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Research article

Mendelian randomization analysis identifies causal associations between serum lipidomic profile, amino acid biomarkers and sepsis

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ABSTRACT

Background: Sepsis is a life-threatening condition marked by a severe systemic response to infection, leading to widespread inflammation, cellular signaling disruption, and metabolic dysregulation. The role of lipid and amino acid metabolism in sepsis is not fully understood, but aberrations in this pathway could contribute to the disease's pathophysiology.

Methods: To explore the potential of lipid and amino acid compounds as biomarkers for the diagnosis and prognosis of sepsis, a two-sample Mendelian Randomization (MR) study was conducted, examining the relationship between sepsis and 249 serum lipid and amino acid-related markers. Key enzymes involved in synthesis of phosphatidylcholine, including choline/ethanolamine phosphotransferase 1 (CEPT1), choline phosphotransferase 1 (CPT1), and ethanolamine phosphotransferase 1 (EPT1), were also targeted for drug-target Mendelian randomization.

Results: The study found that phosphatidylcholines (OR $_{IVW}$: 0.88, 95%CI: 0.80–0.96, p = 0.005) and phospholipids in medium HDL (OR $_{IVW}$: 0.86, 95%CI: 0.77–0.96, p = 0.007) potentially exhibit a protective effect against sepsis nominally. However, the potential drug target of CEPT1, CPT1, and EPT1 was found to be unrelated to septic outcomes.

Conclusion: Our findings suggest that increasing levels of phosphatidylcholines and medium HDL phospholipids may reduce the incidence of sepsis. This highlights the potential of lipid-based biomarkers in the diagnosis and management of sepsis, opening avenues for new therapeutic strategies.

1. Introduction

Sepsis, a critical and often fatal condition, arises when the body's response to an infection spirals out of control, leading to widespread inflammation and severe organ dysfunction [1–5]. This complex syndrome is among the leading causes of mortality in intensive care units worldwide, accounting for substantial healthcare burdens [6–10]. The pathophysiology of sepsis involves a

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cascade of events, including immune system dysregulation, endothelial damage, and coagulopathy, culminating in a state of systemic inflammatory response syndrome (SIRS) [11–13]. Despite advancements in medical care, the incidence of sepsis continues to rise, attributed to an aging population, increased antibiotic resistance, and greater recognition of the condition. The insidious onset and rapid progression of sepsis necessitate prompt diagnosis and intervention; however, its non-specific symptoms often complicate timely identification, thereby increasing the risk of adverse outcomes, including multi-organ failure and death. The complexity of sepsis, coupled with its high mortality rate, underscores the urgency for continued research into its mechanisms and potential biomarkers for early detection and improved treatment strategies.

The intricate interplay between sepsis and metabolic pathways, particularly lipid and amino acid metabolism, is a burgeoning area of research that holds significant implications for understanding and managing this complex condition [14–16]. In the state of sepsis, the body's metabolic demands dramatically alter, with lipid metabolism playing a pivotal role [14,17]. Lipids, primarily known for their energy storage and structural functions, assume critical roles in modulating immune responses and cell signaling pathways during septic conditions. The disruption of lipid homeostasis in sepsis is marked by changes in the composition and function of lipoproteins, alterations in fatty acid metabolism, and the dysregulation of lipid mediators such as eicosanoids, which are vital in inflammation and immune modulation [18,19]. Moreover, the role of amino acids in sepsis extends beyond their basic function as protein building blocks [20,21]. Amino acids, particularly branched-chain amino acids (BCAAs), are essential in modulating immune responses, synthesizing acute-phase proteins, and maintaining gut integrity, all of which are crucial during septic shock [22,23]. The perturbation in amino acid metabolism observed in septic patients often leads to an imbalanced nitrogen homeostasis, contributing to muscle wasting and weakened immune responses, exacerbating the severity of the condition [24,25]. Furthermore, emerging evidence suggests a bidirectional relationship between sepsis and these metabolic pathways [26,27]. Sepsis-induced alterations in lipid and amino acid metabolism can exacerbate the inflammatory response and organ dysfunction, creating a vicious cycle of metabolic derangements and worsening clinical outcomes [28,29]. Conversely, pre-existing metabolic conditions, such as dyslipidemia or amino acid imbalances, can predispose individuals to a more severe septic response, highlighting the importance of metabolic health in the context of sepsis [24]. The exploration of lipid and amino acid profiles in sepsis has led to the identification of several potential biomarkers. These biomarkers not only shed light on the underlying metabolic disturbances in sepsis but also offer prospects for the development of targeted therapeutic strategies [4,30]. For instance, alterations in specific phospholipids and sphingolipids have been correlated with sepsis severity and outcomes, suggesting their role as potential prognostic or diagnostic markers [26,31]. Similarly, changes in amino acid profiles, especially in the concentrations of arginine, glutamine, and BCAAs, have been associated with immune dysfunction and mortality in septic patients [32]. Thus, understanding the complex relationship between sepsis and lipid and amino acid metabolism is crucial for developing novel diagnostic tools and therapeutic interventions. This relationship underscores the necessity of a holistic approach in sepsis management, encompassing not just the immediate infectious insult but also the broader metabolic disturbances that accompany this debilitating condition.

