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Analysis

Exploring the genetic causal inference between plasma lipidome and lung carcinoma: a bidirectional mendelian randomization study

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Abstract

Background Clinical observational studies have highlighted differences in plasma lipid profiles between lung carcinoma patients and healthy individuals. However, the causal relationship underlying these differences remains unclear. This study aims to investigate the bidirectional causal relationship between 179 plasma lipids and lung carcinoma.

Methods A bivariate two-sample Mendelian randomization (MR) study was conducted using data from public genome-wide association studies (GWAS). The primary analytical technique employed was the inverse variance weighting method (IVW), with MR-Egger, weighted-median, and weighted mode as supplementary methods. Sensitivity analyses including Cochran's Q test and MR-Egger intercept test were performed to ensure the robustness of the results.

Results Mendelian randomization analysis revealed positive associations between levels of certain plasma lipidome—Sterol ester 27:1/20:5 levels (OR 1.162, 95% confidence interval (CI) 1.077–1254, P $1.15e^{-4}$), Phosphatidylcholine (PC) 20:4_0:0 levels (OR 1.112, 95%CI 1.051–1.176, P $2.33e^{-4}$), PC 17:0_20:4 levels (OR 1.108, 95%CI 1.051–1.167, P $1.33e^{-4}$, PC 18:0_20:4 levels (OR 1.094, 95%CI 1.046–1.144, P $8.08e^{-5}$), PC O-16:0:4 levels (OR 1.180, 95%CI 1.089–1.277, P$4.61e^{-5}$), PC O-16:1_20:4 levels (OR 1.155, 95%CI 1.077–1.239, P $5.00e^{-5}$)—with the risk of lung carcinoma. Conversely, PC 15:0_18:2 levels (OR 0.823, 95%CI 0.760–0.892, P$1.95e^{-6}$), PC 16:0_18:2 levels (OR 0.863, 95%CI 0.801–0.931, P $1.28e^{-4}$), PC 16:1_18:2 levels (OR 0.856, 95%CI 0.791–0.926, P $1.13e^{-4}$), PC 18:1_18:2 levels (OR 0.847, 95%CI 0.77–0.911, P $9.15e^{-6}$) were inversely associated with the risk of lung carcinoma. Reverse Mendelian randomization analysis indicated that lung carcinoma did not have a significant causal effect on the 179 plasma lipids.

Conclusion Our study reveals the causal relationship between plasma lipidome and lung cancer, provides preliminary genetic evidence, and provides a new idea for understanding the pathogenesis of lung cancer and finding promising therapeutic targets.

Keywords Plasma lipidome · Lung carcinoma · Mendelian randomization · Biomarkers

Abbreviations

MR	Mendelian randomization
GWAS	Genome-wide association studies

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IVW	Inverse variance weighting
CI	Confidence interval
PC	Phosphatidylcholine
SCLC	Small-cell lung carcinoma
NSCLC	Non-small cell lung carcinoma
LUSC	Lung Quamous cell carcinoma
LUAD	Lung adenocarcinoma
OS	Overall survival
PE	Phosphatidylethanolamine
PG	Phosphatidylglycerol
PI	Phosphatidylinositol
PS	Phosphatidylserine
IVs	Instrumental variables
SNP	Single nucleotide polymorphisms
LD	Linkage disequilibrium
VM	Simple weighted median
ADCR	Adenocarcinoma
oxPC	Oxidized phosphatidylcholine

1 Introduction

Lung cearcinoma remains the leading cause of cancer-related mortality worldwide [1], with recent data indicating nearly 2.5 million new cases of lung carcinoma and over 1.8 million deaths annually [2]. Categorically, lung carcinoma can be segmented into small-cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) based on tissue type, with the latter encompassing lung adenocarcinoma and lung squamous cell carcinoma [3]. Despite significant advancements in the comprehensive treatment of lung carcinoma, including surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy, the 5-year overall survival rate (OS) for lung carcinoma remains around 20% [4, 5]. Therefore, the early detection of cancer plays a pivotal role in enhancing the OS rate for individuals with lung carcinoma. Previous studies have unraveled the complexity of lung carcinoma pathogenesis, implicating various risk factors such as smoking, air pollution, and genetic susceptibility [6, 7]. While specific genes associated with lung carcinoma have been identified, along with the development of targeted drugs, challenges persist, including high false-positive rates during detection and therapeutic resistance to targeted drugs, affecting treatment efficacy [8, 9]. Consequently, the quest for novel genetic variants linked to lung carcinoma continues to be demanding, emphasizing the urgency for screening and identifying new biomarkers for early diagnosis of lung carcinoma.

