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ORIGINAL RESEARCH

Lipidomics Reveals Common Mechanisms in Polycystic Ovarian Syndrome, Recurrent Spontaneous Abortion, and Infertility: A Genetic-Based Analysis

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Background: Polycystic ovary syndrome (PCOS), infertility, and recurrent spontaneous abortion (RSA) pose significant challenges to women's reproductive health. While dyslipidemia plays a critical role in these conditions, the causal relationships between specific lipids and these pathologies, as well as their shared mechanisms, remain unclear.

Methods: We conducted genome-wide association studies (GWAS) to identify genetic variants associated with 179 plasma lipid species and obtained outcome data for PCOS, infertility, and RSA from the FinnGen R10 database. Mendelian randomization (MR) was performed with genetic variants as instrumental variables (IVs) to assess causal relationships. The inverse variance weighted (IVW) method was the primary approach in our two-sample MR study. Robustness was validated through assessments of heterogeneity, pleiotropy, and leave-one-out analyses.

Results: IVW analysis identified 17 plasma lipid species significantly associated with PCOS risk ($P < 0.05$), including sphingomyelin (d38:2) (OR = 0.909, 95% CI: 0.835–0.990, P = 0.0277) and triacylglycerol (48:2) (OR = 1.291, 95% CI: 1.097–1.518, P = 0.0020). Similarly, 15 lipid species were significantly associated with infertility risk ($P < 0.05$), such as sphingomyelin (d36:2) (OR = 0.926, 95% CI: 0.888–0.966, P = 0.0003) and triacylglycerol (48:2) (OR = 1.122, 95% CI: 1.059–1.188, $P < 0.0001$). Two lipid species, phosphatidylinositol (18:0_20:4) (OR = 0.790, 95% CI: 0.693–0.900, P = 0.0004) and sphingomyelin (d42:2) (OR = 0.779, 95% CI: 0.672–0.903, P = 0.0009), showed significant inverse associations with RSA risk, suggesting protective effects.

Conclusion: This study establishes causal relationships between specific lipid species and the risk of PCOS, infertility, and RSA, emphasizing lipid metabolism dysregulation as a common pathological mechanism underlying these reproductive disorders. Targeting lipids may offer a promising therapeutic strategy for these diseases.

Keywords: polycystic ovarian syndrome, recurrent spontaneous abortion, infertility, lipidomics, Mendelian randomization, causal relationship

Introduction

Polycystic ovary syndrome (PCOS), infertility, and recurrent spontaneous abortion (RSA) are major reproductive health challenges for women, contributing substantially to the global public health burden.[1–3] Due to their high prevalence and profound impact on quality of life, these conditions have become central focuses in medical research. Recent studies have highlighted that PCOS, infertility, and RSA share common lipid metabolism abnormalities, particularly involving physiological imbalances such as insulin resistance, oxidative stress, and chronic inflammation.[4–6] These factors significantly increase the risk of ovulatory disorders, abnormal embryo development, and pregnancy complications by disrupting hormone regulation, ovarian function, and endometrial receptivity.[7]

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Lipidomics, a crucial subfield of metabolomics, provides comprehensive insights into lipid profiles and their roles in health and disease. Lipids are fundamental components of cell membranes, and different lipid species, due to variations in fatty acid composition, head group structure, and biochemical modifications, exhibit distinct biological functions, playing a vital part in energy storage, signal transduction, and hormone synthesis.[8] Dysregulated lipid metabolism is closely linked to the onset and progression of PCOS, infertility, and RSA. Studies suggest that disturbances in lipid metabolism, particularly in phospholipids, sphingolipids, and glycerolipids, can impair ovarian function and reduce embryo implantation capacity by disrupting insulin signaling, altering hormonal balance, and promoting oxidative stress.[7,9–11] Further exploration of changes in plasma lipids will enhance our understanding of the metabolic mechanisms underlying these conditions and provide a theoretical foundation for lipid metabolism-targeted interventions, offering potential therapeutic strategies for managing female reproductive health.

Although observational studies provide preliminary evidence linking lipid metabolism disorders to these diseases,[12–14] the causal relationship requires further validation. Mendelian randomization (MR) studies utilize genetic variants as instrumental variables and leverage large-scale genome-wide association study (GWAS) data to robustly infer causal relationships.[15] In this framework, the two-sample MR method enhances statistical power and reliability in causal inference by using exposure and outcome variables from two independent samples.[16] The application of this method aids in identifying and validating causal relationships between lipid species and PCOS, infertility, and RSA. This genetic-driven analysis emphasizes the complexity and crucial role of lipidomics in uncovering the pathological processes of reproductive diseases. It provides important scientific evidence for identifying common biological pathways among these diseases and opens new avenues for personalized precision treatments in women's reproductive health.

Methods

Study Design

This study assessed the causal relationship between plasma lipids and female reproductive disorders using the two-sample MR method. We selected single nucleotide polymorphisms (SNPs) closely associated with lipid species from publicly available GWAS databases as genetic instrumental variables (IVs).[17] As illustrated in Figure 1, the study followed the three core assumptions of MR analysis: 1) The relevance assumption: IVs must be significantly associated with the exposure (lipid species); 2) The independence assumption: IVs should be independent of potential confounders to minimize confounding bias; 3) The exclusion assumption: IVs should influence the outcome solely through the exposure (lipid species).[15] Adherence to these assumptions is crucial for ensuring the validity of MR studies.

