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Causal relationship between lipidome and acute respiratory distress syndrome

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Acute respiratory distress syndrome (ARDS), with high morbidity and mortality, is a common clinical syndrome of acute respiratory failure caused by diffuse lung inflammation and edema. ARDS can precipitate in various ways. The complex pathophysiology of ARDS involves the activation and dysregulation of multiple metabolisms and immune responses. Using summary-level data from a genome-wide association study (GWAS), a two-sample Mendelian randomization (MR) analysis of 179 genetically predicted lipid species and ARDS (375 cases, 406,518 controls) was performed and validated in plasma and pulmonary edema fluid from 24 patients. Furthermore, we used a two-step MR to quantify the effect of immune cell-mediated lipids on ARDS. We identified 8 lipids (Cholesterol, Phosphatidylcholine (14:0_16:0), Phosphatidylcholine (16:0_20:5), Phosphatidylcholine (18:0_18:2), Phosphatidylethanolamine (18:1_18:1), Triacylglycerol (51:2), Triacylglycerol (52:4), and Triacylglycerol (54:3)) associated with ARDS. The proportions of genetically-predicted lipids mediated by the four types of immune cells were determined. Sensitivity analysis did not reveal any obvious pleiotropy or heterogeneity. Our study demonstrates the power of multivariate genetic analysis in correlated lipidomic data and reveals genetic links between ARDS and lipid species beyond standard lipids.

Keywords ARDS, Lipid, Mendelian randomization, Causal relationship, GWAS analysis

ARDS, with high morbidity and mortality, is a clinical syndrome marked by acute respiratory failure caused by lung inflammation. It can be triggered by various factors, with pneumonia (both bacterial and viral) being the most common cause[1,2]. Non-pulmonary sepsis is also a frequent contributor. ARDS is characterized by widespread alveolar injury, including excessive inflammation, increased permeability of the lung's epithelial and vascular tissues, alveolar edema, and the formation of hyaline membranes[3–5].

Lipid mediators derived from fatty acids play crucial roles in the natural regulation of infections and inflammation[6,7]. In the past few years, there has been a growing acknowledgment that the resolution of inflammation and the restoration of homeostasis are not passive events. Specialized pro-resolving mediators (SPMs), which are derived from polyunsaturated fatty acids (PUFAs), have emerged as critical signaling molecules in the resolution of inflammation. These SPMs play a significant role in attenuating the inflammatory response without inducing immunosuppression[8,9]. Advancements in lipidomic technologies have greatly expanded our knowledge of the diverse range and abundance of circulating lipids. These lipid species encompass a wide array of compounds, including cholesterol esters (CEs), ceramides (CERs), diacylglycerols (DAGs), lysophosphatidylcholines (LPCs), phosphatidylcholines (PCs), phosphatidylethanolamines (PEs), sphingomyelins (SMs), and triacylglycerols (TAGs). These modern and efficient lipidomic technologies have significantly enhanced our understanding of the complexity and diversity of lipids present in circulation[10–13].

As genomics continues to advance, there is mounting evidence highlighting the influence of heritability in the development of diseases. Mendelian randomization (MR), a methodology built upon genome-wide association studies (GWASs), utilizes specific genetic variants as instrumental variables (IVs). These IVs demonstrate a robust association with the exposure under investigation and remain unaffected by confounding factors. By leveraging MR, researchers can infer the causal effects of exposures on various outcomes[14]. In this context, univariate MR analysis was conducted to investigate the causal effects of different lipid types on the risk of ARDS.

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Materials and methods

Study design

We consecutively included 24 adult patients (> 18 years old) who met the ARDS Berlin definition for the first incidence of ARDS in the medical intensive care unit (ICU) at the China-Japan Friendship Hospital from November 1, 2022 to December 30, 2023 (Clinicaltrials.gov NCT06123962). The exclusion criteria were as follows: chronic respiratory failure due to chronic respiratory diseases, such as chronic obstructive pulmonary disease; bronchiectasis or lung fibrosis; AKI prior to the onset of ARDS; and inability or unwillingness to provide informed consent. Patients with ARDS undergoing invasive ventilation were categorized on the day of ARDS diagnosis based on their Pao_2/Fio_2 ratio into mild ($200 < Pao_2/Fio_2 \leq 300$ mm Hg), moderate ($100 < Pao_2/Fio_2 \leq 200$ mm Hg), and severe ($Pao_2/Fio_2 < 100$ mmHg) based on the Berlin Definition. We examined metabolites in the serum of 24 patients and in the pulmonary edema fluid of 19 of them. The studies involving human participants were reviewed and approved by the Ethics Committee of the China-Japan Friendship Hospital(NO.2023-ky-152). All methods were performed in accordance with the relevant guidelines and regulations. For experiments involving human participants, informed consent from all subjects or their legal guardians have been obtained. We have commissioned Wuhan Maiwei Metabolomics Company to conduct the detection of metabolites using LC-MS/MS.

The GWAS data utilized in our analysis were obtained from publicly available sources and were approved by the institutional review committees of the respective studies. As a result, no additional sanctions or ethical approvals were needed for this study. All the results generated from our analysis are thoroughly presented in this article and its accompanying supplementary materials.

In this study, we explored the reciprocal causal relationship between lipids and ARDS using a two-sample bidirectional MR. In our study, single nucleotide polymorphisms (SNPs) were defined as IVs[15] .

GWAS summary data sources

ARDS data were drawn from the GWAS summary data sources on the FennGenn consortium, (available at https://www.finngen.fi/en). The univariate GWAS summary statistics generated in this study have been deposited in the GWAS catalog under the following accession codes: Lipid species, GCST90277238-GCST90277416; immune cells, GCST90001391-GCST90002121.