Advancements in lipidomics techniques have enriched our understanding of circulating lipids, encompassing a diverse array of lipids such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylinositol (PI), phosphatidylserine (PS), and other subclasses [10]. Lipids play essential roles in various biological functions, contributing to biofilm composition, energy storage, signal transduction, apoptosis, and human cancer [11]. The predictive potential of plasma lipidome has been demonstrated in diagnosing conditions like type 2 diabetes, cardiovascular disease, and cancer [12–15]. Recent studies have increasingly focused on dyslipidemia in lung carcinoma patients. For instance, Zhu et al. investigated plasma lipidome characteristics in lung carcinoma patients, highlighting variations in lipid composition and concentration based on lung carcinoma subtype, gender, age, stage, metastasis status, nutritional condition, and clinical phenotype severity [16]. Han et al. explored the plasma lipid profile of NSCLC patients, revealing abnormal lipid metabolism, 1particularly in fatty acid, phospholipid, and triglyceride metabolism [17]. Furthermore, Sun et al. devised a lung carcinoma-specific scoring model centered on lipid traits, emphasizing dysregulated lipid metabolism in lung carcinoma cells [18]. In addition, some studies based on the correlation between metabolic enzyme genes and plasma lipids have also been carried out, and it has been found that CYP1 A1 Ile462 Val polymorphism is associated with reduced risk of lung adenocarcinoma [19], while the combination of GSTM1, GSTT1 and GSTP1 genotypes is not associated with increased risk of lung cancer [20, 21].The evolution of GWAS has enhanced our understanding of genetic variants influencing lipid levels [22, 23]. Hence, a study design minimally affected by confounding bias is crucial for establishing the causal link between lipidome and lung carcinoma.

Presently, investigations into the relationship between plasma lipids and lung carcinoma are somewhat limited and predominantly observational. Traditional observational studies are hindered by constraints like reverse causality and residual confounding factors [24–26]. MR emerges as a potent causal inference method, leveraging multiple genetic variants as instrumental variables to test specific hypotheses [24, 27]. MR Studies overcome the limitations of observational studies, addressing confounding factors and reverse causality for more robust outcomes [25–30]. In this study, we aggregated recently published GWAS statistics on 179 lipids and lung carcinoma. Through comprehensive two-sample two-way MR Analysis, we aim to unveil the causal relationship between these variables, shedding light on the connection between lung carcinoma pathogenesis and plasma lipid metabolism while identifying potential therapeutic targets.

2 Materials and methods

2.1 Study design

The study utilized publicly available data with the investigator's consent and the approval from their respective institutional ethics review boards. Given the secondary data used in this study, an exemption was obtained from the Medical Ethics Committee of Jiashan First People's Hospital. What's more, we confirm that this study adheres to the STROBE-MR guidelines. The supplementary materials contain detailed findings.

2.2 Investigation of causal relationship

A two-sample MR Analysis was conducted to investigate the causal association between plasma lipid types and lung carcinoma. Single nucleotide polymorphisms (SNPs) were utilized as instrumental variables (IVs), following three core assumptions: (1) Genetic variation is linked to the exposure. (2) Genetic variation is independent of confounders. (3) Genetic variation impacts outcomes solely through exposure pathways [31, 32](Fig. 1).

2.3 Genome-wide association study (GWAS) data sources

Genome-wide significant SNPs associated with lung carcinoma, meeting a significance threshold of $p < 5 \times 10^{-8}$, were selected as IVs from the GWAS dataset: ebi-a-GCST90018875. The GWAS analysis encompassed 24,188,684 SNPs in 492,803 individuals of European descent (nCase = 3791, nControl = 489,012). Due to the heterogeneity of different pathological types of lung cancer, to further investigate the potential causal relationship between plasma lipids and different pathological types of lung cancer, subgroup analyses were performed using lung cancer subtype-specific data. The GWAS summary data from bbj-a-133 data sets (https://gwas.mrcieu.ac.uk/datasets/bbj-a-133/), which covers a total of 8,885,805 SNPs, including 4050 cases and 208,403 controls.

2.4 Plasma lipidome GWAS data sources

Plasma lipid data were derived from a comprehensive GWAS study conducted on Finns, examining 179 lipid species in 7174 Finnish individuals. This research revealed genetic associations between diseases and unconventional lipid species, beyond traditional lipids. It is important to note that the exposure in this study did not overlap with the outcome population.

2.5 Instrumental variable selection

Significant IVs ($P < 5e^{-8}$) were initially extracted from the plasma lipid GWAS dataset. Using the clump program in PLINK software and based on European 1000 Genomes Project linkage disequilibrium (LD) information, SNPs were clustered with an r^2 threshold of 0.001 and an aggregation distance of 10,000. SNPs with LD > 0.8 were identified, with exclusion of palindromic SNPs when harmonizing plasma lipid and lung carcinoma GWAS datasets. Each SNP's F statistics were calculated to assess its instrumental strength, eliminating IVs with low F statistics (< 10) and retaining credible IVs for subsequent analyses.

