scientific reports

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Exploring lipidome mediated inflammatory pathways in acute pancreatitis using mendelian randomization

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Acute pancreatitis (AP) is a severe gastrointestinal condition with an increasing incidence of hyperlipidemic etiology. The investigation employed a two-sample, bidirectional Mendelian randomization method to investigate potential causal relationship between lipidome profiles, inflammatory mediators, and AP. Exploration of genetic variants across the genome in a study population of 10,630 AP cases and 844,679 non-AP individuals revealed multiple lipidome entities significantly associated with AP risk. The study identified 23 lipid species with unidirectional causal effects on AP after accounting for heterogeneity, pleiotropy, and potential reverse causation. Additionally, five inflammatory factors (CD5, IL-13, MMP-1, STAMBP, TNFRSF9) showed significant potential causal relationship with AP. Further analysis elucidated the intricate interplay between specific lipid species and inflammatory mediators in influencing AP incidence. Notably, Sterol ester (27:1/20:4) and several phosphatidylcholine species, including PC (17:0_20:4), PC (18:0_20:4), PC (18:0_20:5), and PC (O-18:2_20:4), were negatively associated with AP risk. This protective effect was partially mediated through decreased levels of inflammatory markers, particularly STAMBP and MMP-1. The study found that these phosphatidylcholines and sterol esters significantly reduced the levels of these pro-inflammatory factors, thereby potentially mitigating AP risk. Conversely, Phosphatidylinositol (16:0_18:1) demonstrated a positive association with AP risk. This detrimental effect was partially mediated by increased levels of MMP-1 and STAMBP, suggesting a pro-inflammatory mechanism. The study provides evidence that this specific phosphatidylinositol species may exacerbate AP risk by promoting inflammatory pathways. These findings elucidate the complex interplay between lipid metabolites, inflammation, and AP pathogenesis, potentially informing novel therapeutic strategies. The study highlights the utility of Mendelian randomization in uncovering potential causal relationship in AP. It underscores the requirement for further study into the molecular mechanisms underlying lipid-mediated inflammation in AP, particularly the roles of phosphatidylcholines and sterol esters in modulating inflammatory responses. Further studies are warranted to confirm our observations in laboratory models and assess their translational value in developing AP preventive and therapeutic strategies.

Keywords Acute pancreatitis, Lipidome, Inflammatory factors, Mendelian randomization

Acute pancreatitis (AP), distinguished by its abrupt commencement within the gastrointestinal system, remains a formidable clinical conundrum attributed to its grave prognosis. Approximately one-fifth of the patients progress to a critical condition, culminating in a mortality rate near 20%. The etiological classification of AP spans biliary, alcoholic, and hyperlipidemic origins, among others. Recent trends show an increasing incidence of hyperlipidemic pancreatitis, possibly due to lifestyle changes, a higher prevalence of metabolic syndrome, and increased caloric intake in China[1]. A marked correlation between hypertriglyceridemia and an escalated risk

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of pancreatitis has been established[2]. Associations between lipid profiles and both the incidence and prognosis of AP have been documented, as exemplified by the role of high-density lipoprotein cholesterol (HDL-C) as a protective prognostic factor linked to shorter hospitalizations in severe AP cases[3]. Furthermore, triglyceride (TG) levels have been positively correlated with both the incidence and severity of AP[4], and notable increases in sphingosine-1-phosphate (S1P) levels, a ceramide metabolite, have been observed in mild AP[5]. Despite these associations, the effects of various lipid metabolites on AP incidence remain insufficiently clarified.

Extensive research into the mechanisms by which lipids initiate AP has highlighted the crucial role of inflammatory activation. Hypercholesterolemia compromises vascular endothelial cells by impairing nitric oxide synthesis and causing dysfunction of endothelial progenitor cells, while also promoting microinflammation of the endothelium[6]. In animal models, high-fat diets have been found to exacerbate intestinal barrier injuries through the TLR4-RIP3 pathway in severe AP[7]. Inflammatory mediators play a pivotal role in AP progression, with cholesterol activating entities such as TLR4, NLRP3, and NETs to induce inflammation, significantly contributing to AP pathogenesis[8]. Furthermore, free fatty acids and triglycerides have been implicated in stimulating pancreatic acinar cells to release chemokines and cytokines. Studies have revealed that obese individuals suffering from severe AP display higher free fatty acid levels, coinciding with amplified NLRP3-Caspase1 expression in their adipose tissue-associated macrophages[9]. However, the specific roles of different lipid components in modulating inflammatory mediators during AP progression are not fully understood. In the realm of Mendelian Randomization (MR) studies, an innovative frontier concurrent with advancements in genome-wide association studies offers an unprecedented approach to establish causal inferences[10]. MR studies have progressively illuminated factors entangled in the etiology and prognosis of AP[11]. Our research is aimed at bridging this knowledge gap by employing an MR paradigm. MR emerges as a critical methodology, unraveling the intricate interactions between lipid entities and inflammatory mediators within the context of AP. This methodological approach holds promise in revolutionizing our comprehension of AP and shaping the development of bespoke treatment regimens. This study aims to elucidate how inflammatory factors mediate the relationship between lipid substances and AP, using a bidirectional MR strategy to gain insights crucial for understanding AP pathophysiology and discovering therapeutic targets.

Materials and methods

Data sources and study design

The foundation of this study was a comprehensive collection of genome-wide association study (GWAS) summary data, with participant consent obtained during the original research. Given that our analysis was based on summary-level data, there was no necessity for further ethical approval. A bidirectional two-sample MR framework was employed to elucidate the reciprocal causal linkages between lipidome profiles and AP, focusing on the intermediary role of inflammatory mediators. Figure 1 illustrates the process in a flowchart. Guided by the STROBE-MR framework (Strengthening the Reporting of Observational Studies in Epidemiology through Mendelian Randomization), we performed this observational analysis. Supplementary Table S1 contains the relevant checklist. Genetic associations were obtained from the GWAS identified by GCST90255375 from the IEU Open GWAS Project, comprising 10,630 AP cases and 844,679 controls of European ancestry[11]. Additionally, data on 179 plasma lipid measures were sourced from identifiers GCST90277238 to GCST90277287. These measures were derived from a comprehensive lipidomics study conducted by Ottensmann L and colleagues, which extensively mapped the genetic components of plasma lipid variations[12], as detailed in Supplementary Table S2. The details of the genetic associations discovered, including effect sizes and potential implications for lipid metabolism, are cataloged in Supplementary Table S2. Furthermore, genetic associations for 91 inflammatory markers were obtained from a range of identifiers from GCST90274758 to GCST90274848. These associations stem from a significant study by Zhao J H and team, which focused on the genetics of circulating inflammatory proteins[13], listed in Supplementary Table S3.

Selection of instrumental variables and data arrangement

This investigation focused on lipidome components and inflammatory mediators as exposure factors, each identified by unique GWAS identifiers. We collected relevant genetic instruments—specifically, single nucleotide polymorphisms (SNPs)—and their associations with both exposures and outcomes. The SNP data included effect sizes, standard errors, allele information, frequencies, p-values, and sample sizes. Similarly, outcome data comprised corresponding SNP associations.

We employed rigorous criteria to select instrumental variables (IVs) that satisfied three fundamental assumptions. Due to the scarcity of available IVs, we adjusted our SNP selection threshold to $p < 5 \times 10^{-5}$, allowing for a more comprehensive set of potentially significant genetic instruments. We conducted linkage disequilibrium clustering using a 10,000 kb window and an R2 threshold of < 0.001, based on European samples from the 1000 Genomes Project. We excluded palindromic or ambiguous SNPs from our analysis.

