Yang H, et al., J Otolaryng Head Neck Surg 2024, 10: 105
DOI: 10.24966/OHNS-010X/100105

HSOA Journal of Otolaryngology, Head and Neck Surgery

Research Article

Exploring the Causal Relationship between Plasma Lipidome and Allergic Diseases: A Mendelian Randomization Study

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Abstract

Background: Allergic diseases, including Allergic Rhinitis (AR), Allergic Asthma (AA), Allergic Conjunctivitis (AC), and Allergic Contact Dermatitis (ACD), affect a significant portion of the global population. Recent advances in lipidomics have highlighted the role of plasma lipids in immune regulation and inflammation. This study aims to investigate the causal relationship between the plasma lipidome and various allergic diseases.

Methods: We conducted a bidirectional two-sample MENDELIAN RANDOMIZATION (MR) analysis, integrating data from multiple Genome-Wide Association Studies (GWAS). Various MR methods, including Inverse Variance Weighted (IVW), MR Egger, Weighted Median, Simple Mode, Weighted Mode, and Bayesian Weighted Mendelian Randomization (BWMR), were employed. Sensitivity analyses were performed to ensure robustness.

Results: Several plasma lipid subtypes were identified as either risk or protective factors for allergic diseases. Sterol ester (27:1/20:5), phosphatidylcholine (20:4_0:0), phosphatidylcholine (18:0_20:4), and phosphatidylcholine (18:0_22:5) were risk factors for AR. Phosphatidylcholine (20:4_0:0), phosphatidylcholine (18:0_20:5), and phosphatidylcholine (O-16:0_20:4) were risk factors for AA, while phosphatidylcholine (18:1_18:2) was a protective factor. For AC, phosphatidylcholine (18:1_18:1), phosphatidylcholine (18:1_18:2), and triacylglycerol (56:3) were protective factors. No significant associations were found for ACD after FDR correction.

Conclusion: This study highlights the significant roles of specific plasma lipid molecular subtypes in allergic diseases, particularly phosphatidylcholines and sterol esters. These findings enhance our understanding of the lipidomic landscape in allergy pathogenesis and suggest potential lipid-based therapeutic targets.

Keywords: Allergic diseases; Genetic epidemiology; Lipidomics, GWAS; Mendelian randomization; Phosphatidylcholine; Plasma lipids

Introduction

Allergic diseases affect approximately 20% of the global population, imposing a significant burden on society [1]. Over the past three decades, the incidence of diseases such as Allergic Rhinitis (AR), Allergic Asthma (AA), Allergic Conjunctivitis (AC), and Allergic Contact Dermatitis (ACD) has increased markedly [2,3]. AR is characterized by paroxysmal sneezing, nasal discharge, itching, and congestion; AA by wheezing, chest tightness, shortness of breath, and mucus production; AC by itchy, red, and tearing eyes; and ACD by itchy, inflamed skin. Current treatments, including glucocorticoids and antihistamines, are not curative, and symptoms often rebound after discontinuation [4]. The chronic nature of these conditions necessitates ongoing medical care, adding to the social and economic burden.

While allergic diseases are influenced by genetic, dietary, and environmental factors, the exact causes remain unclear. Genome-Wide Association Studies (GWAS) have identified numerous genetic susceptibility loci, underscoring the significant role of genetic factors in the development of AR, AA, AC, and ACD [3,5]. Understanding these genetic links is crucial for developing better prevention and treatment strategies for allergic diseases.

Lipid metabolism encompasses the synthesis, breakdown, and regulation of plasma lipids and bioactive lipids. These lipids are crucial for cell structure and energy metabolism and play vital roles in immune responses and allergic diseases. Abnormal lipid metabolism can act as a pro-inflammatory mediator, affecting cytokine secretion (e.g., IL-4, IL-5, IL-10, IL-17, IL-33, and interferons) and contributing to inflammatory and allergic diseases [6]. Inflammation, in turn, alters lipid metabolism, impacting plasma lipid and lipoprotein levels [7].

Bioactive lipids, a subset of plasma lipids, are key regulators of inflammation [8,9]. They are involved in the development of conditions such as asthma, allergic rhinitis, urticaria, anaphylaxis, atopic dermatitis, and food allergies. Advances in lipidomics have revealed the complexity and diversity of these lipids, highlighting their important roles in immune regulation and inflammation [8,10]. Refined lipid species such as Cholesterol Esters (CE), Ceramides (CER), Lysophosphatidylcholines (LPC), and Phosphatidylcholines (PC) modulate immune cell activity, influence cell membrane fluidity, and

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Citation: Yang H, Luo Y, Qiang Liu Q (2024) Exploring the Causal Relationship between Plasma Lipidome and Allergic Diseases: A Mendelian Randomization Study. J Otolaryng Head Neck Surg 10: 105.

Received: September 09, 2024; **Accepted:** September 18, 2024; **Published:** September 25, 2024

impact signal transduction. These processes are crucial in the pathogenesis of allergic diseases [11].

Randomized Controlled Trials (RCTs) are considered the gold standard for establishing causality between exposure factors and disease outcomes. However, conducting RCTs to study the effects of plasma lipids on allergic diseases poses significant design and ethical challenges. Manipulating lipid levels over a long period could pose health risks to participants, and achieving compliance in dietary or pharmacological interventions is difficult. Additionally, RCTs require substantial financial and logistical resources, making them less feasible for large-scale studies on lipidomics and allergic diseases. Thus, alternative approaches like Mendelian Randomization (MR) offer a valuable solution by leveraging genetic variants as proxies for lipid levels, enabling robust causal inference without the ethical and practical constraints of RCTs [12].

Given the public health significance of allergic diseases and the potential role of plasma lipids in immune regulation, this study aims to utilize a bidirectional two-sample Mendelian randomization approach, integrating data from multiple Genome-Wide Association Studies (GWAS), to investigate the causal relationship between the plasma lipidome and allergic diseases. Our objective is to identify specific lipid species and evaluate their potential roles in diseases such as AR, AA, AC, and ACD, thereby providing scientific evidence for future preventive strategies and therapeutic interventions. By doing so, we hope to deepen our understanding of the underlying mechanisms of allergic diseases and explore novel lipid-based therapeutic targets [13].