Mendelian Randomization (MR) offers a unique approach in epidemiological studies, leveraging genetic variants as instrumental variables to infer causal relationships between modifiable exposures and clinical outcomes [33,34]. This method, grounded in the principle of random assortment of alleles at conception, mitigates the confounding factors and reverse causation often encountered in observational studies. MR's robustness stems from its reliance on genetic variants which are fixed at birth and thus not susceptible to the influences that typically bias observational research. This approach has gained prominence in elucidating the etiological roles of various biomarkers and exposures in complex diseases, including sepsis.

In our study, we employed two-sample Mendelian Randomization to investigate the causal role of lipid and amino acid metabolism in sepsis. Utilizing large-scale Genome-wide association studies (GWAS) summary data, we identified genetic variants associated with specific lipid and amino acid levels. These variants served as instrumental variables to assess the impact of these metabolic factors on sepsis risk and outcomes. Additionally, we explored the enzymatic targets involved in phosphatidylcholine metabolism-choline/ethanolamine phosphotransferase 1 (CEPT1), choline phosphotransferase 1 (CPT1), and ethanolamine phosphotransferase 1 (EPT1)-using drug target Mendelian Randomization. This allowed us to assess the potential of these enzymes as therapeutic targets in sepsis.

2. Method

2.1. Instrumental variables

In our comprehensive study, genetic variants associated with 249 serum lipidomic and amino acid traits were extracted from the extensive GWAS dataset (https://gwas.mrcieu.ac.uk/datasets/?gwas_id__icontains=met-d), which encompasses 115,078 individuals of European descent (Supplementary Table S1 for details). The 249 serum lipidomic and amino acid traits were investigated by Nightingale Health and UK Biobank, which launched a significant initiative to analyze 500,000 blood samples using advanced biomarker technology to enhance global medical research. This project, which represents a 10 million EUR investment by Nightingale Health, aims to uncover metabolic signatures that indicate risk factors for diseases such as heart disease and type 2 diabetes. The findings, which integrate lifestyle and genetic data from UK Biobank participants, will be made available to the global scientific community after a 9-month exclusivity period. The analyses will be performed in Nightingale's laboratory in Finland and are expected to provide new insights into health and disease, potentially aiding drug development and improving public health.

In the main analysis of Mendelian randomization, it is crucial to explicitly state the three core instrumental variable (IV) assumptions: relevance, independence, and exclusion restriction. The relevance assumption requires that the genetic variants used as instruments are strongly associated with the exposure of interest. The independence assumption stipulates that the selected genetic

variants are not associated with any confounders that might influence both the exposure and the outcome. Finally, the exclusion restriction assumption mandates that the genetic variants affect the outcomes. Our rigorous selection criteria for single nucleotide polymorphisms (SNPs) included a significance threshold set at $p < 5 \times 10^{-8}$ and a strict linkage disequilibrium cutoff ($R^2 < 0.001$ within a 10,000 kb window) to ensure robust analytical power. Furthermore, the F-statistic for each instrumental variable was calculated, and those with an F-statistic <10 were excluded to avoid weak instrumental bias.