Careful data harmonization ensured consistency in effect direction and allele coding across all SNPs. We thoroughly assessed the instrumental strength of each SNP using R^2 and F-statistics. To maintain the integrity of our instrumental variables, we omitted SNPs with an F-statistic below 10 (refer to Supplementary Table S4 for details).

MR estimation

Causal effects were estimated using MR approaches. For each exposure factor, we calculated Odds Ratios (ORs) and the accompanying p-values, employing a significance level of 0.05 for statistical inference. Our primary analysis employed the Inverse variance weighted (IVW) method, which aggregates Wald ratios from individual SNPs to estimate combined causal effects. This approach assumes all genetic instruments are valid. To address potential violations of MR assumptions and ensure robustness, we implemented complementary methods.

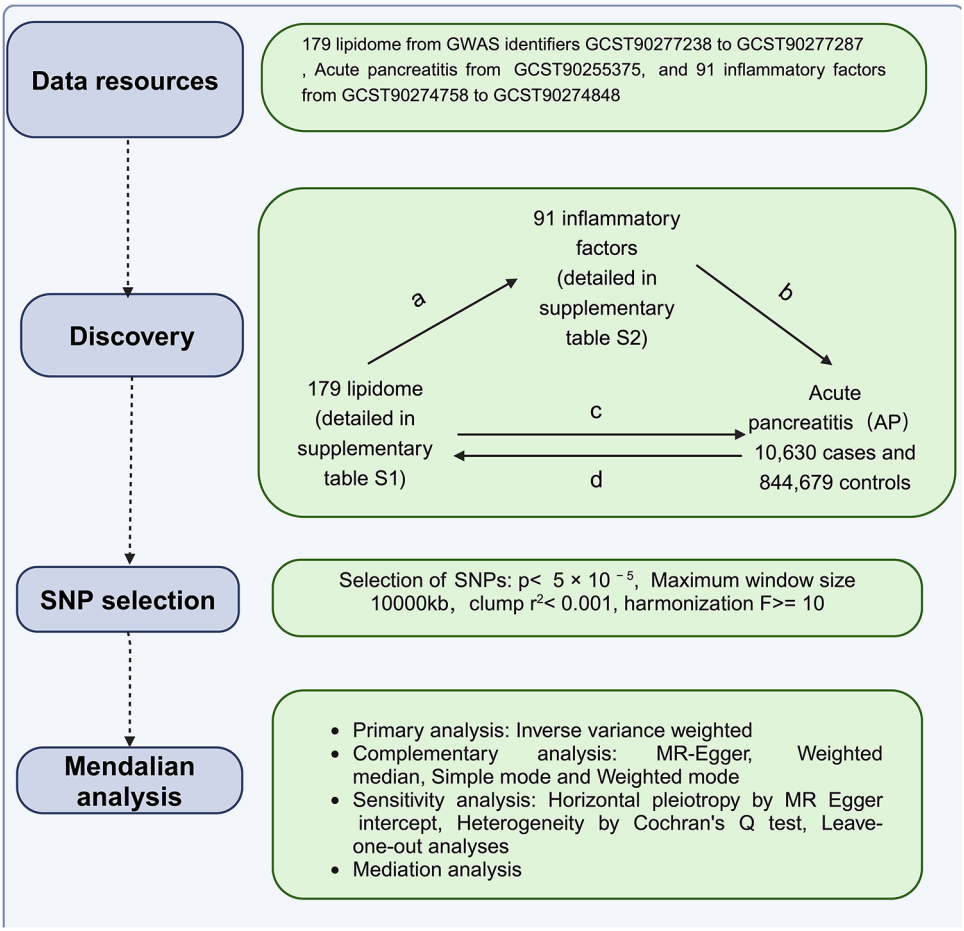


Fig. 1. Schematic overview of the study design using MR. This study investigates potential causal relationship between 179 lipidome entities, 91 inflammatory factors, and AP using bidirectional two-sample Mendelian randomization. The discovery phase examines: (**a**) lipidome effects on inflammatory factors, (**b**) inflammatory factor effects on AP, (**c**) direct lipidome effects on AP, and (**d**) potential reverse causation from AP to lipidome. The procedure includes SNP selection, primary analyses using inverse variance weighted method, complementary analyses, and sensitivity analyses. The study includes GWAS database of AP, 179 lipidome and 91 inflammatory factors with detailed information in supplementary tables S1 and S2.

The MR-Egger regression was utilized to assess and correct for potential directional pleiotropy. Furthermore, our analysis included the Weighted Median approach, which maintains estimate consistency despite potential invalidity in up to 50% of the genetic instruments. This multi-method approach allows for a comprehensive evaluation of potential causal relationship, accounting for various scenarios of instrument validity and potential biases. Results from these methods were compared to assess the consistency and reliability of our findings.

Sensitivity analyses

To assess the reliability of our results, we implemented a comprehensive suite of sensitivity analyses. The directionality of potential causal relationship was examined using MR Steiger filtering. We evaluated SNP heterogeneity through Cochran's Q test and visual inspection of funnel plots. The MR-Egger intercept test and MR-PRESSO method were utilized to examine potential horizontal pleiotropy in our analysis. In cases of persistent heterogeneity, we applied a random effects model to account for variability beyond sampling error. The influence of individual genetic variants on overall estimates was assessed through leave-one-out analysis, systematically excluding each SNP and recalculating the effect estimates. This multi-faceted approach to sensitivity analysis aimed to identify and mitigate potential sources of bias, ensuring the robustness and validity of our causal inferences.

Mediation analysis for inflammatory mediators' intermediary effects

Mutual causality between the plasma lipidome and AP was evaluated using two-sample MR, extending to inflammatory mediators and their effects on AP. Following the derivation of MR estimates, we identified significant associations ($p < 0.05$) using the instrumental variable method. We then investigated the interactions between significant plasma lipidome components and inflammatory markers. Finally, we established a preliminary assessment of the bidirectional total effect between the plasma lipidome and AP. This effect was

decomposed into mediation effects, with indirect influences channeled through inflammatory mediators. To quantify mediation proportions, the indirect effect's magnitude was divided by the total effect's magnitude.

Statistics

R software (version 4.1.0) was utilized for statistical analyses, while Mendelian randomization studies were carried out using the TwoSampleMR package (version 0.5.6). The main analysis employed the IVW method. Data preparation included harmonizing exposure and outcome data, calculating instrument strength (F-statistic > 10), and generating odds ratios. Results with p-values < 0.05 were considered statistically significant. Visualizations were created using the forestploter (version 0.3.0) and ggplot2 (version 3.3.5) packages. Forest plots were customized for optimal data presentation, including adjusted x-axis limits and custom themes. All statistical tests were two-sided. The complete analysis pipeline was implemented in R to ensure reproducibility.

Results

Assessing lipidome-AP associations

We utilized the IVW method to evaluate the relationship between 179 lipidome components and AP. Figure 2 A illustrates the 31 lipidome elements significantly linked to AP. To elucidate causal directionality, we implemented reverse MR, analyzing AP as an exposure and its causal influence on these 31 lipidome components. As shown in Figure B, Sterol ester (27:1/20:2), Phosphatidylcholine (16:0_18:2), Phosphatidylcholine (17:0_18:2), and Phosphatidylinositol (18:0_18:2) were causally associated with AP, while 27 lipidome components demonstrated unidirectional causal effects on AP. Among these 27 lipidome components, Phosphatidylethanolamine (18:2_0:0), Phosphatidylinositol (18:0_18:1), Phosphatidylinositol (18:0_18:2) and Triacylglycerol (54:3) showed heterogeneity when analyzed as exposures to AP (Supplementary Table S6). After excluding bidirectional causality, pleiotropy, and heterogeneity, 23 lipidome components demonstrated unidirectional causal effects on AP.