Instrumental variable selection and data harmonization

We incorporated SNPs that achieved genome-wide significance ($P < 5 \times 10^{-8}$) into our analysis. Subsequently, these SNPs were grouped together based on linkage disequilibrium, utilizing a window size of 10,000 kb and an r2 value below 0.001. Estimated levels of linkage disequilibrium from the 1000 Genomes Project based on European samples[16]. If a specific exposed SNP was not present in the outcome dataset, proxy SNPs were employed through LD tagging. Palindromic and ambiguous SNPs were excluded from the instrumental variables used in the Mendelian randomization analysis[17]. The F statistic was calculated based on the variance explained by SNPs for each exposure, i.e., $[(N–K–1)/K]/[R2/(1–R2)]$, where K represents the number of genetic variants and N is the sample size. Weak instrumental variables (F-statistics < 10) were removed[18].

Statistical analysis

The Mendelian randomization (MR) analysis was conducted using R software (version 4.2.0, http://www.r-project.org) and the "Two-Sample MR" package (version 0.5.6)[19]. To assess and address pleiotropy, we employed MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO), utilizing the R packages "MRPRESSO". Additionally, we calculated the statistical power for Mendelian randomization using mRnd (https://cnsgenomics.shinyapps.io/mRnd/).

Primary analysis

To combine the Wald ratios of causal effects for each SNP, we employed the inverse variance weighting (IVW) method, which utilizes meta-analysis[20]. Additionally, we used complementary approaches to IVW, including MR-Egger[21], weighted-median methods[22], simple mode, and weighted mode as complementary approaches to IVW. These methods were chosen to accommodate different validity assumptions and obtain robust MR estimates. IVW assumes the validity of all instrumental variables, providing accurate estimation results. MR-Egger, on the other hand, assesses directional pleiotropy by estimating the average pleiotropy of genetic variation through the intercept. The weighted median approach maintains higher precision (smaller standard deviation) compared to MR-Egger and provides consistent estimates even in the presence of horizontal pleiotropy, even if 50% of the instrumental variables are invalid[23].

Mediation analysis

To investigate the potential mediation of immune cells in the causal pathway from lipids to ARDS outcome, we conducted a two-step MR design mediation analysis[24]. This analysis allowed us to examine two components: the direct effect of lipids on ARDS, which operates independently of immune cells, and the indirect effect mediated through immune cells. We first assessed the direct effects of lipids on ARDS, representing the causal pathway without mediation. Then, we evaluated the indirect effects, which involve the influence of lipids on immune cells and subsequently the impact of immune cells on ARDS. By separating the total effect of lipids on ARDS into these direct and indirect effects mediated by immune cells[25].

Sensitivity analysis

To determine the causal direction of each SNP in relation to the exposure and outcome, we conducted MR Steiger filtering[26].This method involves calculating the variance explained in the exposure using instrumental

SNPs and examining whether the variance in the outcome is less than that in the exposure. "TRUE" MR Steiger results indicate causality in the expected direction, while "FALSE" results suggest causality in the opposite direction. We excluded SNPs with "FALSE" results, as they indicated a significant impact on the outcome rather than the exposure[27]. Horizontal pleiotropy was detected using the MR-Egger intercept method and the MRPRESSO method[28]. In the case of outlier detection, those outliers were removed, and we re-evaluated the MR causal estimates. If significant heterogeneity persisted even after outlier removal, we employed a random effects model to assess the stability of the results. This model is less sensitive to weaker associations between SNPs and exposure. Lastly, we conducted a leave-one-out analysis to validate the effect of each SNP on the overall causal estimates. This involved systematically removing one SNP at a time and reassessing the causal estimates to evaluate the influence of individual SNPs on the overall results.

Result

Defining the causal link between various lipids and ARDS

To assess the influence of lipid species on the risk of ARDS, two-sample MR analysis of 179 lipids in 357 individuals with ARDS from the total 406,893 FinnGen participants was performed. The univariate MR analysis revealed that eight lipids were associated with ARDS (Table 1, Fig. 1and Supplementary Table 1). Three of these (Cholesterol, Phosphatidylcholine(14:0_16:0), and Phosphatidylcholine(16:0_20:5)) could reduce the risk of ARDS, while the other five (Phosphatidylcholine(18:0_18:2), Phosphatidylethanolamine(18:1_18:1), Triacylglycerol(51:2), Triacylglycerol(52:4), and Triacylglycerol(54:3)) could have the opposite effect. Furthermore, neither the MR-Egger intercept nor the MR-PRESSO global tests provided evidence of directional pleiotropy or heterogeneity for any causal association (Supplementary Table 2).

Reverse MRI analysis was conducted to explore the possibility of reverse causality. The results in Table 2 indicate a lack of reverse causality between Phosphatidylcholine(14:0_16:0), Phosphatidylcholine(18:0_18:2), and Phosphatidylethanolamine(18:1_18:1) and ARDS. Moreover, ARDS was linked with elevated GCST90277257, GCST90277288, GCST90277393, GCST90277398, and GCST90277404 levels.

To verify the results of the MR analysis, we examined the expression of eight lipids in the plasma of patients with no ARDS, mild ARDS, and severe ARDS. We also compared the expression levels in the pulmonary edema fluid and plasma of severe ARDS patients. The results are shown in Fig. 2 and the clinical information of the patients is shown in Supplementary Table 3. We found that in the plasma, Phosphatidylethanolamine (18:1_18:1) and Triacylglycerol (54:3) have a positive association with ARDS, while Cholesterol, Phosphatidylcholine (14:0_16:0), and Phosphatidylcholine (16:0_20:5) have a negative association with ARDS. This result is the same as that of the MR analysis. However, the CV of Phosphatidylcholine (18:0_18:2) was too small, and the raw intensity could not be calculated. No significant differences were observed in the trends of Triacylglycerol (51:2) and Triacylglycerol (52:4) .

Defining the causal link between the lipids and immune cells

According to the IVW, 35 genetically-predicted immune cells were positively associated with increased ARDS risk. The results are shown in Supplementary Tables 4 and 5. As shown in Table 3 and Supplementary Table 6, genetically-predicted immune cells were significantly and positively correlated with lipids using the IVW method. The estimation directions of the five methods (IVW, MR-Egger, weighted median, simple mode, and weighted mode) were consistent.