Materials and Methods

Study Design

A bidirectional Two-Sample Mendelian Randomization (TSMR) analysis was conducted to investigate the causal relationship between the plasma lipidome and allergic diseases, including Allergic Rhinitis (AR), Allergic Asthma (AA), Allergic Conjunctivitis (AC), and Allergic Contact Dermatitis (ACD). The overall design of this study is illustrated in figure 1. For reliable results, three key assumptions must be satisfied in TSMR analysis: 1. There is a strong correlation between genetic variants and exposure factors; 2. There is no correlation between genetic variants and confounders; 3. Genetic variants can only affect the outcome through exposure factors, without influencing the outcome through other pathways, meaning horizontal pleiotropy is not allowed. Genetic variants that meet these three criteria can be included as instrumental variables in the TSMR analysis [14,15].

Overview of the bidirectional MR analyses conducted in this study. The figure illustrates the causal relationships between specific plasma lipid molecular subtypes and allergic diseases, including Allergic Rhinitis (AR), Allergic Asthma (AA), Allergic Conjunctivitis (AC), and Allergic Contact Dermatitis (ACD). The forward MR analysis evaluates the effects of plasma lipid levels on allergic disease risk, while the reverse MR analysis examines the impact of allergic diseases on plasma lipid levels. Key components include the selection of genetic variants as Instrumental Variables (IVs), data harmonization, and the application of various MR methods to ensure the robustness and validity of results. AR, allergic rhinitis; AA, allergic asthma; AC, allergic conjunctivitis; ACD, allergic contact dermatitis; MR, Mendelian randomization; IVs, instrumental variables; SNP, single nucleotide polymorphism.

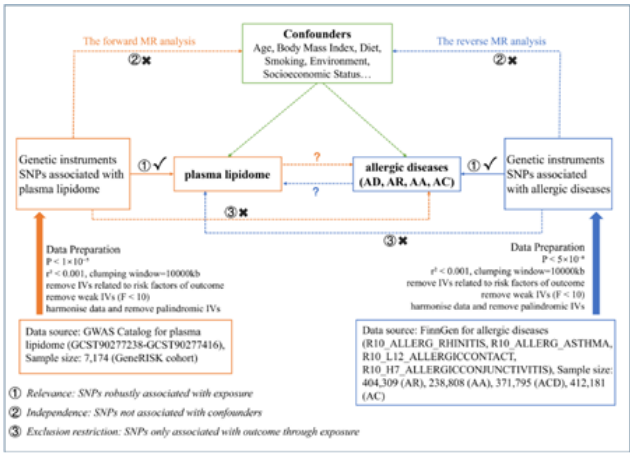


Figure 1: Bidirectional Mendelian Randomization Analysis Framework.

Data Sources

Summary statistics of the plasma lipidome were obtained from a recent large-scale Genome-Wide Association Study (GWAS) conducted by Ottensmann L et al. [16]. This study represents the most comprehensive GWAS to date on the genetic influence on the human plasma lipidome, including univariate and multivariate analyses of 179 lipid species from 13 lipid classes in 7,174 Finnish individuals from the GeneRISK cohort. The study identified 495 genome-trait associations across 56 genetic loci, with 8 novel loci discovered. These data can be accessed from the GWAS Catalog (GCST90277238-GCST90277416).

Outcome information for allergic diseases, including AR, AA, ACD, and AC, was derived from the FinnGen biobank analysis (round 10). The datasets included:

AR: 12,240 cases and 392,069 controls (total: 404,309),

AA: 10,723 cases and 228,085 controls (total: 238,808),

ACD: 4,749 cases and 367,046 controls (total: 371,795),

AC: 23,665 cases and 388,516 controls (total: 412,181).

All cases were identified using ICD-10 codes from hospital records. The genetic data included a comprehensive analysis of 19,345,529 SNPs based on the HG38/GRCh38 build, available from FinnGen documentation [17]. The details of the data sources are summarized in table 1.

Although both the plasma lipidome and FinnGen data involve Finnish individuals, the lipidome data are specifically from the GeneRISK cohort. We used the tool available at [https://sb452.shinyapps.io/overlap/] to calculate the sample overlap rate. Given the significant difference in sample sizes between the exposure (lipidome data) and outcome (FinnGen data) datasets, even if fully overlapping, the proportion would only be 1.7%-3%. This level of overlap is insufficient to introduce bias and type 1 errors into the analysis, thus satisfying the requirements for two-sample MR analysis [18,19].

Selection of Instrumental Variables

In order to ensure an adequate number of SNPs for analysis, a locus-wide significance threshold of $P<1\times10^{-5}$ was used to screen SNPs

Category	Description	Sample Size	Cases	Controls	SNPs	Source	Download Link
Exposure	Plasma Lipidome	7,174 (GeneRISK cohort)	-	-	-	PMID: 37907536	[GWAS Catalog](https://www.ebi.ac.uk/gwas/, GCST90277238-GCST90277416)
Outcome	AR	404,309	12,240	392,069	19,345,529	FinnGen (R10_ALLERG_RHINITIS)	https://finngen.gitbook.io/documentation/data-download
Outcome	AA	238,808	10,723	228,085	19,340,548	FinnGen (R10_ALLERG_ASTHMA)	https://finngen.gitbook.io/documentation/data-download
Outcome	AC	412,181	23,665	388,516	19,345,634	FinnGen (R10_H7_ALLERGICCONJUNCTIVITIS)	https://finngen.gitbook.io/documentation/data-download
Outcome	ACD	371,795	4,749	367,046	19,344,995	FinnGen (R10_L12_ALLERGICCONTACT)	https://finngen.gitbook.io/documentation/data-download

Table 1: Exposure and outcome data information.