Assessing inflammatory factors-AP associations

The IVW method was utilized to analyze the influence of 91 inflammatory factors on AP. Our findings demonstrated positive associations between AP and five inflammatory factors: CD5 (OR = 1.100, 95% CI = 1.002–1.208), IL-13 (OR = 1.063, CI = 1.005–1.125), MMP-1 (OR = 1.085, CI = 1.005–1.172), STAMBP (OR = 1.150, CI = 1.029–1.284), and TNFRSF9 (OR = 1.133, CI = 1.056–1.216) (Fig. 3A). Reverse MR was performed to determine causal directionality, revealing no effect of AP on these inflammatory factors (Fig. 3B). Neither significant pleiotropy (MR-Egger intercept test, Supplementary Table S5) nor heterogeneity (Cochran's Q-test, Supplementary Table S6) was observed.

Associations between AP-relevant lipidome and inflammatory factors

We investigated the impact of 23 lipidome components relevant to AP on five inflammatory markers: CD5, IL-13, MMP-1, STAMBP, and TNFRSF9. Through IVW analysis, we identified significant correlations between six of these lipidome components and three of the inflammatory factors—specifically, MMP-1, STAMBP, and TNFRSF9, as detailed in Fig. 4A. Additionally, Supplementary Table S7 presents data for those lipidome components that did not show significant causal associations with the five inflammatory factors, ensuring comprehensive reporting of our findings. The MR-Egger intercept test showed no evidence of pleiotropy (Supplementary Table S5) and Cochran's Q-test indicated no significant heterogeneity in the potential causal relationship (Supplementary Table S6). To establish causal directionality, we conducted reverse MR, which demonstrated no effect of these inflammatory factors on the lipidome components (Fig. 4B).

Inflammatory factors as mediators in lipidome-AP associations

Our analysis identified that Sterol ester (27:1/20:4), Phosphatidylcholine (17:0_20:4), Phosphatidylcholine (18:0_20:4), Phosphatidylcholine (18:0_20:5) and Phosphatidylcholine (O-18:2_20:4) were negatively correlated with AP. Conversely, Phosphatidylinositol (16:0_18:1) showed positive correlations with AP (Fig. 5). Inflammatory factors such as CD5, IL-13, MMP-1, STAMBP and TNFRSF9 were positively causally associated with AP (Fig. 5). Potential causal relationship between these lipidome components and inflammatory factors were observed (Fig. 6A). Leave-one-out analysis revealed no significant bias from individual SNPs (Supplementary Figure S1).

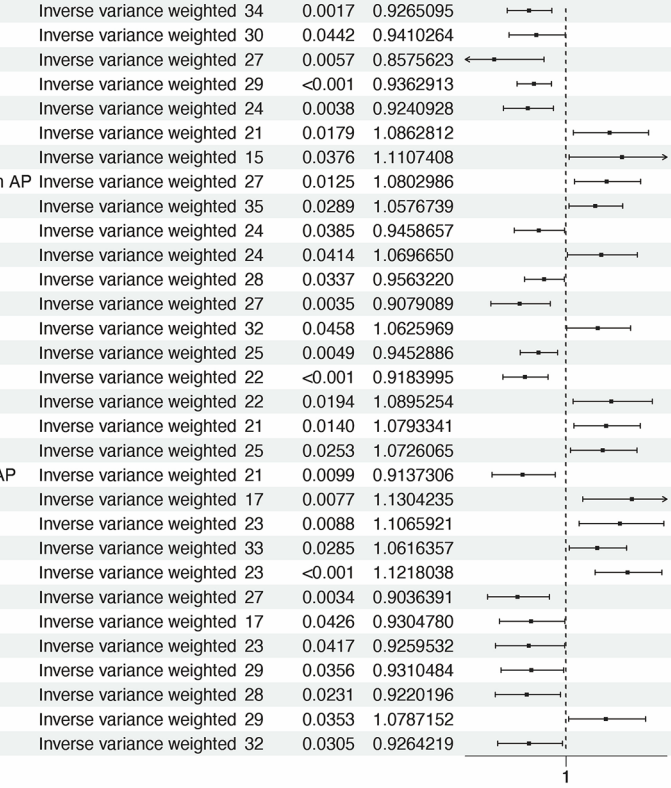
In assessing inflammatory factors as mediators, we found that Phosphatidylinositol (16:0_18:1), while positively correlated with AP, was negatively associated with TNFRSF9. However, TNFRSF9's positive association with AP suggests it unlikely mediates Phosphatidylinositol (16:0_18:1)'s increased AP risk. Several metabolites showed protective effects mediated by inflammatory factors: Sterol ester (27:1/20:4) via STAMBP (7.525%), Phosphatidylcholine (17:0_20:4) via STAMBP (13.551%), Phosphatidylcholine (18:0_20:4) via MMP-1 (4.667%) and STAMBP (11.117%), Phosphatidylcholine (18:0_20:5) via MMP-1 (5.033%), and Phosphatidylcholine (O-18:2_20:4) via STAMBP (8.908%). Conversely, Phosphatidylinositol (16:0_18:1) showed increased AP risk mediated by MMP-1 (5.900%) and STAMBP (4.746%) (Fig. 6B).

Discussion

In recent years, the proportion of hyperlipidemia-associated AP has been on the rise[14,15]. Numerous studies have indicated a positive correlation between hyperlipidemia and the incidence of AP[16,17]. Studies have shown that lipidome play a key role in the development of diseases, and a deep understanding of these lipid molecules can help reveal the underlying mechanisms of diseases and may guide future therapeutic strategies[18,19]. However, the impact of specific lipid species on AP is not fully elucidated, and the exact inflammatory factors through which lipids exert their influence on AP remain to be clarified. In this study, we employed a two-sample Mendelian