Proportion of the association between lipids and ARDS mediated by immune cells

We analyzed immune cells as mediators of the pathway from lipids to ARDS. We found that lipids were associated with immune cells, which, in turn, were associated with the risk of ARDS. As shown in Fig. 3, our study showed that Naive CD4+ %CD4+, CD8dim NKT %T cells, and CD3 on HLA-DR + T cells accounted for 2.22%, 2.85%, and 2.57% of the increased risk of ARDS associated with lipids and FSC-A on lymphocytes, respectively (2.05%).

Discussion

Lipidomics has emerged as a valuable tool in clinical studies for examining lipid metabolism and the interplay between metabolic changes and the immune system by profiling lipid mediators[9]. However, the existing evidence primarily relies on observational studies, which are susceptible to confounding factors. To address this limitation, our study aimed to investigate the causal effects of lipids on ARDS. We employed MR analysis to explore the association between lipids and ARDS, utilizing data from existing GWAS. Furthermore, we sought to determine whether the relationship between lipids and ARDS is mediated by immune cells. By leveraging genetic instrumental variables, our MR analysis provides insights into causal inference. Our findings indicate that genetically predicted elevated levels of cholesterol, PC (phosphatidylcholine), PE (phosphatidylethanolamine), and TAG (triacylglycerol) are associated with an increased risk of ARDS. Additionally, we estimated that approximately 2% of this effect is mediated by immune cells, highlighting their potential role in the mechanism linking lipids and ARDS. These results contribute to a better understanding of the causal relationship between lipids and ARDS, shedding light on the underlying biological pathways involved.

Previous studies have highlighted the diverse roles of cholesterol in normal lung physiology. For instance, cholesterol plays a crucial role in surfactant integration and facilitates the delivery of the antioxidant Vitamin E to type II pneumocytes[29,30]. Moreover, cholesterol is involved in various disease processes. Oxidized LDL (low-density lipoprotein) interacts with Toll-like receptor 4, leading to the upregulation of innate immunity. Additionally, lipoproteins containing cholesterol can bind to and neutralize lipopolysaccharide (LPS), a component of the cell membrane in gram-negative bacteria that triggers inflammation through the innate immune system. This cholesterol-mediated interaction with LPS potentially offers a protective mechanism

Traits	Exposure	SNPs	Method	b	se	p-value	OR (95% CI)
Cholesterol	GCST90277257	33	MR Egger	− 0.5787	0.4088	0.1668	0.5605 (0.2515–1.2492)
			Weighted median	− 0.4422	0.2560	0.0841	0.6425 (0.3889–1.0614)
			Inverse variance weighted	− 0.3882	0.1752	0.0267*	0.6782 (0.4881–0.9561)
			Simple mode	− 0.8989	0.5160	0.0911	0.4070 (0.1480–1.1191)
			Weighted mode	− 0.7599	0.5080	0.1444	0.4676 (0.1727–1.2659)
Phosphatidylcholine (14:0_16:0)	GCST90277272	19	MR Egger	− 0.7817	0.4734	0.1170	0.4576 (0.1809–1.1575)
			Weighted median	− 0.4564	0.2670	0.0873	0.6335 (0.3753–1.0691)
			Inverse variance weighted	− 0.4640	0.1960	0.0179*	0.6287 (0.4281–0.9232)
			Simple mode	− 0.2702	0.4697	0.5722	0.7632 (0.3039–1.9163)
			Weighted mode	− 0.2538	0.4815	0.6045	0.7758 (0.3019–1.9936)
Phosphatidylcholine (16:0_20:5)	GCST90277288	24	MR Egger	− 0.0117	0.2573	0.9640	0.9883 (0.5968–1.6367)
			Weighted median	− 0.0460	0.2000	0.8179	0.9550 (0.6452–1.4134)
			Inverse variance weighted	− 0.2869	0.1438	0.0460*	0.7505 (0.5661–0.9950)
			Simple mode	− 0.1927	0.4664	0.6832	0.8247 (0.3305–2.0574)
			Weighted mode	− 0.0333	0.2001	0.8691	0.9671 (0.6532–1.4319)
Phosphatidylcholine (18:0_18:2)	GCST90277300	33	MR Egger	0.1191	0.3527	0.7377	1.1265 (0.5643–2.2489)
			Weighted median	0.1245	0.2167	0.5655	1.1326 (0.7405–1.7322)
			Inverse variance weighted	0.2912	0.1415	0.0396 *	1.3380 (1.0139–1.7658)
			Simple mode	0.5587	0.3695	0.1403	1.7485 (0.8473–3.6081)
			Weighted mode	0.1509	0.2546	0.5575	1.1629 (0.7059–1.9156)
Phosphatidylethanolamine (18:1_18:1)	GCST90277349	23	MR Egger	0.0856	0.3567	0.8125	1.0894 (0.5414–2.1920)
			Weighted median	0.2286	0.2025	0.2589	1.2568 (0.8450–1.8694)
			Inverse variance weighted	0.3092	0.1500	0.0392*	1.3624 (1.0153–1.8282)
			Simple mode	0.5393	0.3658	0.1545	1.7148 (0.8372–3.5124)
			Weighted mode	0.2239	0.2243	0.3290	1.2509 (0.8058–1.9418)
Triacylglycerol (51:2)	GCST90277393	21	MR Egger	− 0.0730	0.4941	0.8840	0.9295 (0.3528–2.4487)
			Weighted median	0.0059	0.2820	0.9830	1.0060 (0.5787–1.7486)
			Inverse variance weighted	0.4449	0.2071	0.0317*	1.5603 (1.0396–2.3418)
			Simple mode	−0.2174	0.5054	0.6717	0.8046 (0.2987–2.1669)
			Weighted mode	− 0.2068	0.4102	0.6197	0.8131 (0.3638–1.8173)
Triacylglycerol (52:4)	GCST90277398	26	MR Egger	− 0.1854	0.4082	0.6537	0.8307 (0.3731–1.8491)
			Weighted median	0.4559	0.2248	0.0426*	1.5776 (1.0152–2.4516)
			Inverse variance weighted	0.3498	0.1630	0.0319*	1.4189 (1.0306–1.9533)
			Simple mode	0.9145	0.4252	0.0413*	2.4956 (1.0844–5.7431)
			Weighted mode	0.8283	0.3760	0.0370*	2.2895 (1.0955–4.7847)
Triacylglycerol (54:3)	GCST90277404	30	MR Egger	− 0.0152	0.4569	0.9735	0.9848 (0.4022–2.4114)
			Weighted median	0.3113	0.2270	0.1702	1.3652 (0.8749–2.1303)
			Inverse variance weighted	0.3784	0.1816	0.0372*	1.4600 (1.0226–2.0843)
			Simple mode	0.5098	0.4924	0.3091	1.6650 (0.6341–4.3716)
			Weighted mode	0.1965	0.2899	0.5030	1.2172 (0.6896–2.1486)