Note: AR: Allergic Rhinitis, AA: Allergic Asthma, AC: Allergic Conjunctivitis, ACD: Allergic Contact Dermatitis, SNPs: Single Nucleotide Polymorphisms.

related to the exposure factors in the lipidome. This approach provided more complete results by capturing additional SNPs compared to the conventional genome-wide significance threshold of $P<5\times10^{-8}$. We opted for this more lenient threshold to enhance the statistical power of our study. Additionally, sensitivity analyses were performed using the traditional $P<5\times10^{-8}$ threshold to minimize the possibility of false positives and to confirm the robustness of our findings. To avoid weak instrument bias, the F statistic for each IV was calculated using the formula:

$$F = \frac{\beta^2\_\text{exposure}}{SE^2\_\text{exposure}}$$

And IVs with $F<10$ were excluded [20,21]. Linkage Disequilibrium (LD) analysis was performed with $r^2<0.001$and a clumping window >10,000 kb to ensure independence among the selected SNPs. Palindromic SNPs with intermediate allele frequencies were excluded to avoid potential strand orientation ambiguity.

In the reverse MR analysis, a genome-wide significance threshold of $P<5\times10^{-8}$ was used to screen SNPs related to allergic diseases as the exposure. The same LD criteria were applied, and palindromic and incompatible SNPs were excluded. SNPs that could not be matched in the GWAS outcome statistics were also excluded.

To further ensure the validity of our IVs, we utilized the PhenoScanner website (http://www.phenoscanner.medschl.cam.ac.uk/) to exclude SNPs directly associated with the outcomes [22]. This comprehensive selection process helps minimize potential biases and ensures the robustness of our MR analysis.

Statistical Analysis

All analyses were performed using R version 4.3.1 (https://www.r-project.org). To assess the causal relationship between the plasma lipidome and allergic diseases (AR, AA, AC, and ACD), we employed various MR methods using the TwoSampleMR package version 0.5.7. These methods included Inverse Variance Weighted (IVW), MR Egger, weighted median, simple mode, weighted mode, and Bayesian Weighted Mendelian Randomization (BWMR) [23-28].

The IVW method was our primary analytical approach, as it combines multiple random variables to reduce overall variance by weighting each variable based on divergence, providing the most accurate estimates when all genetic variants are valid instruments. MR Egger adjusts for potential pleiotropy by allowing an intercept term. Weighted median offers consistent estimates even with up to 50% invalid instruments. Simple mode and weighted mode methods provide robust estimates under different scenarios of invalid instruments. BWMR reduces potential biases, particularly for high-throughput and highly correlated data.

To enhance the reliability of our findings, P values from the IVW method were adjusted using the False Discovery Rate (FDR) to account for multiple testing [29]. Additionally, the Steiger test was employed to avoid reverse causation, ensuring that the direction of causality was correctly inferred (Figure 1).

Sensitivity Analysis

Sensitivity analysis was conducted to ensure the robustness of our findings. The intercept term of the MR-Egger regression model was examined to assess potential pleiotropic effects [25]. If the P-value of the intercept term exceeded 0.05, it suggested minimal influence of genetic pleiotropy, indicating that the IVs solely impacted the risk of allergic diseases through lipidomes. Cochran's Q test was employed to investigate the heterogeneity of the IVs and its potential impact on the causal estimate [24]. A leave-one-out analysis was performed to assess the sensitivity of the results by conducting MR analysis repeatedly, gradually eliminating one SNP at a time [30].

Funnel plots and scatter plots were used to visually assess the data. Scatter plots demonstrated that outliers had minimal effect on the data, and funnel plots showed a high degree of association and a lack of heterogeneity. Additionally, the MR-PRESSO test was used to evaluate any disparities between the outcomes of MR analysis before and after correction, identifying and correcting for outliers contributing to bias [31].

Results

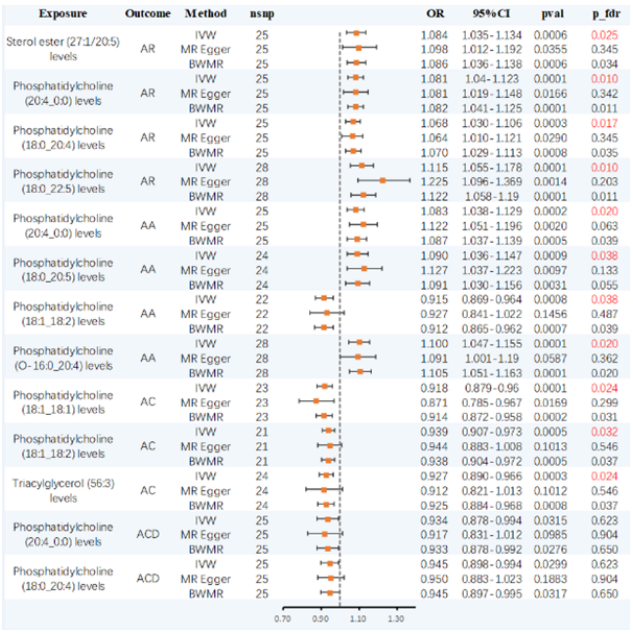
The instrumental Variables (IVs) were screened based on the conditions described earlier. The details of the SNPs included in the Two-Sample Mendelian Randomization (TSMR) analysis of the plasma lipidome and four types of allergic diseases (allergic rhinitis, allergic asthma, allergic conjunctivitis, and allergic contact dermatitis) are presented in Supplementary table 1. After harmonization, the number of SNPs involved in each pair of lipid species and allergic disease ranged from 12 to 43. The F-statistics of all SNPs ranged from 18.79 to 1969.17, indicating the absence of weak instruments. Additionally, all harmonized SNPs passed the Steiger test, confirming no evidence

of reverse causation. In the reverse Mendelian randomization analysis, SNPs related to allergic diseases as exposures were screened using a genome-wide significance threshold of $P<5\times10^{-8}$. The number of SNPs after clumping ranged from 23 to 31. To identify suitable IVs for this study, the PhenoScanner website was utilized. Any exposure SNPs directly associated with the outcomes were excluded prior to the MR analysis. After obtaining positive results, we used the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test to evaluate the potential pleiotropic effects of the selected SNPs. Fortunately, none of the SNPs showed indications for removal after this evaluation.