2.2. Sepsis GWAS summary data

Our study utilized GWAS summary data from the OpenGWAS project (ID: ieu-b-4980, https://gwas.mrcieu.ac.uk/datasets/ieu-b-4980/), derived from the UK Biobank with European population. The sepsis dataset comprised 11,643 cases and 474,841 controls, totaling a sample size of 486,484 individuals. This dataset included an extensive number of 12,243,539 SNPs. The sepsis GWAS data, coded using Hospital Episode Statistics (HES) and confined to secondary care, were analyzed using regenie v2.2.4, with adjustments made for age, sex, chip, and the first 10 principal component analyses (PCAs). Cases of sepsis were identified in UK Biobank linked ICD-coded hospital admission data. ICD-10 codes A02, A39, A40 and A41 were used to identify sepsis. Cases were included if the code was in either the primary or secondary diagnostic position in the linked HES data [35].

2.3. Mendelian randomization

Our study employed the inverse-variance weighted (IVW) method as our primary analytical tool. For traits that exhibited significant IVW results, we conducted further sensitivity analyses utilizing various alternative Mendelian randomization (MR) methods, such as the weighted median estimator, MR-Egger regression, simple mode, and weighted mode. The results were presented with odds ratios (ORs) and corresponding 95 % confidence intervals (CIs). We rigorously tested the validity of MR assumptions, including the absence of pleiotropy and heterogeneity, using the Cochrane Q test and MR-Egger intercept regression, respectively. And he leave-one-out analysis was conducted for robust MR analysis.

2.4. Drug target Mendelian randomization

For the drug target MR, we obtained GWAS summary data specific to phosphatidylcholines. In most mammalian cells, phosphatidylcholine is synthesized primarily through the Kennedy pathway, with its final enzymatic step catalyzed by choline/ethanolamine phosphotransferases, including choline/ethanolamine phosphotransferase 1 (CEPT1), choline phosphotransferase 1A (CPT1A), choline phosphotransferase 1B (CPT1B) and ethanolamine phosphotransferase 1 (EPT1) [36]. SNPs within ±2000 Kb *cis*-windows

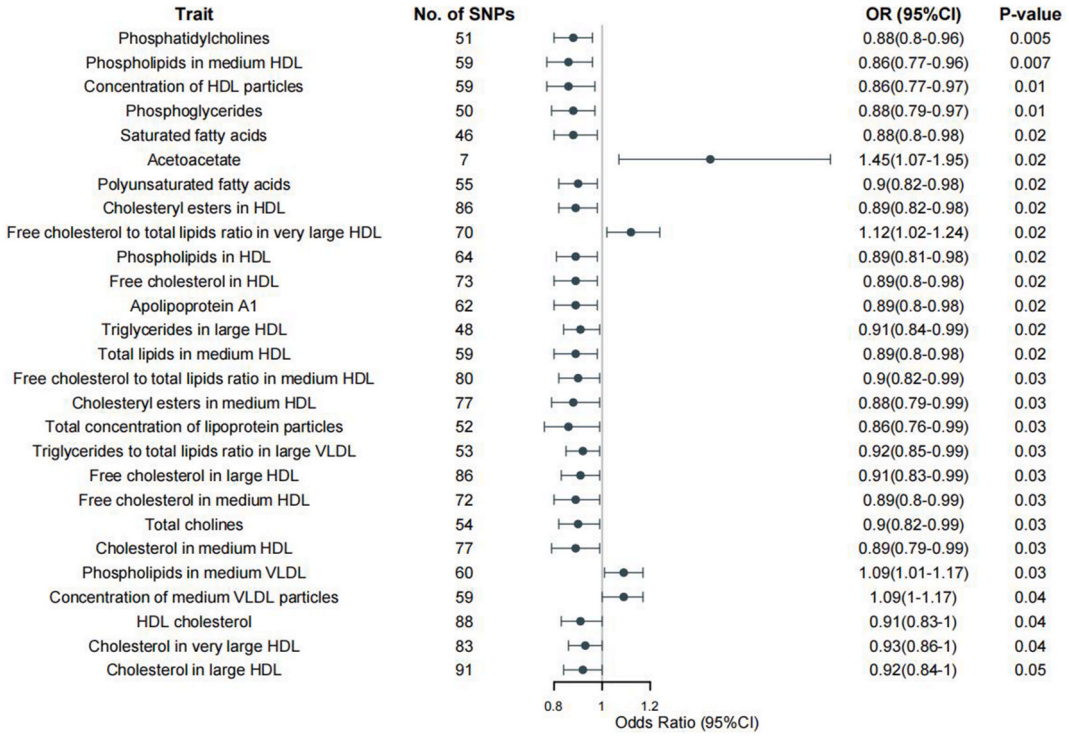

Fig. 1. MR results of 249 serum lipidomic, amino acid traits and sepsis.