A

Exposure	method	nsnp	pval	or	OR (95% CI)
Sterol ester (27:1/16:0) levels on AP	Inverse variance weighted	34	0.0017	0.9265095	0.9265 (0.8833 – 0.9718)
Sterol ester (27:1/18:1) levels on AP	Inverse variance weighted	30	0.0442	0.9410264	0.9410 (0.8869 – 0.9984)
Sterol ester (27:1/20:2) levels on AP	Inverse variance weighted	27	0.0057	0.8575623	0.8576 (0.7691 – 0.9562)
Sterol ester (27:1/20:4) levels on AP	Inverse variance weighted	29	<0.001	0.9362913	0.9363 (0.9027 – 0.9711)
Sterol ester (27:1/20:5) levels on AP	Inverse variance weighted	24	0.0038	0.9240928	0.9241 (0.8759 – 0.9749)
Ceramide (d40:2) levels on AP	Inverse variance weighted	21	0.0179	1.0862812	1.0863 (1.0144 – 1.1633)
Phosphatidylcholine (18:2_0:0) levels on AP	Inverse variance weighted	15	0.0376	1.1107408	1.1107 (1.0060 – 1.2263)
Phosphatidylethanolamine (18:2_0:0) levels on AP	Inverse variance weighted	27	0.0125	1.0802986	1.0803 (1.0167 – 1.1478)
Phosphatidylcholine (16:0_18:2) levels on AP	Inverse variance weighted	35	0.0289	1.0576739	1.0577 (1.0058 – 1.1123)
Phosphatidylcholine (16:0_20:5) levels on AP	Inverse variance weighted	24	0.0385	0.9458657	0.9459 (0.8973 – 0.9971)
Phosphatidylcholine (17:0_18:2) levels on AP	Inverse variance weighted	24	0.0414	1.0696650	1.0697 (1.0026 – 1.1412)
Phosphatidylcholine (17:0_20:4) levels on AP	Inverse variance weighted	28	0.0337	0.9563220	0.9563 (0.9177 – 0.9966)
Phosphatidylcholine (18:0_18:1) levels on AP	Inverse variance weighted	27	0.0035	0.9079089	0.9079 (0.8510 – 0.9687)
Phosphatidylcholine (18:0_18:2) levels on AP	Inverse variance weighted	32	0.0458	1.0625969	1.0626 (1.0011 – 1.1278)
Phosphatidylcholine (18:0_20:4) levels on AP	Inverse variance weighted	25	0.0049	0.9452886	0.9453 (0.9089 – 0.9831)
Phosphatidylcholine (18:0_20:5) levels on AP	Inverse variance weighted	22	<0.001	0.9183995	0.9184 (0.8748 – 0.9642)
Phosphatidylcholine (18:1_18:1) levels on AP	Inverse variance weighted	22	0.0194	1.0895254	1.0895 (1.0139 – 1.1707)
Phosphatidylcholine (18:1_18:2) levels on AP	Inverse variance weighted	21	0.0140	1.0793341	1.0793 (1.0156 – 1.1471)
Phosphatidylcholine (18:1_20:3) levels on AP	Inverse variance weighted	25	0.0253	1.0726065	1.0726 (1.0087 – 1.1405)
Phosphatidylcholine (O–18:2_20:4) levels on AP	Inverse variance weighted	21	0.0099	0.9137306	0.9137 (0.8532 – 0.9785)
Phosphatidylinositol (16:0_18:1) levels on AP	Inverse variance weighted	17	0.0077	1.1304235	1.1304 (1.0329 – 1.2371)
Phosphatidylinositol (18:0_18:1) levels on AP	Inverse variance weighted	23	0.0088	1.1065921	1.1066 (1.0258 – 1.1937)
Phosphatidylinositol (18:0_18:2) levels on AP	Inverse variance weighted	33	0.0285	1.0616357	1.0616 (1.0063 – 1.1200)
Phosphatidylinositol (18:1_18:1) levels on AP	Inverse variance weighted	23	<0.001	1.1218038	1.1218 (1.0576 – 1.1899)
Sphingomyelin (d34:2) levels on AP	Inverse variance weighted	27	0.0034	0.9036391	0.9036 (0.8444 – 0.9670)
Triacylglycerol (48:0) levels on AP	Inverse variance weighted	17	0.0426	0.9304780	0.9305 (0.8679 – 0.9976)
Triacylglycerol (48:2) levels on AP	Inverse variance weighted	23	0.0417	0.9259532	0.9260 (0.8599 – 0.9971)
Triacylglycerol (50:3) levels on AP	Inverse variance weighted	29	0.0356	0.9310484	0.9310 (0.8710 – 0.9952)
Triacylglycerol (50:4) levels on AP	Inverse variance weighted	28	0.0231	0.9220196	0.9220 (0.8596 – 0.9889)
Triacylglycerol (54:3) levels on AP	Inverse variance weighted	29	0.0353	1.0787152	1.0787 (1.0052 – 1.1576)
Triacylglycerol (56:7) levels on AP	Inverse variance weighted	32	0.0305	0.9264219	0.9264 (0.8645 – 0.9928)



B

Exposure	method	nsnp	pval	or	OR (95% CI)
AP on Sterol ester (27:1/16:0) levels	Inverse variance weighted	96	0.0850	0.9402441	0.9402 (0.8766 – 1.0085)
AP on Sterol ester (27:1/18:1) levels	Inverse variance weighted	96	0.2365	0.9630963	0.9631 (0.9050 – 1.0250)
AP on Sterol ester (27:1/20:2) levels	Inverse variance weighted	96	<0.001	0.8572733	0.8573 (0.7861 – 0.9349)
AP on Sterol ester (27:1/20:4) levels	Inverse variance weighted	96	0.3488	0.9736525	0.9737 (0.9208 – 1.0296)
AP on Sterol ester (27:1/20:5) levels	Inverse variance weighted	96	0.4278	0.9787514	0.9788 (0.9281 – 1.0321)
AP on Ceramide (d40:2) levels	Inverse variance weighted	96	0.8485	1.0097135	1.0097 (0.9144 – 1.1150)
AP on Phosphatidylcholine (18:2_0:0) levels	Inverse variance weighted	96	0.2926	0.9699002	0.9699 (0.9162 – 1.0267)
AP on Phosphatidylethanolamine (18:2_0:0) levels	Inverse variance weighted	96	0.2365	0.9659234	0.9659 (0.9120 – 1.0230)
AP on Phosphatidylcholine (16:0_18:2) levels	Inverse variance weighted	96	0.0104	0.9330578	0.9331 (0.8849 – 0.9838)
AP on Phosphatidylcholine (16:0_20:5) levels	Inverse variance weighted	96	0.6112	1.0141870	1.0142 (0.9606 – 1.0708)
AP on Phosphatidylcholine (17:0_18:2) levels	Inverse variance weighted	96	0.0429	0.9439054	0.9439 (0.8926 – 0.9982)
AP on Phosphatidylcholine (17:0_20:4) levels	Inverse variance weighted	96	0.7869	1.0073688	1.0074 (0.9551 – 1.0624)
AP on Phosphatidylcholine (18:0_18:1) levels	Inverse variance weighted	96	0.9974	1.0000957	1.0001 (0.9433 – 1.0603)
AP on Phosphatidylcholine (18:0_18:2) levels	Inverse variance weighted	96	0.0592	0.9492949	0.9493 (0.8993 – 1.0020)
AP on Phosphatidylcholine (18:0_20:4) levels	Inverse variance weighted	96	0.8586	1.0047912	1.0048 (0.9533 – 1.0590)
AP on Phosphatidylcholine (18:0_20:5) levels	Inverse variance weighted	96	0.5364	1.0174461	1.0174 (0.9632 – 1.0748)
AP on Phosphatidylcholine (18:1_18:1) levels	Inverse variance weighted	96	0.7961	1.0078800	1.0079 (0.9496 – 1.0697)
AP on Phosphatidylcholine (18:1_18:2) levels	Inverse variance weighted	96	0.1263	0.9579347	0.9579 (0.9066 – 1.0122)
AP on Phosphatidylcholine (18:1_20:3) levels	Inverse variance weighted	96	0.7964	0.9930338	0.9930 (0.9417 – 1.0472)
AP on Phosphatidylcholine (O–18:2_20:4) levels	Inverse variance weighted	96	0.7528	1.0092529	1.0093 (0.9530 – 1.0688)
AP on Phosphatidylinositol (16:0_18:1) levels	Inverse variance weighted	96	0.8556	1.0052651	1.0053 (0.9500 – 1.0638)
AP on Phosphatidylinositol (18:0_18:1) levels	Inverse variance weighted	96	0.2089	0.9619263	0.9619 (0.9054 – 1.0220)
AP on Phosphatidylinositol (18:0_18:2) levels	Inverse variance weighted	96	<0.001	0.8998748	0.8999 (0.8472 – 0.9558)
AP on Phosphatidylinositol (18:1_18:1) levels	Inverse variance weighted	96	0.4484	0.9767713	0.9768 (0.9192 – 1.0380)
AP on Sphingomyelin (d34:2) levels	Inverse variance weighted	96	0.6548	0.9870029	0.9870 (0.9320 – 1.0453)
AP on Triacylglycerol (48:0) levels	Inverse variance weighted	96	0.3640	1.0285087	1.0285 (0.9679 – 1.0929)
AP on Triacylglycerol (48:2) levels	Inverse variance weighted	96	0.9270	0.9973186	0.9973 (0.9417 – 1.0563)
AP on Triacylglycerol (50:3) levels	Inverse variance weighted	96	0.5386	0.9822325	0.9822 (0.9277 – 1.0400)
AP on Triacylglycerol (50:4) levels	Inverse variance weighted	96	0.4110	0.9751730	0.9752 (0.9184 – 1.0354)
AP on Triacylglycerol (54:3) levels	Inverse variance weighted	96	0.7076	1.0108091	1.0108 (0.9556 – 1.0692)
AP on Triacylglycerol (56:7) levels	Inverse variance weighted	96	0.3176	0.9687467	0.9687 (0.9103 – 1.0310)