Causal Effects of Plasma Lipidomes on Allergic Diseases

Allergic Rhinitis

Through FDR correction (P_{FDR} <0.05), several lipid phenotypes were identified as risk factors for allergic rhinitis (AR): Sterol ester (27:1/20:5) levels, Phosphatidylcholine (20:4_0:0) levels, Phosphatidylcholine (18:0_20:4) levels, and Phosphatidylcholine (18:0_22:5) levels. For detailed data, refer to Supplementary Tables S1-S2. For Sterol ester (27:1/20:5) levels in relation to AR, the IVW method estimated the risk (OR) as 1.084 (95% CI=1.035-1.134, P_{FDR}=0.025, P=0.0006). Similarly, for Phosphatidylcholine (20:4_0:0) levels in relation to AR, the IVW method estimated the risk (OR) as 1.081 (95% CI=1.04-1.123, P_{FDR}=0.010, P=0.0001). For Phosphatidylcholine (18:0_20:4) levels in relation to AR, the IVW method estimated the risk (OR) as 1.068 (95% CI=1.03-1.106, P_{FDR}=0.017, P=0.0003). For Phosphatidylcholine (18:0_22:5) levels in relation to AR, the IVW method estimated the risk (OR) as 1.115 (95% CI=1.055-1.178, P_{FDR}=0.010, P=0.0001). The consistent results from the MR Egger, weighted median, simple mode, weighted mode, and Bayesian Weighted Mendelian Randomization (BWMR) methods further validated these findings figures 2 & 3.



Exposure	Outcome	Method	nsnp	OR	95%CI	pval	p_fdr
Sterol ester (27:1/20:5) levels	AR	IVW	25	1.084	1.035-1.134	0.0006	0.025
		MR Egger	25	1.098	1.012-1.192	0.0355	0.345
		BWMR	25	1.086	1.036-1.138	0.0006	0.034
Phosphatidylcholine (20:4_0:0) levels	AR	IVW	25	1.081	1.04-1.123	0.0001	0.010
		MR Egger	25	1.081	1.019-1.148	0.0166	0.342
		BWMR	25	1.082	1.041-1.125	0.0001	0.011
Phosphatidylcholine (18:0_20:4) levels	AR	IVW	25	1.068	1.030-1.106	0.0003	0.017
		MR Egger	25	1.064	1.010-1.121	0.0290	0.345
		BWMR	25	1.070	1.029-1.113	0.0008	0.035
Phosphatidylcholine (18:0_22:5) levels	AR	IVW	28	1.115	1.055-1.178	0.0001	0.010
		MR Egger	28	1.225	1.096-1.369	0.0014	0.203
		BWMR	28	1.122	1.058-1.19	0.0001	0.011
Phosphatidylcholine (20:4_0:0) levels	AA	IVW	25	1.083	1.038-1.129	0.0002	0.020
		MR Egger	25	1.122	1.051-1.196	0.0020	0.063
		BWMR	25	1.087	1.037-1.139	0.0005	0.039
Phosphatidylcholine (18:0_20:5) levels	AA	IVW	24	1.090	1.036-1.147	0.0009	0.038
		MR Egger	24	1.127	1.037-1.223	0.0097	0.133
		BWMR	24	1.091	1.030-1.156	0.0031	0.055
Phosphatidylcholine (18:1_18:2) levels	AA	IVW	22	0.915	0.869-0.964	0.0008	0.038
		MR Egger	22	0.927	0.841-1.022	0.1456	0.487
		BWMR	22	0.912	0.865-0.962	0.0007	0.039
Phosphatidylcholine (O-16:0_20:4) levels	AA	IVW	28	1.100	1.047-1.155	0.0001	0.020
		MR Egger	28	1.091	1.001-1.19	0.0587	0.362
		BWMR	28	1.105	1.051-1.163	0.0001	0.020
Phosphatidylcholine (18:1_18:1) levels	AC	IVW	23	0.918	0.879-0.96	0.0001	0.024
		MR Egger	23	0.871	0.785-0.967	0.0169	0.299
		BWMR	23	0.914	0.872-0.958	0.0002	0.031
Phosphatidylcholine (18:1_18:2) levels	AC	IVW	21	0.939	0.907-0.973	0.0005	0.032
		MR Egger	21	0.944	0.883-1.008	0.1013	0.546
		BWMR	21	0.938	0.904-0.972	0.0005	0.037
Triacylglycerol (56:3) levels	AC	IVW	24	0.927	0.890-0.966	0.0003	0.024
		MR Egger	24	0.912	0.821-1.013	0.1012	0.546
		BWMR	24	0.925	0.884-0.968	0.0008	0.037
Phosphatidylcholine (20:4_0:0) levels	ACD	IVW	25	0.934	0.878-0.994	0.0315	0.623
		MR Egger	25	0.917	0.831-1.012	0.0985	0.904
		BWMR	25	0.933	0.878-0.992	0.0276	0.650
Phosphatidylcholine (18:0_20:4) levels	ACD	IVW	25	0.945	0.898-0.994	0.0299	0.623
		MR Egger	25	0.950	0.883-1.023	0.1883	0.904
		BWMR	25	0.945	0.897-0.995	0.0317	0.650

Figure 2: Forest plots of MR analysis for plasma lipid levels and allergic diseases.