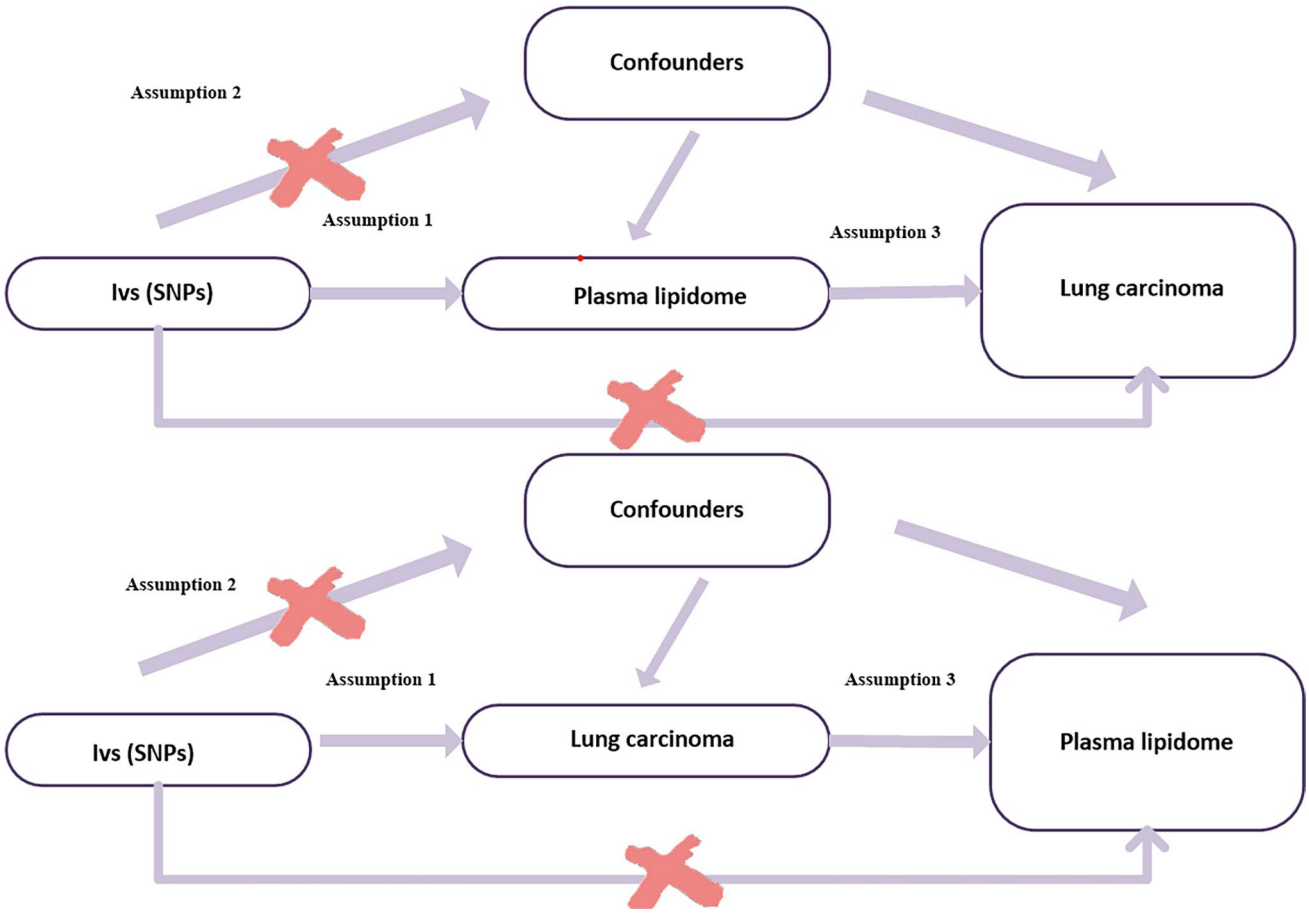

Fig. 1 Directed acyclic diagram of MR Framework to explore the causal relationship between Plasma Lipidome and Lung carcinoma

2.6 Statistical analysis

R software (version 4.2.1) was employed for all statistical analyses. The "TwoSample MR" R package facilitated the two-sample MR Analysis and graph generation. Various methods, including inverse-variance weighted (IVW), MR-Egger, simple weighted median (WM), and Weighted mode, were utilized to evaluate the bidirectional causal relationship between plasma lipids and lung carcinoma. The IVW analysis, serving as the primary approach, provided robust estimates without an intercept term in regression [33]. Cochrane's Q values were used to assess heterogeneity among SNPs in IVW analyses, and potential outlier influences were examined through scatterplot and funnel plot assessments. In addition, the scatter plot shows that the results are not affected by outliers. The funnel plot shows the robustness of the correlation without heterogeneity.

3 Results

3.1 Analysis of causality between plasma lipids and lung carcinoma

The study investigating the causal relationship between plasma lipidome and lung carcinoma employed a two-sample Mendelian randomization (MR) Analysis with the IVW method as the primary analytical tool. To counteract false positives, Bonferroni correction was applied, establishing the significance threshold at $P < 2.79e^{-4}$ for multiple tests. The MR Analysis revealed 17 plasma lipids significantly linked to lung carcinoma, with 9 posing as risk factors and 8 as protective factors (Table S1). Notably, 15 of these lipids were predominantly phosphatidylethanolamines,