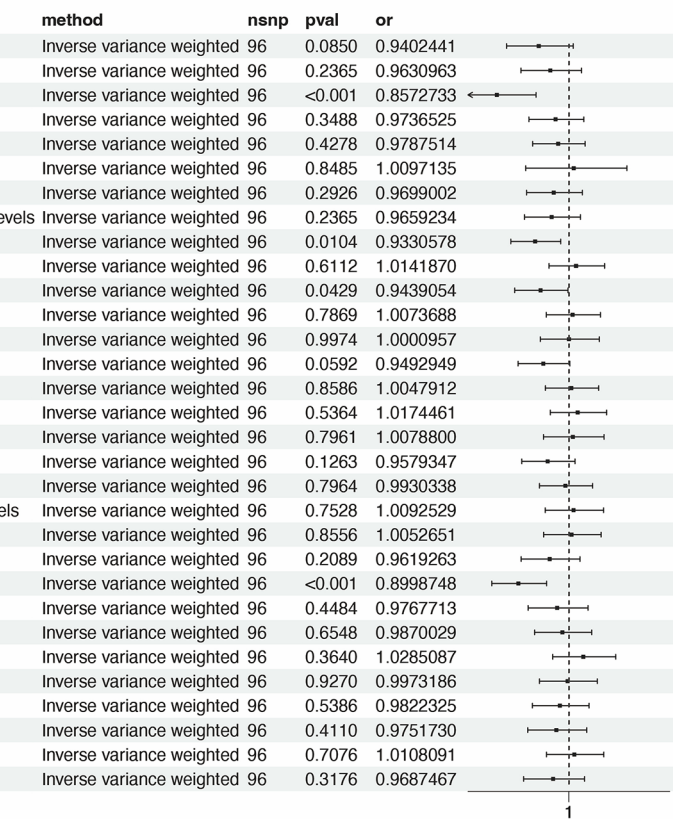


Fig. 2. Forest plot of bidirectional causal associations between lipidome and AP. This figure illustrates the significant potential causal relationship between various lipidome components and AP. (**A**) Depicts the effects of lipidome entities on AP risk. (**B**) Shows the reverse causal influences of AP on lipidome profiles. The forest plots present effect sizes with confidence intervals for each significant association.

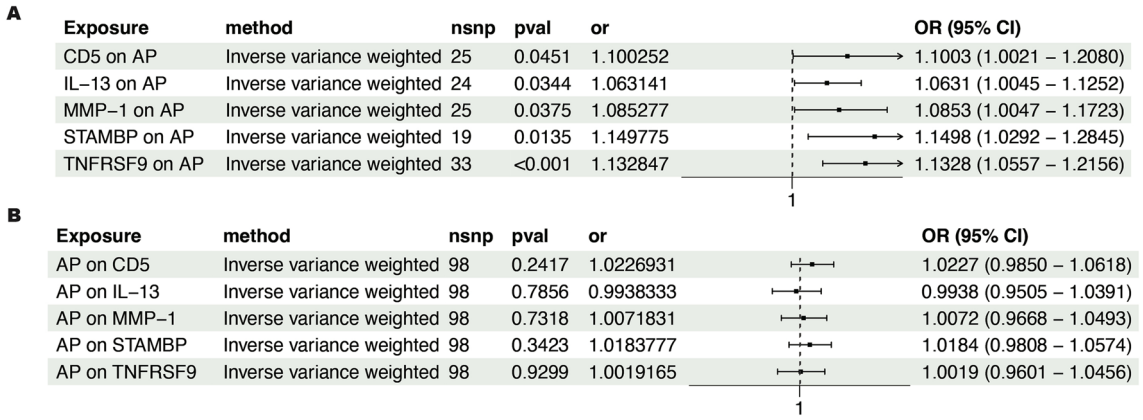


Fig. 3. Forest plot of bidirectional causal associations between inflammatory factors and AP. This figure illustrates the significant potential causal relationship between inflammatory factors and AP. (**A**) Displays the effects of various inflammatory factors on AP risk. (**B**) Demonstrates the reverse causal influences of AP on inflammatory factor levels. Effect sizes and confidence intervals are presented for each significant association.

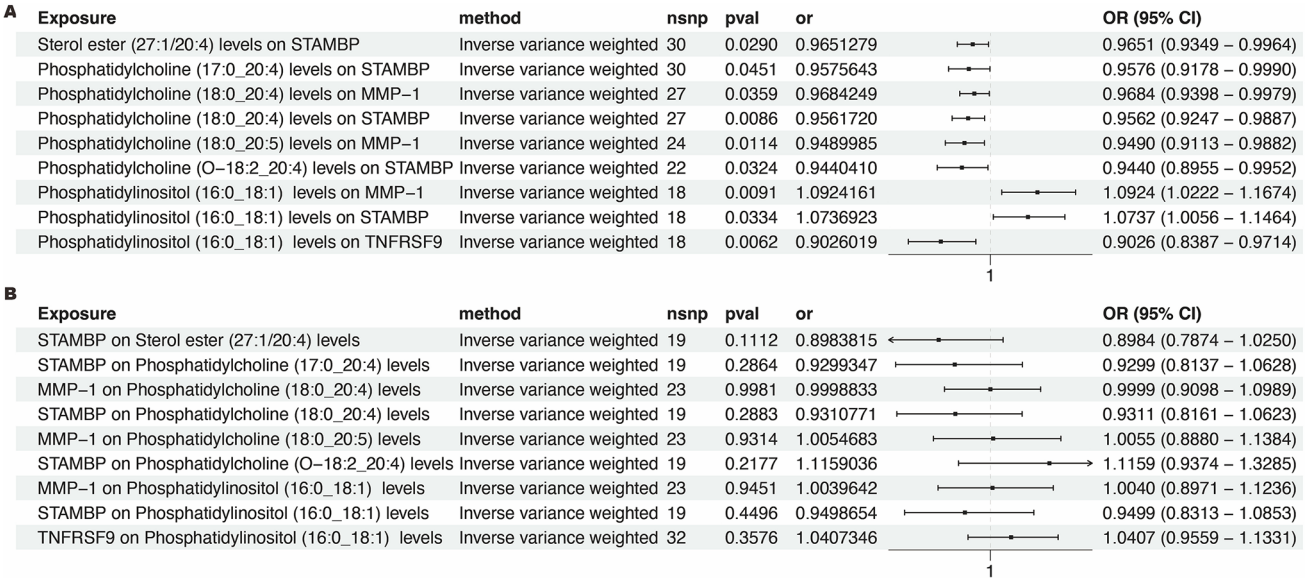


Fig. 4. Forest plot of bidirectional causal associations between lipidome and inflammatory factors. This figure illustrates the significant potential causal relationship between lipidome components and inflammatory factors. (**A**) Depicts the effects of key lipidome entities on inflammatory factor levels. (**B**) Shows the reverse causal influences of prominent inflammatory factors on lipidome profiles. Effect sizes and confidence intervals are presented for each significant association.