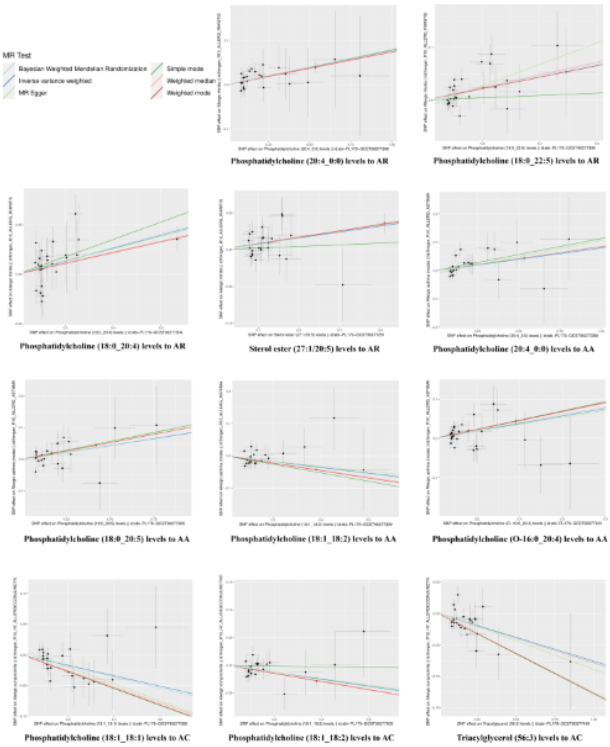


Figure 3: Scatter plots of MR analysis for plasma lipid levels and allergic diseases.

Note: AR, allergic rhinitis; AA, allergic asthma; AC, allergic conjunctivitis; ACD, allergic contact dermatitis; SNP, single nucleotide polymorphism.

Allergic Asthma

Through FDR correction (P_{FDR} <0.05), several lipid phenotypes were identified as risk factors for allergic asthma (AA): Phosphatidylcholine (20:4_0:0) levels, Phosphatidylcholine (18:0_20:5) levels, and Phosphatidylcholine (O-16:0_20:4) levels. For detailed data, refer to Supplementary Tables S3-S4. For Phosphatidylcholine (20:4_0:0) levels in relation to AA, the IVW method estimated the risk (OR) as 1.083 (95% CI = 1.038-1.129, P_{FDR} = 0.020, P = 0.0002). Similarly, for Phosphatidylcholine (18:0_20:5) levels in relation to AA, the IVW method estimated the risk (OR) as 1.090 (95% CI = 1.036-1.147, P_{FDR} = 0.038, P = 0.0009). For Phosphatidylcholine (O-16:0_20:4) levels in relation to AA, the IVW method estimated the risk (OR) as 1.100 (95% CI = 1.047-1.155, P_{FDR} = 0.020, P = 0.0001). Additionally, Phosphatidylcholine (18:1_18:2) levels were identified as a protective factor for allergic asthma (AA). For Phosphatidylcholine (18:1_18:2) levels in relation to AA, the IVW method estimated the protective effect (OR) as 0.915 (95% CI = 0.869-0.964, P_{FDR} = 0.038, P = 0.0008). The consistent results from the MR Egger, weighted median, simple mode, weighted mode, and BWMR methods further validated these findings figures 2 & 3.

Allergic Conjunctivitis

Through FDR correction (P_{FDR}<0.05), several lipid phenotypes were identified as protective factors for Allergic Conjunctivitis (AC): Phosphatidylcholine (18:1_18:1) levels, Phosphatidylcholine (18:1_18:2) levels, and Triacylglycerol (56:3) levels. For detailed

data, refer to Supplementary Tables S5-S6. For Phosphatidylcholine (18:1_18:1) levels in relation to AC, the IVW method estimated the protective effect (OR) as 0.918 (95% CI=0.879-0.960, P_{FDR}=0.024, P=0.0001). Similarly, for Phosphatidylcholine (18:1_18:2) levels in relation to AC, the IVW method estimated the protective effect (OR) as 0.939 (95% CI=0.907-0.973, P_{FDR}=0.032, P=0.0005). For Triacylglycerol (56:3) levels in relation to AC, the IVW method estimated the protective effect (OR) as 0.927 (95% CI=0.890-0.966, P_{FDR}=0.024, P=0.0003). The consistent results from the MR Egger, weighted median, simple mode, weighted mode, and BWMR methods further validated these findings figures 2 & 3.

Allergic Contact Dermatitis

Although Allergic Contact Dermatitis (ACD) did not yield positive results after FDR correction, there were suggestive findings (P<0.05) for some lipid phenotypes shared with other allergic diseases. For instance, Phosphatidylcholine (20:4_0:0) levels were suggestively associated with ACD. For detailed data, refer to Supplementary Tables S7-S8. For Phosphatidylcholine (20:4_0:0) levels in relation to ACD, the IVW method estimated the risk (OR) as 0.934 (95% CI=0.878-0.994, P_{FDR}=0.623, P=0.031). Similarly, for Phosphatidylcholine (18:0_20:4) levels in relation to ACD, the IVW method estimated the risk (OR) as 0.945 (95% CI=0.898-0.994, P_{FDR}=0.623, P=0.030). The consistent results from the MR Egger, weighted median, simple mode, weighted mode, and BWMR methods further validated these findings.

Forest plots depicting the Odds Ratios (OR) and 95% Confidence Intervals (CI) for the association between specific plasma lipid levels and various allergic diseases identified in the MR analysis. The lipid levels are specified by their molecular compositions, such as Phosphatidylcholine (20:4_0:0) and Sterol ester (27:1/20:5), where the numbers indicate the carbon chain lengths and the degree of unsaturation of the fatty acid components. Only significant results after FDR correction and suggestive findings for Allergic Contact Dermatitis (ACD) are presented. Comprehensive results can be found in the supplementary data (Tables S9-S10).

Scatter plots illustrating the causal relationships between specific plasma lipid levels and various allergic diseases identified in the MR analysis. Lipid levels are denoted by their specific molecular compositions, such as Phosphatidylcholine (20:4_0:0) and Sterol ester (27:1/20:5), where the numbers indicate the carbon chain lengths and the degree of unsaturation of the fatty acid components. Comprehensive results can be found in the supplementary data.

Sensitivity Analysis Results

To validate the robustness of our findings, sensitivity analyses were performed using the stricter P<5×10^{-8} threshold. Although this stricter threshold resulted in fewer SNPs (ranging from 2 to 8), the positive associations identified with the P<1×10^{-5} threshold remained significant after FDR correction, reinforcing the reliability of our causal inferences. Interestingly, using the P<5×10^{-8} threshold allowed us to identify more positive results, which was crucial for maintaining sufficient statistical power. However, using fewer SNPs with the stricter threshold increased the risk of results being influenced by individual SNP effects. Therefore, the more inclusive threshold was preferred to ensure a robust Mendelian Randomization (MR) analysis (Table S11).