while one was a sterol ester (27:1/20:5) and another a phosphatidylcholine (18:2:0). It is important to note that among the 7 plasma lipids with only 2 SNPs. MR-Egger, Weighted-median, Weighted mode analyses, and horizontal pleiotropy testing were impractical due to weak instrumental variable bias, leading to their exclusion. Six plasma lipids were found to be risk factors for lung cancer: Phosphatidylcholine (20:4_0:0) was associated with an increased risk of lung cancer (OR = 1.112, 95%CI: 1.051–1.176, P = 2.33e^{-4}). Sterol ester (27:1/20:5) was associated with lung cancer (OR = 1.162, 95%CI: 1.077–1,254, P = 1.15e^{-4}). Phosphatidylcholine (17:0_20:4) was associated with lung cancer (OR = 1.108, 95%CI: 1.051–1.167, P = 1.33e^{-4}). Phosphatidylcholine (18:0_20:4) was associated with lung cancer (OR = 1.094, 95%CI: 1.046–1.144, P = 8.08e^{-5}). Phosphatidylcholine (O-16:0_20:4) was associated with lung cancer (OR = 1.180, 95%CI: 1.089–1.277, P = 4.61e^{-5}). Phosphatidylcholine (O-16:1_20:4) was associated with lung cancer (OR = 1.155, 95%CI: 1.077–1.239, P = 5.00e^{-5}). Four plasma lipids were found to be protective factors for lung cancer: Phosphatidylcholine (15:0_18:2) was associated with8 lung cancer (OR = 0.823, 95%CI: 0.760–0.892, P = 1.95e^{-6}). 1.95283275425699E-06 and lung cancer OR 0.863(95%CI, 0.801–0.931, P = 1.28e^{-4}); Phosphatidylcholine (16:1_18:2) and lung cancer OR 0.856(95%CI, 0.791–0.926, P = 1.13e^{-4}); Phosphatidylcholine (18:1_18:2) was associated with lung cancer (OR = 0.847, 95%CI: 0.787–0.91, P = 9.15e^{-6}). Evaluation of genetic variation heterogeneity was conducted using the Cochran Q test, revealing P > 0.05 and signifying homogeneity in the results (Fig. 2).

To explore the causal effect of plasma lipids on different lung cancer subtypes, we performed batch two-sample MR Analysis with different lung cancer subtypes as outcome indicators. The results of the IVW method showed that a total of 8 SNPS showed statistically significant causal relationship between plasma lipids and lung cancer in different subtypes of lung cancer (Fig. 3).

Four of them were protective factors: Phosphatidylcholine (16:1_18:1) versus non-small cell lung cancer (NSCLC), OR = 0.76 (95%CI, 0.59–0.99, P = 4.5e^{-2}); The OR of Phosphatidylcholine (18:2_0:0) in lung squamous cell carcinoma (LUSC) was 0.38 (96%CI, 0.18 ~ 0.81, P = 1.2e^{-2}). Sphingomyelin (d40:1) were associated with LUSC (OR = 0.62, 95%CI: 0.43–0.89, P = 9.64e^{-3}). Sterol ester (27:1/16:1) was associated with LUAD (OR = 0.37, 95%CI: 0.15–0.91, P = 3.0e^{-2}). There are four risk factors: The OR of Sphingomyelin (d34:1) and SCLC was 2.05 (95%CI, 1.08–3.89, P = 2.76e^{-2}) and 2.92 (95%CI, 1.08–3.89, P = 2.76e^{-2}), respectively. 1.33–6.38, P = 7.43e^{-3}). The Ceramide (d42:2) was positively correlated with LUSC (OR = 1.52, 95%CI: 1.03–2.24, P = 3.35e^{-2}). The OR of Phosphatidylinositol (18:0_18:2) versus LUAD was 1.28 (95%CI, 1.04–1.59, P = 2.26e^{-2}) (Table S4).

3.2 Sensitivity analysis

A sensitivity analysis was additionally undertaken to verify the robustness of the findings (Table S2). This analysis assessed the level of pleiotropy in 17 plasma lipids with more than 2 SNPs (totaling 10 plasma lipids). Results indicated no statistically significant deviation from a zero egger_intercept for the 10 plasma lipids in MR-Egger (P value > 0.05), indicating an absence of horizontal pleiotropy (Table S3). Furthermore, the reliability of the results was reaffirmed through a leave-one analysis, with corresponding charts from the sensitivity analysis and leave-one analysis included in the article (Figs. 4, 5).

3.3 Reverse causality analysis of plasma lipids and lung carcinoma

A reverse MR Analysis was conducted on plasma lipids and lung carcinoma GWAS data, unveiling no evidence of reverse causality between the 17 genetically predicted plasma lipids and lung carcinoma. The odds ratio for lung carcinoma against sterol ester (27:1/20:5) was 0.990 (95% CI 0.863–1.136, P = 0.887) using the IVW method. Similarly, the odds ratio between lung carcinoma and phosphatidylcholine (18:2:0) was 1.057 (95% CI 0.922–1.211, P = 0.427), with neither the odds ratio nor P value indicating reverse causality between lung carcinoma and the remaining 15 phosphatidylethanolamines (Table S5). In addition, no reverse causality was found between GWAS data of lung cancer subtypes and plasma lipids by reverse MR analysis.