randomization approach to investigate the potential causal relationship between various lipid species and AP, as well as between inflammatory factors and AP. Furthermore, we explored whether inflammatory mediators could serve as intermediary factors in the lipid-AP causal relationship.

MR serves as a powerful tool to infer potential causal relationships between exposures and outcomes by using genetic variants as instrumental variables. This approach effectively minimizes confounding factors and reverse causation that often plague observational studies. By leveraging publicly available GWAS summary statistics from different cohorts, MR allows for the integration and normalization of results across studies, enhancing the robustness of findings. However, combining datasets from different sources introduces potential challenges such as heterogeneity, pleiotropy, and reverse causation[20]. We applied rigorous selection criteria for instrumental variables, ensuring they satisfied the core MR assumptions. Heterogeneity was assessed using Cochran's Q-test. We evaluated pleiotropy through the MR-Egger intercept test and the MR-PRESSO method, excluding instruments exhibiting horizontal pleiotropy[21]. Reverse causation was addressed by conducting bidirectional MR analyses to confirm the directionality of associations.

After accounting for heterogeneity, pleiotropy, and potential reverse causation in lipidomic data, 23 lipidome entities were found to be significantly causally correlated with AP, and 5 inflammatory factors showed a

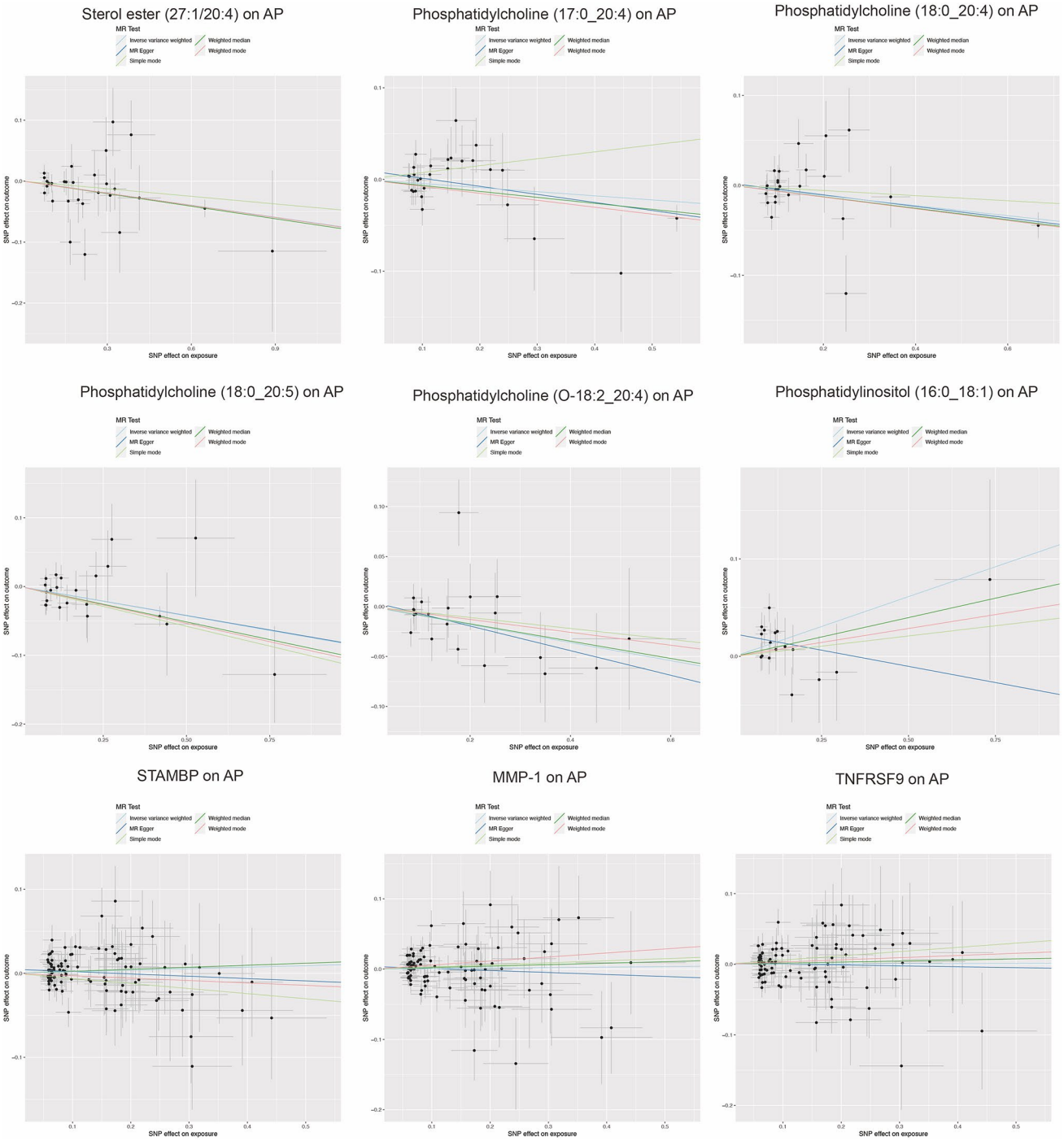


Fig. 5. Scatter plots of statistically significant causal effects on acute pancreatitis (AP) from MR analysis. (**A**) Causal effects of statistically significant lipidome components on AP risk identified through MR analysis. (**B**) Causal effects of statistically significant inflammatory factors on AP risk identified through MR analysis.

significant causal relationship with AP. Subsequent analyses revealed that some lipid species could affect the incidence of AP by influencing inflammatory factors. Our study identified a negative association between Sterol ester (27:1/20:4) and the incidence of AP. This particular sterol ester, composed of a sterol with 27 carbons and one unsaturated bond and a fatty acid with 20 carbons and four unsaturated bonds, implies a cholesterol molecule esterified with arachidonic acid. Despite the lack of direct reports linking Sterol ester (27:1/20:4) with AP, it is plausible that arachidonic acid, in its esterified form, is less readily metabolized into pro-inflammatory mediators, thereby reducing the inflammatory response. Our findings suggest that STAMBP (STAM binding protein), which deubiquitinates NALP7 and increases its abundance by preventing lysosomal trafficking, may promote inflammatory factors[22]. The role of STAMBP in promoting AP has not been directly reported previously,