around those genes, which had strong association with phosphatidylcholines ($p < 5 \times 10^{-8}$) and with an $R^2 < 0.3$ were selected as instrumental variables for drug target MR.This approach enabled us to investigate the potential of these enzymes as therapeutic targets in sepsis, examining their activity in relation to the development of the condition through downstream effects on phosphatidylcholines synthesis. Given the large number of lipidomic and amino acid traits analyzed (252 in total with TSMR and drug target MR), we considered $p < 0.01$ as nominally significant, and significant association was determined based on a Bonferroni-adjusted p-value threshold of 0.00019 (calculated as 0.05/252). However, due to the interdependencies among these exposures, we recognized that the Bonferroni correction might be overly stringent. The remaining analytical methods mirrored those used in the two-sample MR analysis described above.

2.5. Statistical analysis

Our MR study adheres to the STROBE-MR guidelines (as shown in Supplementary File 1) [37]. All statistical analyses were meticulously performed using the R software (Version 4.1.3).

3. Result

3.1. Two-sample Mendelian randomization analysis

Our analysis encompassed 249 serum lipidomic and amino acid traits, with the instrumental variables for each trait detailed in Table S2. This table includes information including the SNP rsid, chromosomal location, effect sizes (betas), standard errors (SEs), and p-values for both the exposure and outcome variables. Comprehensive results of all MR analysis are presented in Table S3. As shown in Fig. 1, we found that 26 serum lipidomic and amino acid traits have p-values <0.05 with sepsis. After applying the stringent Bonferroni correction, none of the results retained significance under the adjusted threshold. However, when a more lenient threshold of $p = 0.01$ was used, two lipid traits emerged as nominally significant: Phosphatidylcholines, $OR_{IVW} = 0.88$,95%CI = 0.8–0.96, $p = 0.005$, Phospholipids in medium HDL, $OR_{IVW} = 0.86$,95%CI = 0.77–0.96, $p = 0.007$. These findings suggest a protective effect of these lipid traits against sepsis, as illustrated in Figs. 2 and 3. Tests for heterogeneity and pleiotropy revealed no significant issues, indicating the robustness of our findings. The MR-Egger intercept regression indicated no apparent horizontal pleiotropy (all p-values >0.05) (Supplementary Table S4). Cochrane Q test found that heterogeneity did not exist in the study outcomes (all p-values >0.05) (Supplementary Table S5). Our analysis was further supported by a leave one out analysis, the results of which are shown in Supplementary Figs. S1 and S2.

3.2. Drug target Mendelian randomization analysis

In the drug target MR analysis focusing on phosphatidylcholine synthesis, no significant SNPs were found within the *cis*-window regions of choline/ethanolamine phosphotransferase 1 (CEPT1) and choline phosphotransferase 1 (CPT1). This suggests that these two enzymes are not suitable drug targets for regulating phosphatidylcholine levels in the context of sepsis treatment. Conversely, significant SNPs were identified in the *cis*-window region of ethanolamine phosphotransferase 1 (EPT1), which were used as instrumental variables after clumping ($r^2 < 0.3$), as detailed in Table S6. However, our results indicated no significant association between the concentration of phosphatidylcholine using SNPs from EPT1 and sepsis, as shown in Table S6. Therefore, none of the three enzymes examined-CEPT1, CPT1, and EPT1-appear to be viable drug targets for manipulating phosphatidylcholine levels in the treatment of