Table 1. Causal association of lipids on ARDS estimated by univariable mendelian randomization analysis ($^*P < 0.05$).

in sepsis. Our current study's findings align with previous research, supporting the existing body of evidence regarding the multifaceted roles of cholesterol in physiological and pathological contexts[31].

In 2018, Ahilanandan et al. conducted a study that demonstrated a significant decrease in total plasma PC concentrations in patients with ARDS. Specifically, they observed lower levels of PC16:0_18:2 and PC species derived from polyunsaturated fatty acids (PUFAs). Furthermore, their findings indicated a global reduction in the overall flux of phosphatidylcholine through the phosphatidylethanolamine N-methyltransferase (PEMT) pathway in individuals with ARDS. These results provide valuable insights into the dysregulation of PC metabolism in the context of ARDS[32]. In the present study, we identified a causal association between plasma PC and ARDS, particularly between PC14:0_16:0 and PC16:0_20:5. However, the expression trends in the pulmonary edema fluid were quite different. The pathophysiological hallmark of ARDS is the impairment of the alveolar barrier, and pulmonary surfactant, which is crucial for maintaining cellular barriers, undergoes significant changes during ARDS injury[33]. The concentrations of PC(14:0_16:0) and PC(16:0_20:5) in peripheral blood plasma decrease with the severity of the condition. This may be attributed to the metabolic pathways that result in increased PC consumption as inflammation levels rise, thereby reducing its concentration in peripheral
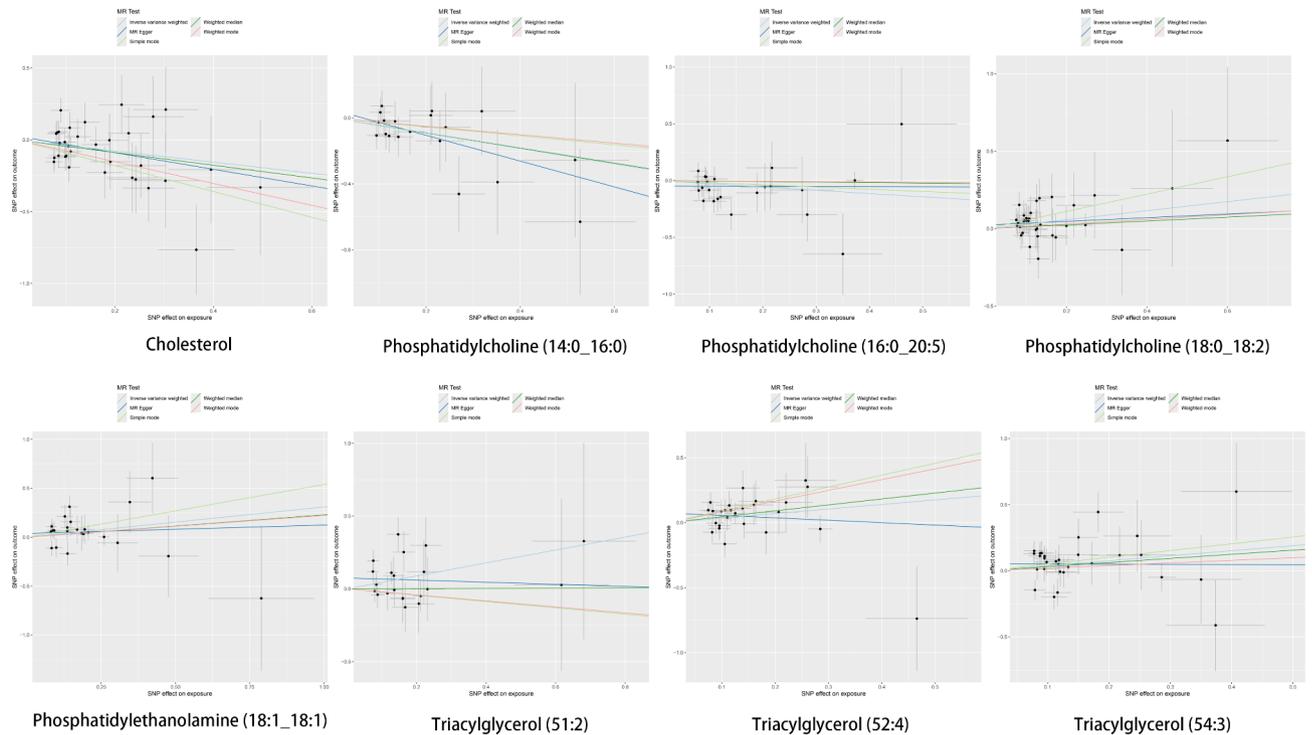
Fig. 1. Scatter diagram about the causal association of different kinds of lipid species on ARDS. Five Mendelian randomization methods (IVW, MR egger, Simple mode, Weighted median, Weighted mode) were used to show the casual association of different kinds of lipid species on ARDS. Eight representative lipid species with causal effect on ARDS were shown by scatter diagram.

blood. Furthermore, PC(14:0_16:0) and PC(18:0_18:2) are detected at significantly higher levels in pulmonary edema fluid than in plasma, likely due to their role as key components of pulmonary surfactant. The impairment of the barrier leads to their increased dissolution in pulmonary edema fluid, which is then collected and detected.