4 Discussion

The plasma lipidome, an integral component of clinical metabolomics, proves to be an effective tool in identifying lipid biomarkers for various diseases [14, 15]. Studies have highlighted the prevalent abnormal lipid metabolism in lung carcinoma cells [34], showcasing the specificity of the plasma lipidome in differentiating lung carcinoma and its subtypes. Research indicates differences in circulating levels of PC and PE between patients with NSCLC and

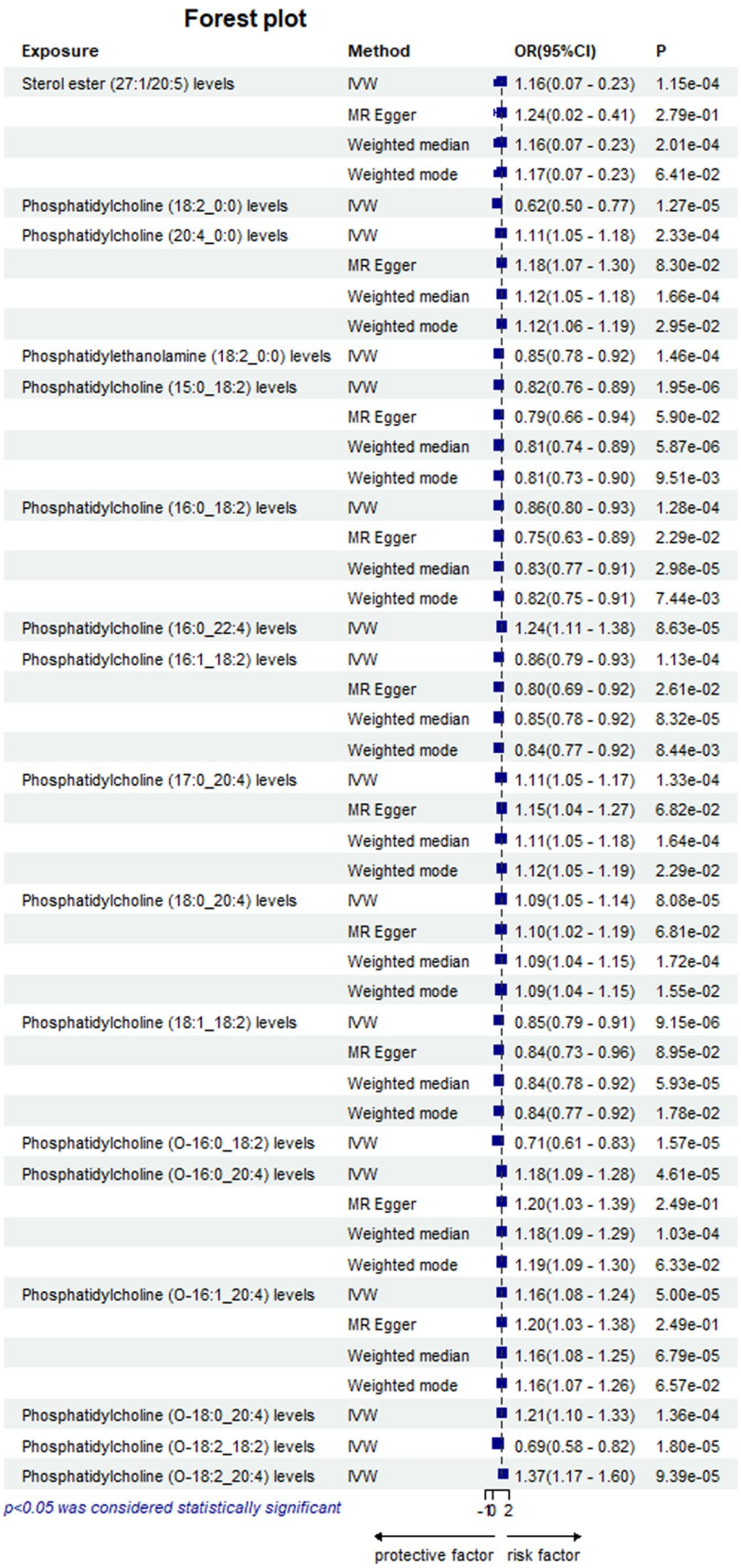

Fig. 2 Forest plot with different methods show a causal relationship between plasma lipidome and lung carcinoma. *IVW* inverse variance weighting, *CI* confidence interval