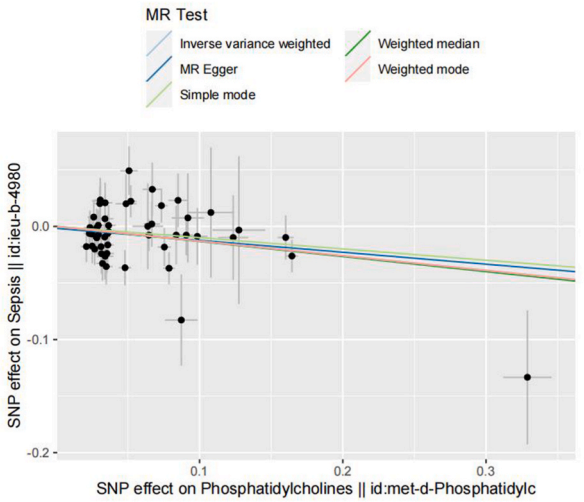

Fig. 2. The scatter plot of MR analysis of phosphatidylcholines on sepsis.

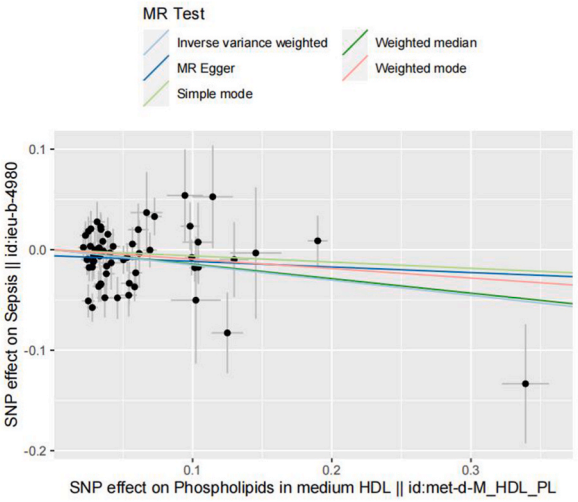

Fig. 3. The scatter plot of MR analysis of phospholipids on sepsis.

sepsis.

4. Discussion

In this study, we conducted a comprehensive two-sample Mendelian Randomization (MR) analysis to explore the potential causal associations between serum lipidomic and amino acid biomarkers and sepsis. Utilizing genetic variants associated with 249 serum lipidomic and amino acid traits, we identified potential associations between several lipid traits and sepsis nominally. Notably, phosphatidylcholines and phospholipids in medium HDL nominally exhibited a protective effect against sepsis. Additionally, we conducted a drug target MR analysis focusing on the synthesis of phosphatidylcholines, targeting key enzymes like CEPT1, CPT1, and EPT1. This analysis revealed that none of these enzymes were suitable drug targets for regulating phosphatidylcholine levels in sepsis treatment, as significant associations were not found between their related SNPs and sepsis outcomes. Our results suggest a potential protective role of certain lipid traits against sepsis and underscore the complexity of the lipidomic profile in relation to this severe condition. This opens new avenues for further research into lipid-based biomarkers for the diagnosis and management of sepsis, although the potential for direct therapeutic targeting remains uncertain. The robustness of our findings is supported by the absence of significant issues in tests for heterogeneity and pleiotropy, and further reinforced by leave one out analyses.

Recent Mendelian randomization studies have identified significant associations between lipids and sepsis. One study found that genetically predicted levels of omega-3 and DHA are suggestively associated with a reduced risk of sepsis and sepsis-related mortality. In contrast, a higher genetic predisposition for the omega-6:3 ratio increases the risk of sepsis-induced mortality, with sensitivity analyses confirming no significant horizontal pleiotropy [38]. Another study indicated that elevated LDL-C levels may increase the risk of sepsis, although the association was not statistically significant. No causal relationships were found between triglyceride and HDL-C levels and the risk of sepsis [39]. Furthermore, higher levels of phospholipids in medium, large, and very large HDL particles are suggestively associated with a reduced risk of sepsis [40]. Additionally, higher levels of ApoA-I and HDL-C were found to be associated with a reduced risk of total sepsis and 28-day mortality, while HMGCR and CETP inhibitors, influenced by lipid levels, showed a protective effect against sepsis. Reverse MR analysis suggested that sepsis can lead to altered HDL-C and triglyceride levels, with BMI negatively affecting the efficacy of HMGCR inhibitors in sepsis treatment [41]. These findings indicate a close relationship between lipids and their related pathways and sepsis. However, our study did not find any association between amino acids, including alanine, glycine, histidine, isoleucine, leucine, phenylalanine, tyrosine, and valine, and the risk of sepsis, which is consistent with the conclusions of similar studies [42,43].