Research indicates that in COVID-19 patients, lipid release is positively correlated with various subsets of memory CD4+ and CD8+ T cells, dendritic cells, and NK cells[34]. Through mediation analysis, we found that PC(14:0_16:0) is positively correlated with the percentage of Naive CD4+T cells and CD8 dim NK T cells, and PE(18:1_18:1) is positively correlated with CD3+HLA-DR+T cells, which is consistent with literature reports. PC(18:0_18:2) is negatively correlated with a certain subtype of lymphocyte, which requires further validation and research.

PE, a multifunctional phospholipid that is enriched in cells, has been proven to be directly involved in autophagy which is closely associated with inflammation[35]. In response to inflammatory activation by pathogens, macrophages accumulate triglycerides in intracellular lipid droplets. Xanthe et al. provided evidence that the LPS-mediated activation of macrophages suppresses lipolysis via the induction of HILPDA, thereby reducing the availability of pro-inflammatory lipid precursors and suppressing the production of PGE2 and IL-6[36]. However, the findings of the current study do not reveal a clear role of PE or TAG in ARDS.

Lipids and their metabolites, acting as pro-inflammatory mediators, are implicated in the pathogenesis of ARDS. Therefore, these metabolic entities and their enzymatic catalysts present themselves as promising therapeutic targets for ARDS. A case in point is cytosolic Phospholipase A2 (cPLA2), which selectively liberates arachidonic acid from cellular membrane phospholipids, thereby triggering the synthesis of potent pro-inflammatory agents like thromboxanes and leukotrienes[37]. By inhibiting cPLA2, compounds such as Arachidenyl trifluoromethyl ketone and FFD have been shown to suppress cPLA2 activity, consequently reducing the production of cytokines, chemokines, and the downstream metabolites of cPLA2, including arachidonic acid and leukotriene B4[38]. This inhibition not only effectively alleviates lung injury but also diminishes leukocyte infiltration, inflammatory reaction and enhances gas exchange, offering a potential avenue for ARDS treatment.

Our study provides a new potential therapeutic target, such as PC(14:0_16:0), for the treatment of ARDS by targeting lipid metabolic pathways and modulating immune cell responses.

There are several limitations to acknowledge in this study. Firstly, our analysis was conducted specifically in a European population, which may restrict the generalizability of the findings to other ethnic groups. It is important to replicate these analyses in diverse populations for broader applicability. Secondly, the ARDS GWAS dataset utilized in this study had a relatively small number of cases, and future studies with larger GWAS datasets will be valuable for validating and strengthening the results. Thirdly, although we made efforts to identify and exclude outlier variants, the presence of horizontal pleiotropy, where genetic variants affect multiple traits, may still have influenced our results. It is crucial to acknowledge this potential confounding factor. Fourthly, our study relied on summary-level statistics rather than individual-level data. As a result, we were unable to investigate

Traits	Outcome	SNPs	Method	b	se	p− value	OR (95% CI)
Cholesterol	GCST90277257	28	MR Egger	0.2899	0.1131	0.0165*	1.3363 (1.0704–1.6683)
			Weighted median	0.2541	0.0567	7.5881×10^{-6}****	1.2894 (1.1536–1.4412)
			Inverse variance weighted	0.2268	0.0488	3.3351×10^{-6}****	1.2546 (1.1402–1.3806)
			Simple mode	0.2831	0.1175	0.0230*	1.3273 (1.0541–1.6712)
			Weighted mode	0.2831	0.1091	0.0151*	1.3273 (1.0716–1.6439)
Phosphatidylcholine (14:0_16:0)	GCST90277272	28	MR Egger	− 0.1363	0.1226	0.2764	0.8725 (0.6861–1.1096)
			Weighted median	− 0.0581	0.0647	0.3687	0.9435 (0.8311–1.0710)
			Inverse variance weighted	− 0.0178	0.0539	0.7412	0.9823 (0.8838–1.0918)
			Simple mode	− 0.1233	0.1134	0.2868	0.8839 (0.7076–1.1041)
			Weighted mode	− 0.1157	0.1048	0.2793	0.8907 (0.7252–1.0938)
Phosphatidylcholine (16:0_20:5)	GCST90277288	28	MR Egger	0.1628	0.3127	0.6070	1.1768 (0.6375–2.1722)
			Weighted median	0.4127	0.0599	5.6037×10^{-12}****	1.5109 (1.3435–1.6991)
			Inverse variance weighted	0.6216	0.1404	9.6071×10^{-6}****	1.8620 (1.4139–2.4522)
			Simple mode	0.5570	0.1194	7.5325×10^{-5}****	1.7455 (1.3811–2.2061)
			Weighted mode	0.5399	0.1084	3.2078×10^{-5}****	1.7159 (1.3874–2.1221)
Phosphatidylcholine (18:0_18:2)	GCST90277300	28	MR Egger	0.1993	0.2701	0.4673	1.2205 (0.7187–2.0726)
			Weighted median	0.0092	0.0544	0.8644	1.0093 (0.9071–1.1230)
			Inverse variance weighted	− 0.0423	0.1177	0.7190	0.9585 (0.7609–1.2074)
			Simple mode	− 0.0275	0.1056	0.7960	0.9728 (0.7909–1.1965)
			Weighted mode	− 0.0028	0.0982	0.9769	0.9971 (0.8225–1.2087)
Phosphatidylethanolamine (18:1_18:1)	GCST90277349	28	MR Egger	− 0.0497	0.2910	0.8656	0.9515 (0.5378–1.6832)
			Weighted median	0.0020	0.0585	0.9716	1.0020 (0.8935–1.1238)
			Inverse variance weighted	0.0090	0.1247	0.9421	1.0090 (0.7901–1.2886)
			Simple mode	0.0516	0.1077	0.6353	1.0530 (0.8525–1.3006)
			Weighted mode	0.0318	0.1136	0.7816	1.0323 (0.8262–1.2898)
Triacylglycerol (51:2)	GCST90277393	28	MR Egger	0.4669	0.1917	0.0220*	1.5950 (1.0954–2.3226)
			Weighted median	0.1906	0.0627	0.0023**	1.2100 (1.0700− 1.3684)
			Inverse variance weighted	0.2957	0.0835	0.0003***	1.3440 (1.1411–1.5831)
			Simple mode	0.1843	0.1059	0.0931	1.2024 (0.9769− 1.4800)
			Weighted mode	0.1680	0.0988	0.1003	1.1830 (0.9747–1.4358)
Triacylglycerol (52:4)	GCST90277398	28	MR Egger	0.7768	0.2001	0.0006***	2.1745 (1.4690–3.2189)
			Weighted median	0.3664	0.0618	3.1784×10^{-9}****	1.4425 (1.2777–1.6285)
			Inverse variance weighted	0.5341	0.0885	1.6484×10^{-9}****	1.7059 (1.4340–2.0293)
			Simple mode	0.3786	0.1072	0.0015**	1.4602 (1.1834–1.8018)
			Weighted mode	0.3675	0.1036	0.0014**	1.4441 (1.1787–1.7693)
Triacylglycerol (54:3)	GCST90277404	28	MR Egger	0.6220	0.2472	0.0183*	1.8628 (1.1473–3.0245)
			Weighted median	0.3105	0.0621	5.7923×10^{-7}****	1.3641 (1.2077–1.5407)
			Inverse variance weighted	0.3771	0.1082	0.0004***	1.4581 (1.1793–1.8028)
			Simple mode	0.3632	0.1035	0.0016**	1.4379 (1.1738–1.7615)
			Weighted mode	0.2484	0.0988	0.0182*	1.2819 (1.0562–1.5560)