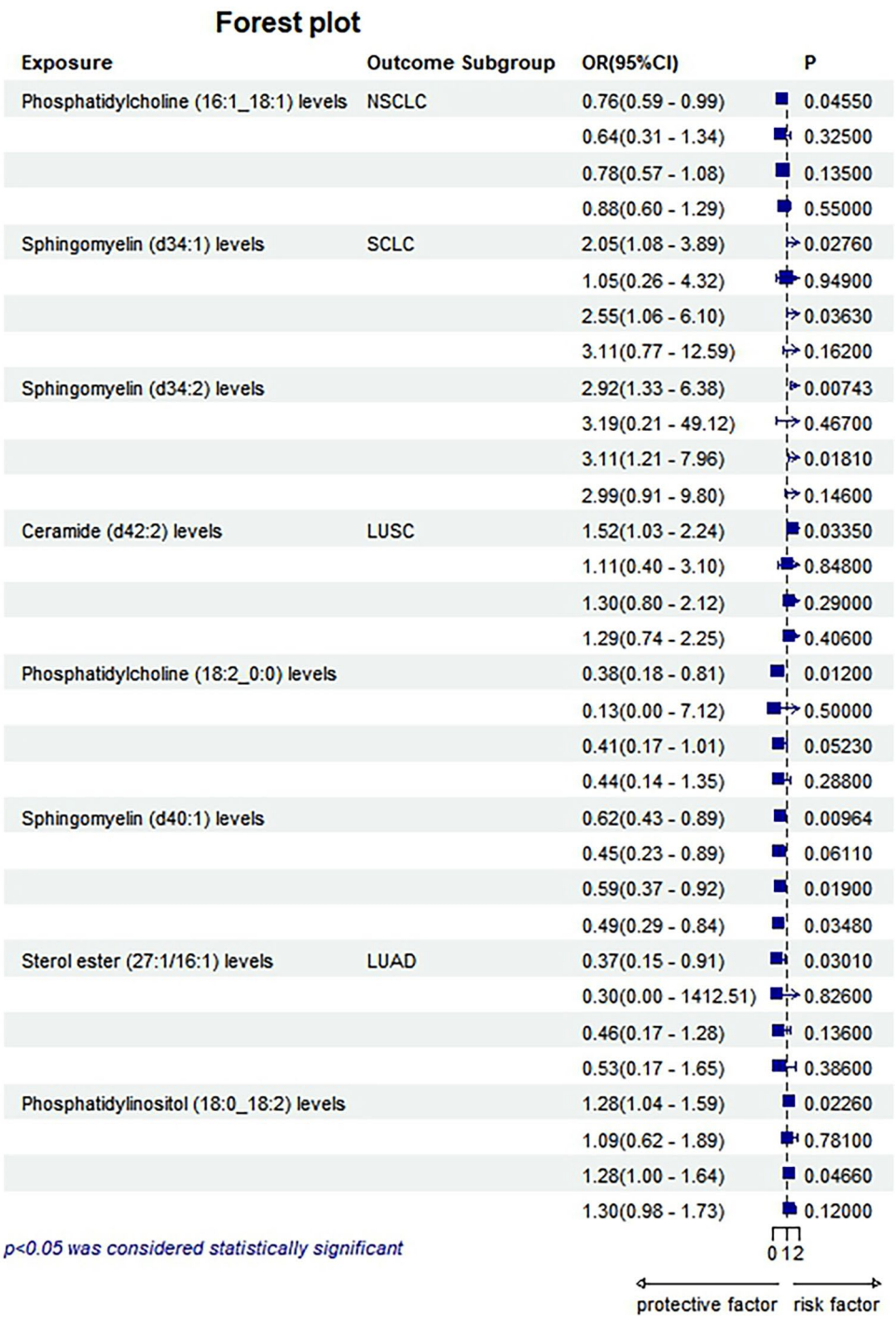

Fig. 3 Forest plot with different methods show a causal relationship between plasma lipidome and lung carcinoma subtypes. *IVW* inverse variance weighting, *CI* confidence interval

those with non-cancerous lung diseases or healthy individuals [35]. Notably, significant diversity in lipid profiles is observed among patients with squamous cell lung carcinoma, while correlations between the genetic expressions of lipid-associated proteins, enzymes, and lipid metabolomics are evident in adenocarcinoma (ADC) and SCLC [36].

Existing studies have unveiled a robust connection between the plasma lipidome and lung carcinoma [16–18, 34–36]. However, these studies are confined to clinical observational research and bioinformatics analysis, rendering them susceptible to various confounding biases. MR, a method in epidemiological research, emerges as a crucial tool for diminishing the impact of confounding factors. MR facilitates the isolation of genetic variations from confounding factors through fixed random allocation and allows for inferring causal effects amidst subtle confounding factors