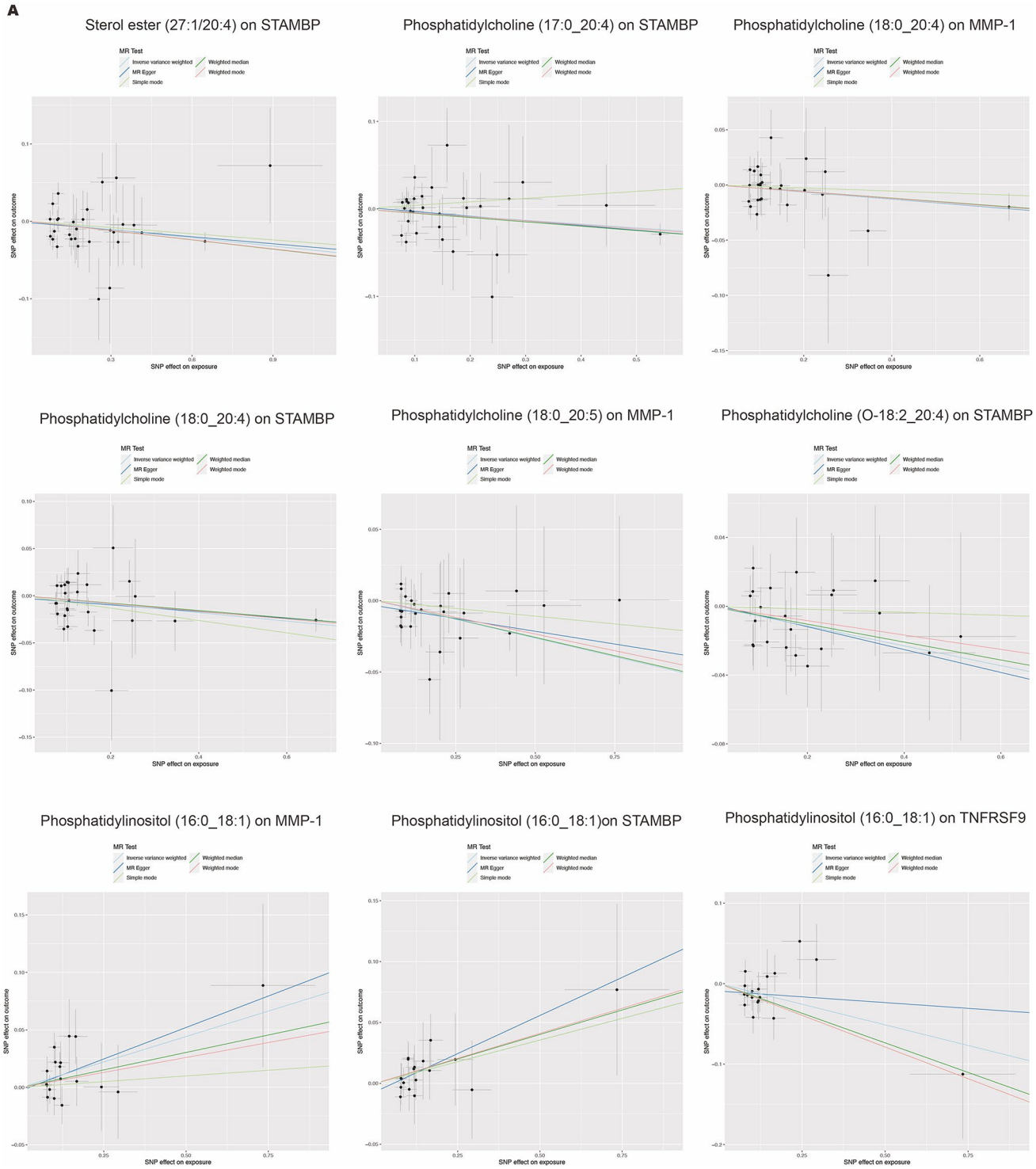


Fig. 6. Mediation analysis of lipidome-inflammatory factor-AP interactions. (**A**) Scatter plot illustrating the causal effects of statistically significant lipidome components on inflammatory factors. (**B**) Visual summary of the mediation analysis, depicting how inflammatory factors mediate the relationship between lipidome and AP. The diagram highlights the indirect pathways through which lipidome influences AP risk via modulation of inflammatory responses.

and the detailed mechanisms underlying its involvement warrant further investigation. In our analysis, Sterol ester (27:1/20:4) was inversely correlated with STAMBP levels, and STAMBP accounted for 7.525% of the variance in the protective effect of Sterol ester (27:1/20:4) against AP. The molecular and biological impact of Sterol ester (27:1/20:4) on STAMBP is understudied, and future research is needed to reveal the mechanisms involved.

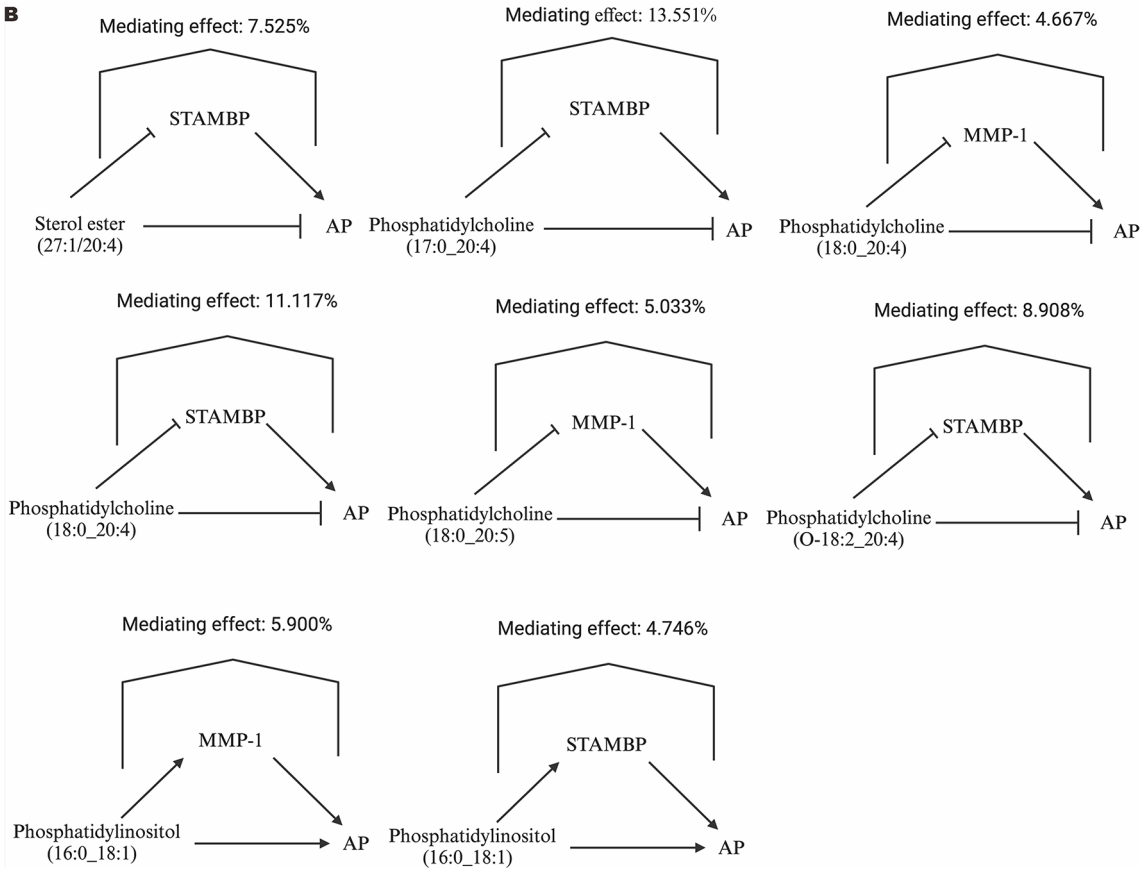


Figure 6. (continued)

