediate effect was calculated as $\beta_2 \times \beta_3$, and the percentage of the intermediate effect was calculated as $\beta_2 \times \beta_3 / \beta_1$. We obtained an intermediate effect of 0.12, with an intermediate effect percentage of 10.31%, using the results of the calculations (Fig. 3).
### Table 2
Significant Mendelian mediation for the effects of inflammatory factors as mediators of sepsis

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Mediator</th>
<th>IVW-derived p-value</th>
<th>β (95% CI)</th>
<th>Outcome</th>
<th>p-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>CHI3L1</td>
<td>3.13× 10⁻²</td>
<td>0.12 (0.01 to 0.22)</td>
<td>Sepsis</td>
<td>3.51× 10⁻²</td>
<td>1.04 (1.00 to 1.09)</td>
</tr>
<tr>
<td></td>
<td>SELE</td>
<td>3.49× 10⁻³</td>
<td>0.16 (0.05 to 0.27)</td>
<td>Sepsis</td>
<td>3.19× 10⁻¹</td>
<td>1.01 (0.99 to 1.05)</td>
</tr>
<tr>
<td></td>
<td>t-PA</td>
<td>4.44× 10⁻²</td>
<td>0.11 (0.00 to 0.21)</td>
<td>Sepsis</td>
<td>7.61× 10⁻¹</td>
<td>0.96 (0.79 to 1.19)</td>
</tr>
<tr>
<td></td>
<td>TRAIL-R2</td>
<td>1.89× 10⁻²</td>
<td>0.14 (0.02 to 0.26)</td>
<td>Sepsis</td>
<td>7.73× 10⁻¹</td>
<td>1.01 (0.96 to 1.06)</td>
</tr>
<tr>
<td></td>
<td>MMP-12</td>
<td>3.98× 10⁻³</td>
<td>0.17 (0.05 to 0.29)</td>
<td>Sepsis</td>
<td>2.31× 10⁻¹</td>
<td>0.98 (0.94 to 1.01)</td>
</tr>
<tr>
<td></td>
<td>LEP</td>
<td>1.96× 10⁻⁴</td>
<td>0.22 (0.10 to 0.33)</td>
<td>Sepsis</td>
<td>8.93× 10⁻¹</td>
<td>0.99 (0.81 to 1.21)</td>
</tr>
<tr>
<td></td>
<td>LOX-1</td>
<td>1.34× 10⁻²</td>
<td>0.15 (0.03 to 0.27)</td>
<td>Sepsis</td>
<td>9.43× 10⁻¹</td>
<td>1.00 (0.88 to 1.15)</td>
</tr>
<tr>
<td></td>
<td>IL-16</td>
<td>2.10× 10⁻²</td>
<td>0.14 (0.02 to 0.26)</td>
<td>Sepsis</td>
<td>1.24× 10⁻¹</td>
<td>0.97 (0.93 to 1.01)</td>
</tr>
<tr>
<td></td>
<td>IL-6RA</td>
<td>5.93× 10⁻³</td>
<td>0.16 (0.05 to 0.27)</td>
<td>Sepsis</td>
<td>4.07× 10⁻¹</td>
<td>1.01 (0.99 to 1.03)</td>
</tr>
<tr>
<td></td>
<td>IL-1RA</td>
<td>2.28× 10⁻³</td>
<td>0.16 (0.07 to 0.31)</td>
<td>Sepsis</td>
<td>6.27× 10⁻¹</td>
<td>1.01 (0.96 to 1.07)</td>
</tr>
<tr>
<td></td>
<td>CCL-20</td>
<td>9.39× 10⁻⁵</td>
<td>0.26 (0.13 to 0.38)</td>
<td>Sepsis</td>
<td>8.72× 10⁻¹</td>
<td>0.99 (0.86 to 1.13)</td>
</tr>
</tbody>
</table>

IVW, inverse variance weighting; CI, confidence interval; OR, odds ratio; CHI3L1, chitinase 3-like 1; SELE, selectin E; t-PA, tissue plasminogen activator; TRAIL-R2, tumour necrosis factor-related apoptosis inducing ligand receptor 2; MMP-12, matrix metalloproteinase-12; LEP, leptin; LOX-1, lectin-like oxidized low-density lipoprotein receptor 1; IL, interleukin; RA, receptor alpha; CCL, C-C motif chemokine ligand

### 4 Discussion

Many studies have suggested a relationship between emotions and disease. However, the relationship between NEI and sepsis has not been reported. This study investigated the causal relationship between NEI and sepsis using MR, which revealed a causal relationship between depression and sepsis. Additionally, our study found that CHI3L1 can serve as a mediator and regulate the impact of depression on sepsis. This finding provides theoretical support for the impact of NEI on sepsis and offers a
preliminary exploration of the possible mechanisms involved. Therefore, our study can be a beneficial resource for future in-depth research.