For all associations, the MR-Egger intercept test excluded the notion of horizontal pleiotropy, indicating no pleiotropic bias. The MR-Egger intercept test showed no significant evidence of directional pleiotropy (P values >0.05), suggesting minimal influence of genetic pleiotropy on the IVs' impact on allergic diseases through lipidomes. Cochran's Q test was used to evaluate the heterogeneity of the IVs, with Q_pval values ranging from 0.214 to 0.955, indicating no substantial heterogeneity. The leave-one-out analysis confirmed that no single SNP significantly influenced the overall results, reinforcing the stability of our findings. Funnel plots and scatter plots demonstrated a high degree of association and a lack of heterogeneity, further validating the robustness of the identified causal relationships. We used the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test to evaluate the potential pleiotropic effects of the selected SNPs for positive results, and none of the SNPs showed indications for removal after this evaluation. These results collectively ensure the reliability and robustness of our causal inferences between plasma lipid levels and allergic diseases (Table 2) figures 4 & 5.

Exposure	Outcome	Pleiotropy			Heterogeneity	
		MR-Egger intercept		MR-PRESSO	Cochrane's Q P-value	
		egger_intercept	pval	Global Test`$Pvalue	IVW	MR-Egger
Sterol ester (27:1/20:5) levels	AR	-0.002	0.705	0.788	0.749	0.706
Phosphatidylcholine (20:4_0:0) levels	AR	0.000	0.976	0.967	0.955	0.938
Phosphatidylcholine (18:0_20:4) levels	AR	0.001	0.859	0.320	0.230	0.190
Phosphatidylcholine (18:0_22:5) levels	AR	-0.014	0.070	0.267	0.215	0.331
Phosphatidylcholine (20:4_0:0) levels	AA	-0.009	0.176	0.472	0.386	0.438
Phosphatidylcholine (18:0_20:5) levels	AA	-0.007	0.333	0.472	0.390	0.389
Phosphatidylcholine (18:1_18:2) levels	AA	-0.002	0.754	0.669	0.621	0.565
Phosphatidylcholine (O-16:0_20:4) levels	AA	0.001	0.831	0.595	0.536	0.483
Phosphatidylcholine (18:1_18:1) levels	AC	0.008	0.285	0.439	0.428	0.439

Phosphatidylcholine (18:1_18:2) levels	AC	-0.001	0.880	0.674	0.639	0.577
Triacylglycerol (56:3) levels	AC	0.003	0.750	0.399	0.369	0.320

Table 2: Assessment of pleiotropy and heterogeneity in MR analysis.

Note: MR-Egger intercept and p-values are used to assess pleiotropy, where non-significant p-values indicate no pleiotropic bias. The MR-PRESSO Global Test's p-values further evaluate pleiotropy. Cochrane's Q p-values assess heterogeneity, with non-significant values indicating no substantial heterogeneity. Exposure factors are specified with the corresponding outcomes (AR: Allergic Rhinitis, AA: Allergic Asthma, AC: Allergic Conjunctivitis).

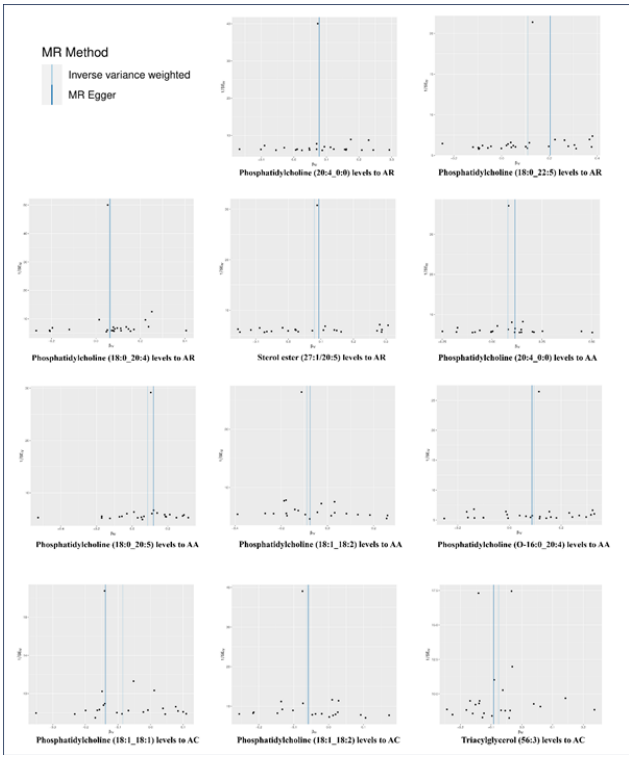


Figure 4: Funnel plots for MR analysis of plasma lipid levels and allergic diseases.

Note: AR, allergic rhinitis; AA, allergic asthma; AC, allergic conjunctivitis; SNP, single nucleotide polymorphism.

Funnel plots illustrating the distribution of individual SNP effects on plasma lipid levels associated with various allergic diseases. The plots show the results from both Inverse Variance Weighted (IVW) and MR Egger methods. Each dot represents an SNP, with the x-axis showing the estimated effect size (β) and the y-axis showing the precision (standard error). The vertical lines represent the overall estimated effect. These plots help assess the presence of publication bias or heterogeneity among the SNPs used in the analysis.

Leave-one-out analysis plots showing the effect estimates of individual SNPs on plasma lipid levels associated with various allergic diseases. Each plot represents the result of iteratively removing one SNP at a time to assess its impact on the overall causal estimate. The x-axis shows the Odds Ratio (OR) of each lipid level to allergic disease, while the y-axis lists the individual SNPs. The red vertical line indicates the overall estimated effect when all SNPs are included, and each black dot represents the effect estimate with one SNP removed. These plots ensure the robustness of the MR findings by confirming that no single SNP drives the overall result.