Table 2. The results of reverse MR analysis of ARDS and lipids. (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$)

causal links specifically within ARDS subgroups or explore potential interactions with other factors. In light of these limitations, future studies should aim to address these issues and conduct more comprehensive analyses to enhance our understanding of the causal mechanisms underlying ARDS and its interactions with immune cells.

Conclusion

In conclusion, our study identified a causal relationship between lipids and ARDS, with a small proportion of the effect mediated by immune cells, but a majority of the effect of lipids on ARDS remains unclear. Further research is needed on additional risk factors as potential mediators. In clinical practice, lipids metabolism in ARDS patients need to be given more attention.
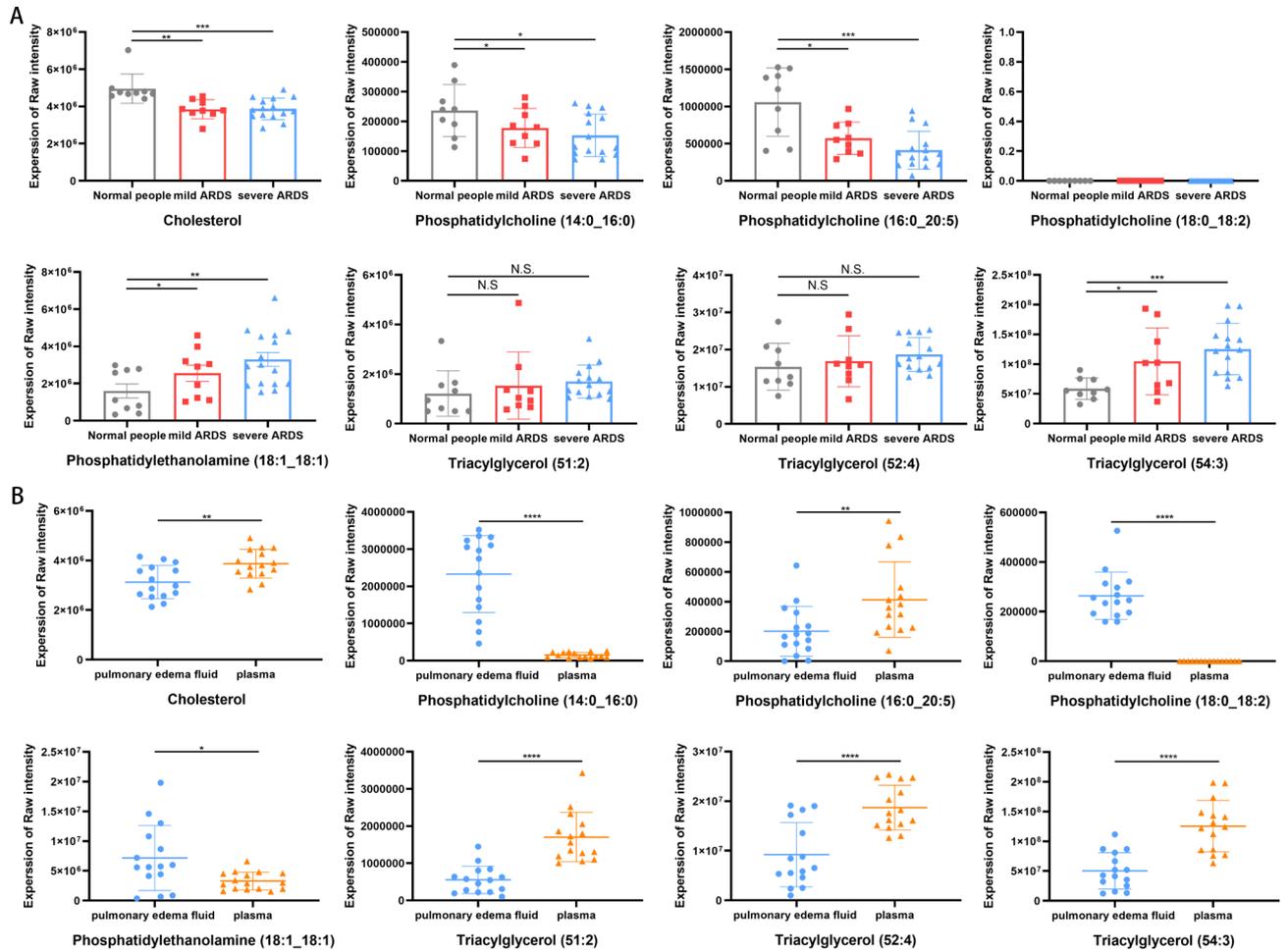
Fig. 2. The expression of 8 lipids in normal people, mild ARDS patients and severe ARDS patients. (**A**) The expression of 8 lipids in plasma of normal people, mild ARDS patients and severe ARDS patients.****$p < 0.0001$, ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$. P-values were calculated using one-way ANOVAA, Tukey's multiple comparisons test. (**B**) The expression of 8 lipids in pulmonary edema fluid and plasma of severe patients. ****$p < 0.0001$,***$p < 0.001$,**$p < 0.01$, *$p < 0.05$. P-values were calculated using paired t-test.