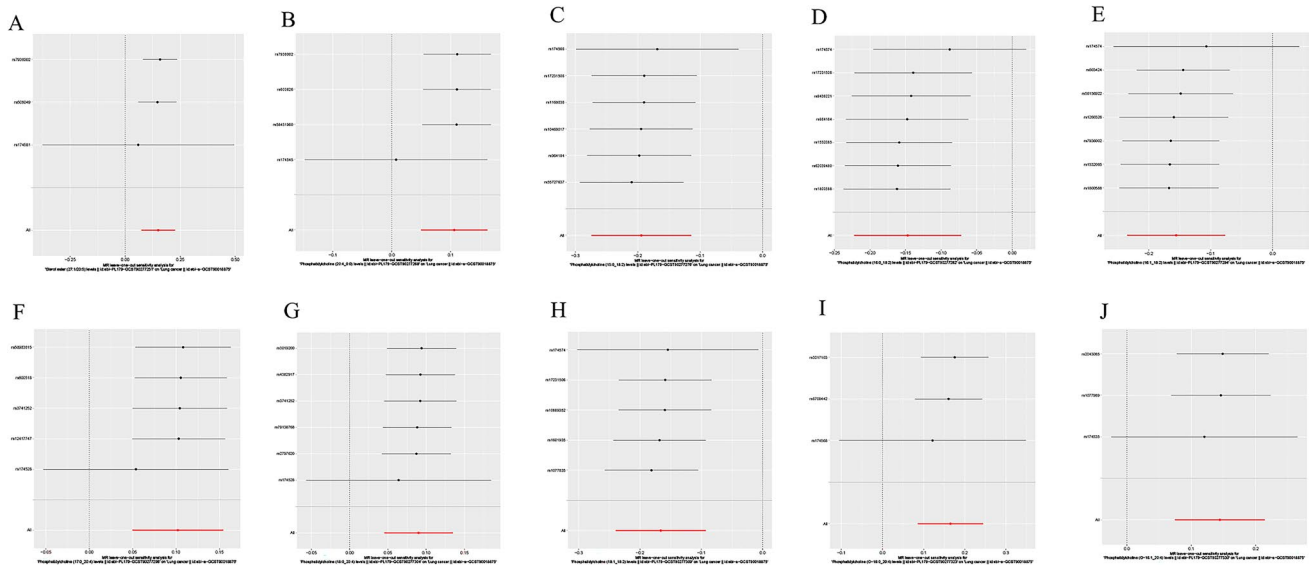

Fig. 4 (A) Sterol ester (27:1/20:5) levels ; (B) Phosphatidylcholine (20:4_0:0) levels ; (C) Phosphatidylcholine (15:0_18:2) levels ; (D) Phosphatidylcholine (16:0_18:2) levels ; (E) Phosphatidylcholine (16:1_18:2) levels ; (F) Phosphatidylcholine (17:0_20:4) levels ; (G) 'Phosphatidylcholine (18:0_20:4) levels ; (H) Phosphatidylcholine (18:1_18:2) levels ; (I) Phosphatidylcholine (O−16:0_20:4) levels; (J) Phosphatidylcholine (O−16:1_20:4) levels

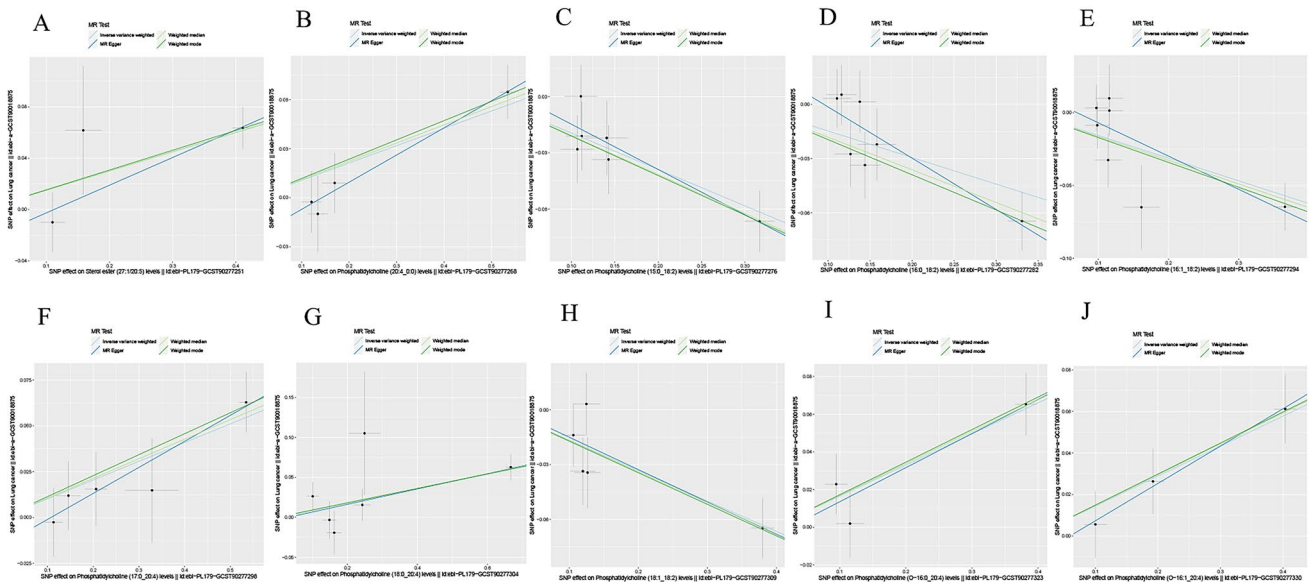

Fig. 5 Sensitivity analysis results of causal effects of lung carcinoma on plasma lipidome. (A) Sterol ester (27:1/20:5) levels ; (B) Phosphatidylcholine (20:4_0:0) levels ; (C) Phosphatidylcholine (15:0_18:2) levels ; (D) Phosphatidylcholine (16:0_18:2) levels ; (E) Phosphatidylcholine (16:1_18:2) levels ; (F) Phosphatidylcholine Phosphatidylcholine (16:0_18:2) levels ; (E) Phosphatidylcholine (16:1_18:2) levels ; (F) Phosphatidylcholine Phosphatidylcholine (O−16:0_20:4) levels; (J) Phosphatidylcholine (O−16:1_20:4) levels

[37]. This study marks the first comprehensive evaluation of the bidirectional causal relationship between plasma lipids and lung carcinoma utilizing available GWAS data.