Depression has become a public health problem of great concern because of its high global incidence and disability rates [29]. Alteration in the levels of cytokines and inflammatory mediators, such as IL-1β, TNF-α, CCL-2, and C-reactive protein, have been found to be closely related to the severity of depression through the study of genetic networks [30–32]. IL-1β is a major pro-inflammatory factor, and its main role is coordinating multiple host responses to microbial infection or sterile tissue damage [33, 34]. The plasma concentration of TNF-α, which also acts as an inflammatory agent, is associated with sepsis-related mortality [35]. Thus, inflammatory factors may become a bridge connecting depression and sepsis. Our study found that there was a causal relationship between depression and 11 inflammatory factors, including SELE, t-PA, TRAIL-R2, MMP-12, CHI3L1, LEP, LOX-1, IL16, IL-6RA, IL-1RA, and CCL-20. However, only CHI3L1 was found to mediate the effects of depression on sepsis. CHI3L1 is a member of the glycoside hydrolase family, also known in humans as YKL-40, and is important in various physiological processes, including tissue damage, inflammation, tissue repair, and remodelling responses [36, 37]. CHI3L1 is strongly linked to infection, and studies have found that levels of CHI3L1 rise in response to lung infections, as CHI3L1 regulates M2 macrophage activation and Th2 immune response during respiratory syncytial virus infection [38]. CHI3L1 also acts against *Streptococcus pneumoniae* by inhibiting caspase-1-dependent macrophage phagocytosis [36]. CHI3L1 plays an important role in pulmonary infections; further, proteomics studies have shown that YKL-40 is significantly elevated in patients admitted to the intensive care unit who have positive blood cultures or septic shock, those undergoing hemofiltration, and those receiving hormone therapy, suggesting that YKL-40 can be a biomarker for sepsis [39]. These findings are consistent with our conclusion that a causal relationship exists between CHI3L1 and sepsis. CHI3L1 plays an important role in various neurological disorders [40, 41]. However, few studies have explored the correlation between negative emotions and CHI3L1, and increased expression of YLK-40 was found only in patients with bipolar disorder [42]. Our study not only established the causal relationship between depression and CHI3L1 but also found that CHI3L1 can mediate the relationship between depression and sepsis, providing theoretical support for the hypothesis that depression can lead to sepsis. The results provide support for the need for follow-up research on these mechanisms.

A few factors have hampered research into the causal relationship between NEI and sepsis. The occurrence of NEI can be easily overlooked, especially in patients with critical illnesses such as sepsis, which makes it difficult for clinicians to relate them to NEI. However, the diagnosis of NEI must be documented in the patient's medical history, which will inevitably include confounding factors. Therefore, it is difficult to obtain an accurate assessment, and funds and resources are often wasted on large-scale randomised controlled trials. Mendelian randomisation has reduced the requirement for time-consuming and expensive studies, making it a favourable method for studying the causal relationship between NEI and sepsis.
4.1 Limitations of the study

This study's data on sepsis are not perfect. For example, we did not include data related to the oxygenation index and Glasgow Coma Scale score in the analyses, which is a limitation of this study. The results support further assessment of the relationship between depression and sepsis and its mediating factors despite this limitation.

5 Conclusions

This study used Mendelian randomisation to investigate the causal effect of NEI on sepsis. The results showed a causal relationship between depression and sepsis, and we found that CHI3L1 mediates the effects of depression on sepsis through Mendelian mediation. These findings highlight the role of depression in the development of sepsis, and the mediating role of CHI3L1 may support future studies on the pathogenesis of sepsis.

Abbreviations

CCL, C-C motif chemokine ligand; CHI3L1, chitinase 3-like 1; GWAS, genome-wide association study; IL, interleukin; IVW, inverse variance weighting; LD, linkage disequilibrium; LDSC, linkage disequilibrium score regression; LEP, leptin; LOX-1, lectin-like oxidized low-density lipoprotein receptor 1; MMP-12, matrix metalloproteinase-12; MR, Mendelian randomisation; MRPRESSO, Mendelian randomisation pleiotropy residual sum and outlier; NEI, negative emotions and insomnia; RA, receptor alpha; SELE, selectin E; SNP, single nucleotide polymorphism; SOFA, Sequential Organ Failure Assessment; TNF, tumour necrosis factor; t-PA, tissue plasminogen activator; TRAIL-R2, tumour necrosis factor-related apoptosis inducing ligand receptor 2.

Declarations

Ethics approval and consent to participate

This study involved the re-analysis of data from a previous study, and no further ethical approval or consent was required.

Consent for publication

Not applicable.

Availability of data and materials

The sepsis data used in this study are from the UK Biobank, while the anxiety, insomnia, and stress data are from the FinnGen project. See the Study Design and Methods for information about the remaining data sources.
Competing interests

The authors declare that they have no competing interest.

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None.

Authors’ contributions

SW conducted the data analysis and wrote the original manuscript draft. SW and ND developed the study design and conducted critical revision of the manuscript. The manuscript draft was edited by JX, TX, and YL. All authors contributed to the article and approved the submitted version.

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None.

References


Figures
Figure 1

Flow chart of the Mendelian randomisation analysis of the causal relationship between NEI and sepsis.

GWAS, genome-wide association study; MR, Mendelian randomisation; NEI, Negative emotions and insomnia; SNP, single nucleotide polymorphism

Figure 2

Inverse variance weighting (IVW) estimates of anxiety, depression, insomnia, irritability, stress, the Sequential Organ Failure Assessment (SOFA) organ evaluation index score, and lactate levels. The colour of each block represents the IVW-derived p-values in the Mendelian randomisation (MR) analysis. A larger p-value is indicated by a bluer colour, and a smaller p-value is indicated by a redder colour. A p-value of < 0.05 indicates nominal significance, whereas p < 1.79 × 10⁻³ indicates significance.
Mendelian randomisation frameworks. Depression causally influences sepsis. The effect of chitinase 3-like 1-mediated depression on sepsis has been shown. P-values for inverse variance weighting (IVW) estimates that are < $1.79 \times 10^{-3}$ are significant and have been represented with a solid line, whereas p < 0.05 indicates nominal significance and has been represented with a dotted line.

**Supplementary Files**

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- SupplementaryTable.2.docx