Exposure	Outcome	SNPs	Method	b	se	p-value	OR (95% CI)
GCST90277257	GCST90001795	31	MR Egger	0.2170	0.1224	0.0869	1.2423 (0.9772–1.5794)
			Weighted median	0.0703	0.0806	0.3832	1.0728 (0.9159–1.2566)
			Inverse variance weighted	0.1185	0.0580	0.0412*	1.1258 (1.0047–1.2615)
			Simple mode	0.0986	0.1362	0.4744	1.1036 (0.8450–1.4414)
			Weighted mode	0.0847	0.0981	0.3946	1.0884 (0.8979–1.3193)
GCST90277272	GCST90001541	18	MR Egger	−0.0169	0.1376	0.9033	0.9831 (0.7506–1.2876)
			Weighted median	−0.1679	0.0793	0.0343*	0.8454 (0.7236–0.9876)
			Inverse variance weighted	−0.1331	0.0569	0.0192*	0.8752 (0.7828–0.9786)
			Simple mode	−0.1471	0.1463	0.3287	0.8631 (0.6479–1.1498)
			Weighted mode	−0.1668	0.1415	0.2547	0.8463 (0.6413–1.1168)
GCST90277272	GCST90001634	18	MR Egger	−0.0378	0.1492	0.8032	0.9628 (0.7186–1.2901)
			Weighted median	−0.1479	0.0838	0.0774	0.8624 (0.7318–1.0164)
			Inverse variance weighted	−0.1357	0.0611	0.0264*	0.8730 (0.7743–0.9842)
			Simple mode	−0.1935	0.1430	0.1939	0.8240 (0.6224–1.0908)
			Weighted mode	−0.1807	0.1380	0.2080	0.8346 (0.6367–1.0940)
GCST90277288	GCST90001863	24	MR Egger	−0.0743	0.0975	0.4541	0.9283 (0.7667–1.1239)
			Weighted median	−0.0741	0.0739	0.3163	0.9285 (0.8032–1.0734)
			Inverse variance weighted	−0.1298	0.0558	0.0200*	0.8782 (0.7872–0.9797)
			Simple mode	−0.1294	0.1337	0.3431	0.8785 (0.6759–1.1419)
			Weighted mode	−0.0897	0.0739	0.2370	0.9141 (0.7907–1.0567)
GCST90277300	GCST90001971	31	MR Egger	−0.1670	0.1154	0.1585	0.8461 (0.6747–1.0609)
			Weighted median	−0.1548	0.0732	0.0346*	0.8565 (0.7419–0.9888)
			Inverse variance weighted	−0.1195	0.0476	0.0120*	0.8872 (0.8082–0.9740)
			Simple mode	−0.2100	0.1193	0.0886	0.8105 (0.6414–1.0241)
			Weighted mode	−0.1874	0.0910	0.0484*	0.8290 (0.6935–0.9911)
GCST90277349	GCST90001847	23	MR Egger	0.1035	0.1185	0.3921	1.1091 (0.8791–1.3993)
			Weighted median	0.1139	0.0737	0.1220	1.1207 (0.9699–1.2949)
			Inverse variance weighted	0.1407	0.0541	0.0093**	1.1511 (1.0352–1.2799)
			Simple mode	0.1101	0.1104	0.3292	1.1164 (0.8991–1.3862)
			Weighted mode	0.1134	0.0819	0.1800	1.1201 (0.9539–1.3152)
GCST90277393	GCST90001630	21	MR Egger	0.0248	0.0874	0.7793	1.0251 (0.8636–1.2169)
			Weighted median	0.0257	0.0750	0.7311	1.0261 (0.8857–1.1886)
			Inverse variance weighted	0.1157	0.0528	0.0283*	1.1227 (1.0123–1.2452)
			Simple mode	0.2238	0.1141	0.0640	1.2508 (1.0000−1.5646)
			Weighted mode	0.0116	0.0758	0.8797	1.0116 (0.8719–1.1737)
GCST90277393	GCST90001847	21	MR Egger	0.2168	0.1058	0.0546	1.2421 (1.0093–1.5286)
			Weighted median	0.1437	0.0918	0.1175	1.1546 (0.9643–1.3823)
			Inverse variance weighted	0.1462	0.0629	0.0202*	1.1574 (1.0230–1.3095)
			Simple mode	0.0684	0.1409	0.6323	1.0708 (0.8123–1.4117)
			Weighted mode	0.1461	0.0825	0.0917	1.1573 (0.9845–1.3606)
GCST90277398	GCST90001762	22	MR Egger	−0.0525	0.1274	0.6845	0.9488 (0.7391–1.2179)
			Weighted median	−0.0973	0.0741	0.1894	0.9072 (0.7845–1.0492)
			Inverse variance weighted	−0.1144	0.0545	0.0359*	0.8918 (0.8014–0.9925)
			Simple mode	−0.0549	0.1203	0.6528	0.9465 (0.7476–1.1983)
			Weighted mode	−0.1029	0.1005	0.3172	0.9021 (0.7407–1.0986)
GCST90277404	GCST90001630	29	MR Egger	0.0453	0.1300	0.7301	1.0463 (0.8109–1.3502)
			Weighted median	0.1660	0.0745	0.0258*	1.1806 (1.0201–1.3663)
			Inverse variance weighted	0.1019	0.0504	0.0434*	1.1072 (1.0029–1.2224)
			Simple mode	0.2066	0.1339	0.1341	1.2295 (0.9456–1.5986)
			Weighted mode	0.1707	0.1197	0.1648	1.18623 (0.9380−1.5000)
GCST90277404	GCST90001747	29	MR Egger	−0.1658	0.1290	0.2096	0.8471 (0.6578–1.0910)
			Weighted median	−0.0819	0.0740	0.2680	0.9212 (0.7968–1.0651)
			Inverse variance weighted	−0.0982	0.0497	0.0482*	0.9064 (0.8221–0.9992)
			Simple mode	−0.0552	0.1235	0.6579	0.9462 (0.7427–1.2053)
			Weighted mode	−0.1471	0.1084	0.1856	0.8631 (0.6978–1.0675)
Continued							