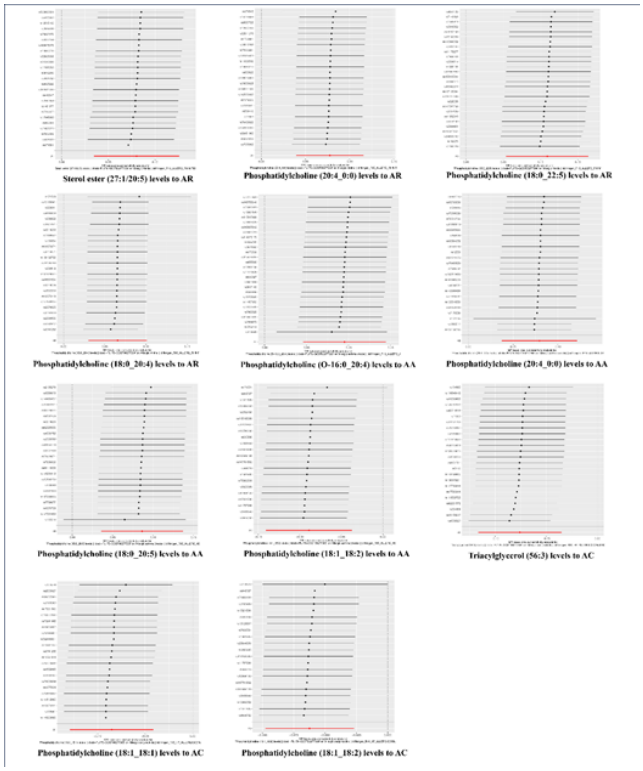


Figure 5: Leave-one-out analysis for MR analysis of plasma lipid levels and allergic diseases.

Note: AR, allergic rhinitis; AA, allergic asthma; AC, allergic conjunctivitis; ACD, allergic contact dermatitis; SNP, single nucleotide polymorphism.

Reverse Mendelian Randomization Analysis

In our exploration of the causal effects of allergic diseases on the plasma lipidome, we utilized the IVW method as the principal analysis in a two-sample MR study. Despite conducting a thorough analysis and applying False Discovery Rate (FDR) correction, we did not identify any lipid subtypes with significant associations (Supplementary Table S9). This indicates that allergic diseases do not have a robust causal effect on the plasma lipidome.

Discussion

This study comprehensively investigated the causal relationship between specific plasma lipid molecular subtypes and various allergic diseases, including Allergic Rhinitis (AR), Allergic Asthma (AA), Allergic Conjunctivitis (AC), and Allergic Contact Dermatitis (ACD). Using a robust Mendelian Randomization (MR) framework and multiple analytic methods, we identified several significant lipid traits as either risk factors or protective factors for these diseases.

Among the lipid molecular subtypes, Phosphatidylcholine (PC) was particularly prominent in its association with allergic diseases.

PC is a major phospholipid found in cell membranes, consisting of glycerol, two fatty acid chains, and a phosphate-containing choline head group. It plays a crucial role in maintaining membrane fluidity and integrity, participating in cellular signaling, and influencing cellular responses. In the lungs, PC is a key component of pulmonary surfactant, reducing alveolar surface tension and preventing collapse [32]. PCs are also precursors to other significant bioactive lipids, such as Platelet-Activating Factor (PAF) and lysophosphatidylcholine, which are involved in inflammatory processes [33]. In the liver, PCs are essential for the packaging and secretion of fatty acids into lipoproteins, playing a pivotal role in lipid transport [34]. Aberrations in PC metabolism have been linked to various diseases, including cardiovascular diseases and liver disorders [35]. The role of PCs in allergic diseases can be discussed from several biological perspectives. They are integral to cell membrane function, influencing the immune response to allergens by affecting membrane fluidity and signal transduction. PCs can be metabolized into inflammatory mediators like PAF, which recruits and activates immune cells, exacerbating allergic inflammation [36]. Additionally, in the lungs, changes in PC levels may affect surfactant function, impacting respiratory conditions such as asthma [35].

Sterol Esters (SEs) were also highlighted in our findings, particularly in their role as risk factors for AR. SEs are compounds formed by the esterification of a sterol (such as cholesterol) with a fatty acid. They serve as storage forms of cholesterol, regulating cellular free cholesterol levels, and can be hydrolyzed to release cholesterol and fatty acids for energy [37]. SEs also participate in the biosynthesis of steroid hormones and are involved in lipid transport via lipoproteins [38]. Triacylglycerols (TAGs) were identified as protective factors for AC. TAGs are the most common form of lipids, consisting of one glycerol molecule and three fatty acid chains. They are primarily involved in energy storage and supply, protecting organs, and participating in lipid transport. High TAG levels are typically associated with metabolic disorders, but their role in immune response modulation suggests a complex interplay in allergic diseases [5]. Our study highlights the intricate roles of specific lipid molecular subtypes, particularly phosphatidylcholines and sterol esters, in the development and progression of allergic diseases. These findings expand our understanding of the lipidomic landscape in allergy pathogenesis and suggest potential lipid-based therapeutic targets for managing allergic diseases [39].

Plasma lipids, such as those studied in this research, offer several advantages over traditional lipids like HDL-C, LDL-C, TG, and TC in understanding disease mechanisms. Traditional lipids provide a broad overview of lipid metabolism and cardiovascular health but may not capture the nuanced roles of specific lipid species [40]. In contrast, plasma lipidomics allows for the detailed examination of lipid subtypes, revealing specific molecules that contribute to disease pathology. This precision can lead to more targeted therapeutic strategies and a better understanding of disease etiology. High-fat diets can significantly alter plasma lipid profiles, influencing both lipid metabolism and the risk of developing allergic diseases [41]. Dietary fats affect the synthesis and breakdown of plasma lipids, potentially leading to changes in the levels of various lipid subtypes [42]. For instance, high intake of saturated fats may increase levels of certain phosphatidylcholines and sterol esters, which could impact immune cell function and inflammation [43]. This dietary influence highlights the importance of considering nutritional factors when studying lipidomics and allergic disease development [44].