The relationship between phosphatidylcholines and sepsis, as illuminated by our study, offers intriguing insights into the pathophysiology of sepsis and its potential therapeutic avenues. Phosphatidylcholines, a major class of phospholipids, play a crucial role in cellular membrane integrity and function [44,45]. In the context of sepsis, these compounds appear to exert a protective effect, as evidenced by the reduced odds of sepsis with higher levels of phosphatidylcholines. One possible pathway through which phosphatidylcholines may influence sepsis outcomes is via their role in modulating inflammation [46,47]. Sepsis is characterized by an uncontrolled inflammatory response, and phosphatidylcholines are known to be involved in the regulation of inflammatory processes. They may act as anti-inflammatory agents, helping to dampen the excessive immune response seen in sepsis. This could be through the alteration of membrane lipid composition, which in turn affects the function of membrane-bound proteins involved in signaling pathways critical to the inflammatory response. Another potential mechanism is through the maintenance of endothelial barrier integrity [48,49]. The endothelial dysfunction observed in sepsis leads to increased vascular permeability, contributing to organ dysfunction and failure. Phosphatidylcholines are integral components of cell membranes and are essential for maintaining the structural integrity of endothelial cells. By stabilizing these cells, phosphatidylcholines might reduce the vascular leakage and

subsequent tissue edema that are hallmark features of sepsis. Additionally, phosphatidylcholines play a significant role in lipid metabolism and transport [50,51]. In sepsis, dysregulation of lipid metabolism is common, and phosphatidylcholines could help in normalizing these disturbances. They are involved in the formation of lipoproteins, which are crucial for the transport of lipids in the blood. Therefore, higher levels of phosphatidylcholines might facilitate the efficient transport and utilization of lipids, which is vital in the energy-demanding condition of sepsis. It's also worth considering the role of phosphatidylcholines in modulating the immune response. They are involved in the formation of lipid rafts, specialized microdomains in cell membranes, which are important for the signaling of immune cells. Thus, phosphatidylcholines might influence the behavior of immune cells during sepsis, possibly contributing to a more regulated immune response. In conclusion, the relationship between phosphatidylcholines and sepsis is multifaceted, involving mechanisms like modulation of inflammation, maintenance of endothelial and gut barrier integrity, normalization of lipid metabolism and transport and regulation of immune cell signaling. These findings open multiple pathways for further research and potential therapeutic interventions in the management of sepsis. However, the exact mechanisms and the extent of the impact of phosphatidylcholines on sepsis need to be explored in more detail in future studies.

The association between phospholipids and sepsis, as highlighted in our study, provides valuable insights into the potential mechanisms underlying sepsis pathophysiology. Phospholipids, a diverse group of lipids that include phosphatidylcholines, are key components of cell membranes and play vital roles in various cellular processes. In the context of sepsis, these lipids could have significant implications for the disease's progression and outcomes. Phospholipids are crucial in maintaining cellular membrane stability and integrity [52,53]. During sepsis, cellular membranes are subjected to oxidative stress and inflammatory damage, leading to cell dysfunction and death. By maintaining membrane integrity, phospholipids might help protect cells from the detrimental effects of sepsis-induced inflammation and oxidative stress. This protective role is especially critical in maintaining the function of vital organs that are commonly affected in sepsis, such as the lungs, kidneys, and heart. Furthermore, phospholipids are involved in the modulation of inflammation, a core aspect of sepsis. They can influence the activity of various signaling molecules and pathways involved in the inflammatory response. For instance, certain phospholipids can act as precursors to pro-inflammatory or anti-inflammatory mediators [54–56]. The balance between different types of phospholipids might therefore influence the severity and progression of the inflammatory response in sepsis. The role of phospholipids in coagulation is also noteworthy. Sepsis often leads to coagulation abnormalities, contributing to organ dysfunction [11,12]. Phospholipids play a role in the coagulation cascade, and alterations in their levels or composition could impact the coagulation process during sepsis [57–59]. By modulating coagulation, phospholipids may influence the risk of disseminated intravascular coagulation, a serious complication of sepsis. In addition, phospholipids are integral to the function of immune cells. They participate in the formation of lipid rafts, which are important in the signaling of immune cells. Changes in phospholipid composition can alter immune cell function, potentially affecting the body's ability to fight the infection underlying sepsis. In summary, phospholipids may influence sepsis pathophysiology through various mechanisms, including maintaining cellular membrane integrity, modulating inflammation and coagulation, influencing immune cell function. These multifaceted roles underscore the potential of phospholipids as biomarkers and therapeutic targets in sepsis, warranting further investigation into their specific functions and impacts in this complex condition.