In our study, a causal relationship between certain phosphatidylcholine species and the incidence of AP has been established. Specifically, levels of Phosphatidylcholine (17:0_20:4), Phosphatidylcholine (18:0_20:4), Phosphatidylcholine (18:0_20:5), and Phosphatidylcholine (O-18:2_20:4) were inversely correlated with AP occurrence. Phosphatidylcholines (PCs) are integral membrane constituents known for their roles in signaling and immune regulation[23]. Prior research has indicated a reduction in phosphatidylcholine levels in the plasma of AP patients compared to healthy individuals[24]. The diminution of steatohepatitis development through mechanisms involving LRH-1/PPARγ2/NFκB signaling pathways has been linked to phosphatidylcholine[25]. Additionally, phosphatidylcholine has been shown to remodel the gut microbiome structure, particularly in LPS-treated mice, by increasing the relative abundance of Rikenellaceae and Lachnospiraceae families, thereby mitigating inflammation[26]. It has been reported that polyenoylphosphatidylcholine ameliorates pancreatic damage by enhancing the membrane fluidity of pancreatic acinar cells and the activity of pancreatic tissue calcium pumps. Furthermore, polyenoylphosphatidylcholine scavenges oxygen free radicals and decreases lipid peroxide levels[27]. STAMBP was found to account for 13.551% of the inhibitory effect of Phosphatidylcholine (17:0_20:4) on AP, and similarly for the effects of Phosphatidylcholine (18:0_20:4) and Phosphatidylcholine (O-18:2_20:4). While no direct studies have yet demonstrated the influence of these lipid species on STAMBP, their impact on inflammation has been increasingly substantiated. Future investigations are warranted to explore the effects of phosphatidylcholine on STAMBP and its role in AP pathogenesis.

Phosphatidylcholine (18:0_20:4) and Phosphatidylcholine (18:0_20:5) levels are inversely associated with MMP-1 levels, with MMP-1 accounting for 4.667% and 5.033% respectively of the variance in the negative correlation of Phosphatidylcholine (18:0_20:4) and Phosphatidylcholine (18:0_20:5) with AP. MMPs are endopeptidases that degrade extracellular matrix proteins and potentiate pro-inflammatory cytokine activity. An increase in MMP-1 activity can facilitate inflammatory cell infiltration and tissue remodeling, potentially exacerbating inflammation and damage within the pancreatic architecture during AP. Higher serum levels of activated matrix metalloproteinase have been predictive of more severe acute pancreatitis[28]. Pretreatment with a matrix metalloprotease inhibitor was found to attenuate the development of acute pancreatitis-induced lung injury by suppressing IL-6 in a rat model[29]. Polyene phosphatidylcholine has been suggested to reduce the generation of reactive oxygen species (ROS), which are key activators of MMP-1 expression[30]. Thus, Phosphatidylcholine (18:0_20:4) and Phosphatidylcholine (18:0_20:5) may suppress MMP-1 expression by inhibiting ROS production, thereby mitigating the onset of AP. However, the underlying mechanisms require further elucidation through experimental research.

Conversely, Phosphatidylinositol (16:0_18:1) was found to be positively causally associated with AP. MMP1 and STAMBP account for 5.9% and 4.746% respectively of the positive correlation between Phosphatidylinositol (16:0_18:1) and AP. Phosphatidylinositol is a crucial component of the cellular membrane, with its downstream molecules PI3K and Akt playing pivotal roles in inflammation-related diseases. Specifically, the PI3K-Akt pathway was enriched in severe acute pancreatitis (SAP), and the phosphorylation levels of Akt and NF-κB p65 are known to play important roles in the inflammatory processes of AP[31]. The PI3K/Akt signaling pathway has been shown to be a key pathway in the regulation of MMP1 expression, and Akt activates NF-κB by phosphorylating its downstream targets, such as IKK or other molecules related to the NF-κB pathway, which subsequently migrate to the nucleus and enhance MMP1 gene expression[32]. Thus, Phosphatidylinositol (16:0_18:1) may promote MMP-1 level by influencing PI3K/AKT, thereby influencing the onset of AP. However, there lacks of study reporting the regulation of Phosphatidylinositol to STAMBP. The impact of Phosphatidylinositol (16:0_18:1) on MMP1 and STAMBP expression and its subsequent effects on AP pathogenesis merit further investigation.

In examining the complex associations between lipidome profiles, inflammatory factors, and AP, we acknowledge certain limitations in our methodology. While MR provides a powerful tool for exploring potential causal relationship, its reliability is fundamentally dependent on the quality of the instrumental variables. Although we implemented stringent selection criteria, the possibility of residual confounding—particularly through linkage disequilibrium or pleiotropy among the investigated lipidome components and inflammatory factors—cannot be entirely excluded. This potential confounding may impact the accuracy of our conclusions. This could potentially affect the accuracy of our findings. Secondly, our SNP selection threshold ($p < 5 \times 10^{-5}$) was less stringent than the conventional genome-wide significance level ($p < 5 \times 10^{-8}$). This methodological choice, while increasing our sample of SNPs and bolstering statistical power, may have inadvertently introduced weak instrument bias, a factor that warrants careful consideration[33]. Such bias can skew causal estimates towards observational associations, potentially increasing the risk of false-positive results[34]. Although our study provides insights into specific lipidome components and inflammatory factors, it does not capture the entire spectrum of molecules involved in AP pathophysiology. Thus, our findings illuminate only a portion of the complex AP landscape. The clinical application of these results requires additional validation through rigorous experimental studies and clinical trials. To develop efficacious AP treatments targeting lipid metabolism and inflammatory pathways, a thorough comprehension of the underlying molecular mechanisms and their clinical implications is essential.

In conclusion, our study identified specific lipid species that potentially modulate acute pancreatitis risk through inflammatory pathways. Phosphatidylcholines and sterol esters appear to exert protective effects against AP, partially mediated by reductions in pro-inflammatory mediators like STAMBP and MMP-1. Conversely, phosphatidylinositol (16:0_18:1) may increase AP risk by elevating these inflammatory factors. These findings enhance our understanding of the lipidome's role in AP pathogenesis and may inform the development of targeted therapeutic strategies. Future research should focus on experimental validation of these relationships and exploration of underlying molecular mechanisms.

Data availability

All the data were obtained from IEU Open GWAS project (https://gwas.mrcieu.ac.uk/).

Received: 11 October 2024; Accepted: 2 January 2025
Published online: 08 January 2025

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Author contributions

Wenbin Liu, Song Yang and Yuhan Li did statistics and wrote the main manuscript text and prepared figures. Dava Tenzing, Ruizi Shi, Yang Jiang and Hao Deng did the data curation and formal analysis. Yihui Wang, Ying Chen and Enqiang Mao did the supervisor jod. All authors reviewed the manuscript.

Funding

(1) Xizang Autonomous Region Natural Science Foundation Group Medical Aid Project (XZ2023ZR-ZY35[Z]); (2) Natural Science Foundation (Joint) Project of Shigatse City (RKZ2023ZR-013[Z]); (3) Natural Science Foundation (Joint) Project of Shigatse City (RKZ2023ZR-017[Z]).

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-85354-y.

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