The use of Mendelian Randomization (MR) in this study provides several advantages. MR leverages genetic variants as Instrumental Variables (IVs) to infer causality, minimizing confounding and reverse causation issues often encountered in observational studies [45]. The consistency of our findings across different MR methods, including Inverse Variance Weighted (IVW), MR Egger, Weighted Median, Simple Mode, Weighted Mode, and Bayesian Weighted Mendelian Randomization (BWMR), alongside sensitivity analyses, reinforces the reliability and robustness of our conclusions [46]. The absence of horizontal pleiotropy and low heterogeneity further supports the validity of our results [47]. However, MR also has limitations. The validity of MR results depends on the strength and specificity of the genetic instruments used. Weak or pleiotropic instruments can bias the results. Additionally, MR assumptions such as no horizontal pleiotropy and no confounders of the IV-outcome relationship must be carefully considered and tested. This study is also limited by the available data, restricting our analysis to a narrow range of allergic diseases. Moreover, the data used were predominantly from European populations, which may limit the generalizability of the findings to other ethnic groups.

The findings of this study have significant public health and clinical implications. Understanding the specific plasma lipid subtypes associated with allergic diseases can inform preventive strategies and therapeutic interventions. For example, targeting lipid metabolic pathways or modifying dietary lipid intake could potentially reduce the risk of developing allergic diseases [45]. Moreover, the identification of lipid biomarkers can aid in early diagnosis and personalized treatment approaches, improving patient outcomes.

Conclusion

In conclusion, our study suggests that specific plasma lipid molecular subtypes, particularly phosphatidylcholines and sterol esters, may play important roles in allergic diseases. These findings contribute to our understanding of the lipidomic landscape in allergy pathogenesis and point towards potential lipid-based therapeutic targets. The use of robust MR methods and comprehensive sensitivity analyses enhances the reliability of our conclusions, offering valuable insights into the complex interactions between plasma lipids and allergic diseases. However, further research is needed to validate these associations and explore their clinical implications.

Author's Contribution

The study was designed by HY and QL. Statistical analyses were performed by HY. The manuscript was written by HY and YL. All authors contributed to the interpretation of data and commented on the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by funding from Dr. Qiang Liu's Southwest Medical University University-level Research Project 2023 (No. 2023QN112).

Informed Consent Statement

Patient consent was not required as the research utilized publicly available GWAS summary statistics data, which had already obtained informed consent from all participating studies in accordance with approved protocols by their respective institutional re-view boards.

Data Availability Statement

All data used in this study are available in the public repository. The code involved in the data analysis process can be obtained by contacting the corresponding author.

Acknowledgment

We thank the teams of the GWAS Catalog, FinnGen, and GeneRISK cohort for making the summary data publicly available. We would also like to acknowledge the principal investigators of the studies for their contributions and for making their data accessible for this research.

Conflicts of Interest

The authors declare no competing interests.

Ethical Approval

The GWAS data used in this study were public de-identified data, which were approved by the ethics committee. Therefore, no additional ethical approval was required.

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Supplementary Materials

https://www.heraldopenaccess.us/fulltext/Otolaryngology-Head-&-Neck-Surgery/Table-S1-harmonise-data-AR-as-outcome.csv

Table S1: Harmonise data (AR as outcome).

https://www.heraldopenaccess.us/fulltext/Otolaryngology-Head-&-Neck-Surgery/Table-S2-MR-Analysis-results-with-fdr-correction-AR-as-outcome.csv

Table S2: MR Analysis results with fdr correction (AR as outcome).

https://www.heraldopenaccess.us/fulltext/Otolaryngology-Head-&-Neck-Surgery/Table-S3-harmonise-data-AA-as-outcome.csv

Table S3: Harmonise data (AA as outcome).

https://www.heraldopenaccess.us/fulltext/Otolaryngology-Head-&-Neck-Surgery/Table-S4-MR-Analysis-results-with-fdr-correction-AA-as-outcome.csv

Table S4: MR Analysis results with fdr correction (AA as outcome).

https://www.heraldopenaccess.us/fulltext/Otolaryngology-Head-&-Neck-Surgery/Table-S5-harmonise-data-AC-as-outcome.csv

Table S5: Harmonise data (AC as outcome).

https://www.heraldopenaccess.us/fulltext/Otolaryngology-Head-&-Neck-Surgery/Table-S6-MR-Analysis-results-with-fdr-correction-AC-as-outcome.csv

Table S6: MR Analysis results with fdr correction (AC as outcome).

https://www.heraldopenaccess.us/fulltext/Otolaryngology-Head-&-Neck-Surgery/Table-S7-harmonise-data-ACD-as-outcome.csv

Table S7: Harmonise data (ACD as outcome).

https://www.heraldopenaccess.us/fulltext/Otolaryngology-Head-&-Neck-Surgery/Table-S8-MR-Analysis-results-with-fdr-correction-ACD-as-outcome.csv

Table S8: MR Analysis results with fdr correction (ACD as outcome).

https://www.heraldopenaccess.us/fulltext/Otolaryngology-Head-&-Neck-Surgery/Table-S9-AA-as-exposure.csv

https://www.heraldopenaccess.us/fulltext/Otolaryngology-Head-&-Neck-Surgery/Table-S9-AC-as-exposure.csv

https://www.heraldopenaccess.us/fulltext/Otolaryngology-Head-&-Neck-Surgery/Table-S9-AR-as-exposure.csv

Table S9: Reverse Mendelian Randomization results.

https://www.heraldopenaccess.us/fulltext/Otolaryngology-Head-&-Neck-Surgery/Table-S10-STROBE-MR-checklist.docx

Table S10: STROBE-MR checklist.

https://www.heraldopenaccess.us/fulltext/Otolaryngology-Head-&-Neck-Surgery/Table-S11-MR-analysis-results-threshold.xls

Table S11: MR analysis results with P 5×10^-8 threshold.

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