Our study, while providing valuable insights into the potential associations between serum lipidomic profile, amino acid biomarkers, and sepsis, does have several limitations that should be considered. First and foremost, the nature of Mendelian Randomization implies that our findings are observational and cannot definitively establish causality. Despite the robust statistical methods employed, the possibility of residual confounding cannot be completely excluded. Another limitation is the reliance on data from individuals of European descent, which may limit the generalizability of our findings to other populations. The genetic diversity and environmental factors that vary across different ethnicities and geographical locations could influence the associations observed in our study. Additionally, our study focused on a predefined set of lipid and amino acid markers, which may not encompass all the relevant biomarkers involved in sepsis. The complexity of sepsis pathophysiology means that there could be other important metabolic pathways and markers that were not considered in our analysis. The application of the Bonferroni correction for multiple testing, while necessary to reduce the chance of false positives, might have been overly stringent. This could have led to the underestimation of potentially significant associations. Similarly, the use of a more lenient threshold for significance might have increased the risk of type I errors. Furthermore, the drug target Mendelian Randomization analysis did not identify any significant associations with the enzymes targeted for phosphatidylcholine synthesis in the context of sepsis treatment. This highlights the complexity of targeting metabolic pathways in sepsis and suggests that the potential therapeutic targets may be more intricate than initially presumed. Another notable limitation of our study is the inability to perform a reverse Mendelian Randomization analysis, where sepsis would be treated as the exposure rather than the outcome. This approach could have provided valuable insights into whether sepsis risk influences lipid and amino acid metabolism. Unfortunately, suitable instrumental variables for sepsis are currently unavailable, which precludes this line of investigation. This absence of appropriate instruments limits our ability to explore the bidirectional causal relationship between sepsis and lipid or amino acid biomarkers. Understanding whether sepsis itself can causally influence lipid and amino acid metabolism could reveal critical aspects of disease progression and recovery. Without the reverse MR analysis, our understanding remains unidirectional. Future research should prioritize developing and validating genetic instruments for sepsis. This would allow for a comprehensive bidirectional analysis, shedding light on the complex interplay between sepsis and metabolic profiles. Finally, we acknowledge that the potential sample overlap between the exposure and outcome datasets, both derived from the UK Biobank, represents a significant limitation of our study. This overlap could introduce bias into our two-sample MR analyses, potentially affecting the reliability of our findings. While previous research has suggested that two-sample MR methods can be safely utilized within large biobanks, except for MR-Egger, it is crucial to interpret our results with caution [60]. The possibility of shared participants between the metabolic biomarkers and sepsis datasets may confound our associations, and thus, the conclusions drawn from our analyses should be considered with this limitation in mind. Future studies utilizing independent datasets would be beneficial to validate our findings and further

elucidate the relationships between lipids, metabolic pathways, and sepsis risk. In conclusion, while our study contributes to the understanding of lipid and amino acid metabolism in sepsis, the findings should be interpreted with caution due to the aforementioned limitations. Future research, ideally incorporating diverse populations and a broader range of biomarkers, is needed to validate and expand upon our findings.

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Data Availability Statement

Data included in article/supp. material/referenced in article. The original contributions made to this study are included in the article/supplementary material, and further inquiries can be directed to the corresponding author.

Ethical Approval

Not applicable.

CRediT authorship contribution statement

Zi-gang Zhu: Writing – original draft, Investigation. **Jia-wei Ma:** Investigation, Funding acquisition, Formal analysis. **Dan-dan Ji:** Formal analysis, Data curation. **Qian-qian Li:** Formal analysis, Data curation. **Xin-yu Diao:** Investigation, Formal analysis. **Jie Bao:** Writing – review & editing, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32779.

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