Exposure	Outcome	SNPs	Method	b	se	p-value	OR (95% CI)
GCST90277404	GCST90001752	29	MR Egger	−0.1757	0.1286	0.1833	0.8388 (0.6518–1.0794)
			Weighted median	−0.1440	0.0703	0.0406*	0.8658 (0.7542–0.9938)
			Inverse variance weighted	−0.1162	0.0497	0.0194*	0.8902 (0.8076–0.9813)
			Simple mode	−0.1200	0.1168	0.3131	0.8868 (0.7052–1.1151)
			Weighted mode	−0.1685	0.1076	0.1287	0.8448 (0.6841–1.0434)
GCST90277404	GCST90001909	29	MR Egger	−0.0946	0.1522	0.5394	0.9096 (0.6749–1.2260)
			Weighted median	−0.2435	0.0812	0.0027**	0.7838 (0.6683–0.9192)
			Inverse variance weighted	−0.1771	0.0582	0.0023**	0.8376 (0.7472–0.9388)
			Simple mode	−0.3827	0.1577	0.0219*	0.6820 (0.5006–0.9291)
			Weighted mode	−0.2818	0.1251	0.0323*	0.7543 (0.5902–0.9641)

Table 3. Predicting the correlation of immune cells and lipids by using the IVW method. (*$P < 0.05$, **$P < 0.01$)
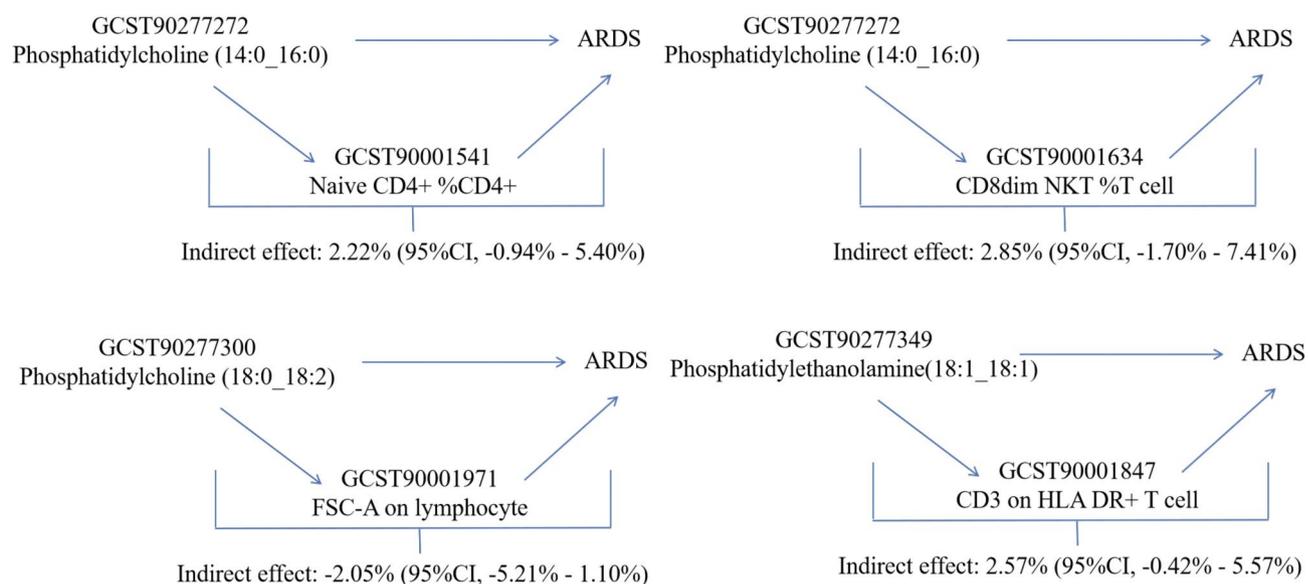
Fig. 3. Schematic diagram of the immune cells mediation effect. Three kinds of lipid species were found to have mediation effect on ARDS by immune cells. Two kinds of immune cells (Naive CD4+ %CD4+, and CD8dim NKT %T cell) showed mediation effect between Phosphatidylcholine(14:0_16:0) and ARDS. One kind of immune cell (FSC-A on lymphocyte) showed mediation effect between Phosphatidylcholine(18:0_18:2) and ARDS. One kind of immune cell (CD3 on HLA DR + T cell) showed mediation effect between Phosphatidylcholine(18:1_18:1) and ARDS.

Data availability

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Author contributions

All authors designed this study. R.S., Z.Q., and X.H. performed the catalog and literature search and data extraction with suggestions and help from J.X. and Q.Z. Q.Z. and J.X. performed the statistical analyses. All authors contributed to the data interpretation and manuscript writing. All authors contributed to the article and approved the submitted version.

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Declarations

Ethics approval and consent to participate
The information used in the current Mendelian randomization study is publically accessible. All original investigations had received ethical approval. The studies involving human participants were reviewed and approved by Ethics Committee of the China-Japan Friendship Hospital (NO.2023-ky-152). All methods were performed in accordance with the relevant guidelines and regulations.

Competing interests
The authors declare no competing interests.

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