The study delineates that all six circulating plasma lipidomes predicted by genes are linked to an escalated risk of lung carcinoma: Phosphatidylcholine 15:0_18:2, Phosphatidylcholine 16:0_18:2, Phosphatidylcholine 16:1_18:2, and Phosphatidylcholine 18:1_18:2.

Conversely, four plasma lipidomes appear to mitigate the risk of lung carcinoma. A reverse MR Analysis of the plasma lipids and lung carcinoma revealed no reverse causal link. Moreover, the forward MR Analysis demonstrated the absence of horizontal pleiotropy or heterogeneity, with the sensitivity analysis reinforcing the robustness of the study's findings.

Existing research on lung carcinoma and PC has pointed to elevated sterol levels in NSCLC samples [38], potentially stemming from an internal mechanism that triggers the EGFR pathway, ultimately fostering PC biosynthesis [39, 40]. A study based on lipidomics and scRNA-seq revealed that five abnormally metabolized PC subclasses can be used as important diagnostic features for early lung cancer [41]. Basic studies have found that DHA-PC and EPA-PC can inhibit the migration and invasion of 95D human lung cancer cells by destroying intracellular F-actin that drives cell movement, and EPA-PC shows a more obvious anti-tumor effect [42]. However, investigations into lung carcinoma and PC are presently limited to the overall PC level and lack specificity to particular sites. PC, one of the predominant phospholipids in cell membranes, is regulated by a pathway implicated in various human diseases, including cancer [43]. The rich presence of easily oxidized phospholipids in alveolar tissue leads to the production of bioactive oxidized phosphatidylcholine (oxPC). While studies have primarily focused on oxPC detection in alveolar tissue, the examination of the oxidized PC spectrum in lung carcinoma unveils a significant increase in oxPC 18:0_20:4 levels in tumor alveolar tissues compared to normal counterparts, aligning with the study's assertion that PC 18:0_20:4 levels pose a risk factor for lung carcinoma. Unfortunately, there remains a dearth of clinical and fundamental studies exploring potential discrepancies in unoxidized PC 18:0_20:4 levels in lung carcinoma tissues. Other research indicates notable differences in the PC group between early NSCLC cases and non-cancer individuals through high-throughput mass spectrometry [44].

PE is an important phospholipid compound, which plays a key role in cell membrane structure, biological metabolism and multiple applications. Julia et al. [45] evaluated ex vivo lung cancer explants from six patients using stable isotope labeling and found that the turnover rate of PE in lung cancer tissue was higher than that in normal lung tissue. In addition, a basic study has found that PE in CD8 + T cells of lung cancer is lower than PE in circulating CD8 + T cells, which can be used as an entry point for immunotherapy [46]. However, no study has clearly demonstrated whether PE can be used as a prognostic indicator of lung cancer. The present study suggests that PE may be a protective factor for lung cancer.

Ceramides emerged in cancer research for their potential role in proliferation and intercellular communication via exosomes [47]. Ceramide kinase (CerK) plays a key role in tumor promotion and dissemination, and has anti-inflammatory effects in lung cancer [48]. However, the Ceramide (d42:2) in LUSC has not been reported. This study will provide a reference for the future exploration of Ceramide (d42:2) in the field of lung cancer.

Sphingomyelin is the major component of myelin sheath. Existing studies have found that sphingomyelin (d18:0/22:0) is positively correlated with the risk of lung cancer [49]. The sphingomyelin (d34:1) identified in this study is a risk factor for SCLC, but it has not been confirmed in other basic studies so far.

Our study still has several limitations. First, the GWAS was restricted to European and East Asian populations, which may have introduced confounding effects related to regional and dietary factors. Bias due to racial differences may have influenced the results. Second, our study still lacks a validation set with a larger sample size as a reference for validation. Third, it would add to the current strength of evidence if the identified causal associations could be validated in subsequent experiments such as in vitro/in vivo models or clinical trials.

5 Conclusion

In conclusion, our two-sample MR Analysis indicates a causal nexus between genetically determined circulating plasma lipidomes and lung carcinoma, identifying PC 18:0_20:4 levels as potential therapeutic targets for combating lung carcinoma. Further exploration of the role of plasma lipids in lung carcinoma pathogenesis is warranted.

Author contributions Y.F and S.G were involved in the study concept and design; and J.H and H.P collected data and conducted analyses; H.P wrote the draft of the article; Y.F revised the manuscript and had primary responsibility for the final content. All authors reviewed and approved the final version of the manuscript.

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Data availability If reasonably requested, data may be obtained from the corresponding author.

Declarations

Ethics approval and consent to participate This study was based on publicly available summary data and required no ethics approval or participant consent.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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