Data Sources

Summary statistics from large-scale GWAS on the plasma lipids were obtained from the GWAS catalog, published on October 31, 2023 (https://www.ebi.ac.uk/gwas/, GCST90277238-GCST90277416). As shown in Figure 2, the dataset includes SNPs associated with 179 lipid species (spanning four major lipid categories and thirteen specific lipid types) in 7174 Finnish individuals.[18] For detailed GWAS results, please refer to STable 1.

The GWAS summary data for female reproductive disorders were obtained from the FinnGen R10 database (https://www.finngen.fi/en/), released on December 18, 2023. This dataset includes data on PCOS (1639 cases and 218,970 controls), infertility (14,759 cases and 111,583 controls), and RSA (651 cases and 111,583 controls). The FinnGen database is a large biomedical project based on the Finnish population, incorporating data from national longitudinal health registers that have been collected from all Finnish residents since 1969.[19] The diagnostic criteria for each condition were defined as follows: 1) PCOS cases were identified using ICD-10 code E28.2 with confirmation through Rotterdam criteria (presence of ≥2 features: oligo/anovulation, biochemical/hirsutism signs, polycystic ovaries); 2) RSA required ≥3 consecutive pregnancy losses before 20 weeks gestation; 3) Infertility was defined as ≥12 months of unprotected intercourse without conception. The exclusion criteria for the three diseases were as follows: 1) Known chromosomal abnormalities; 2) Active cancer treatment; 3) Documented endocrine disorders (eg, Cushing syndrome, congenital adrenal hyperplasia); 4) Current use of ovulation induction drugs.

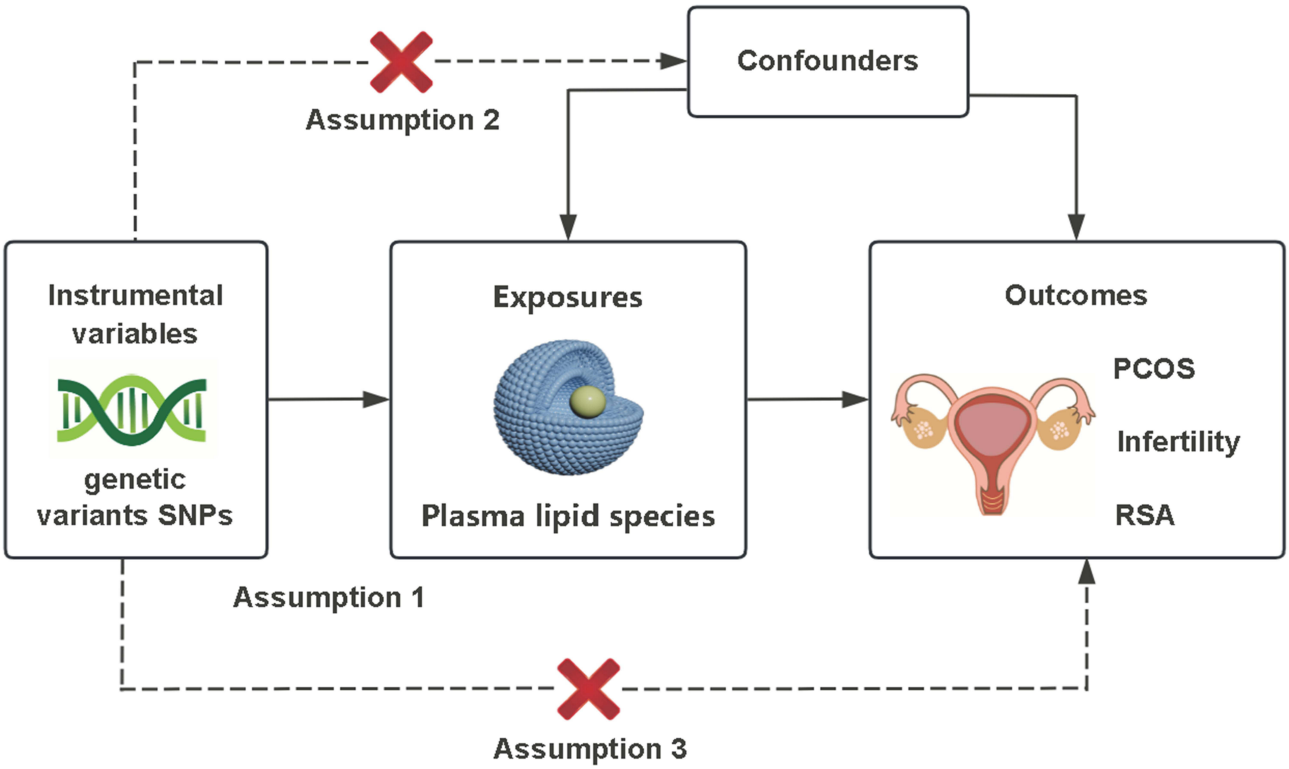

Figure 1 Three basic assumptions of the Mendelian randomization study.

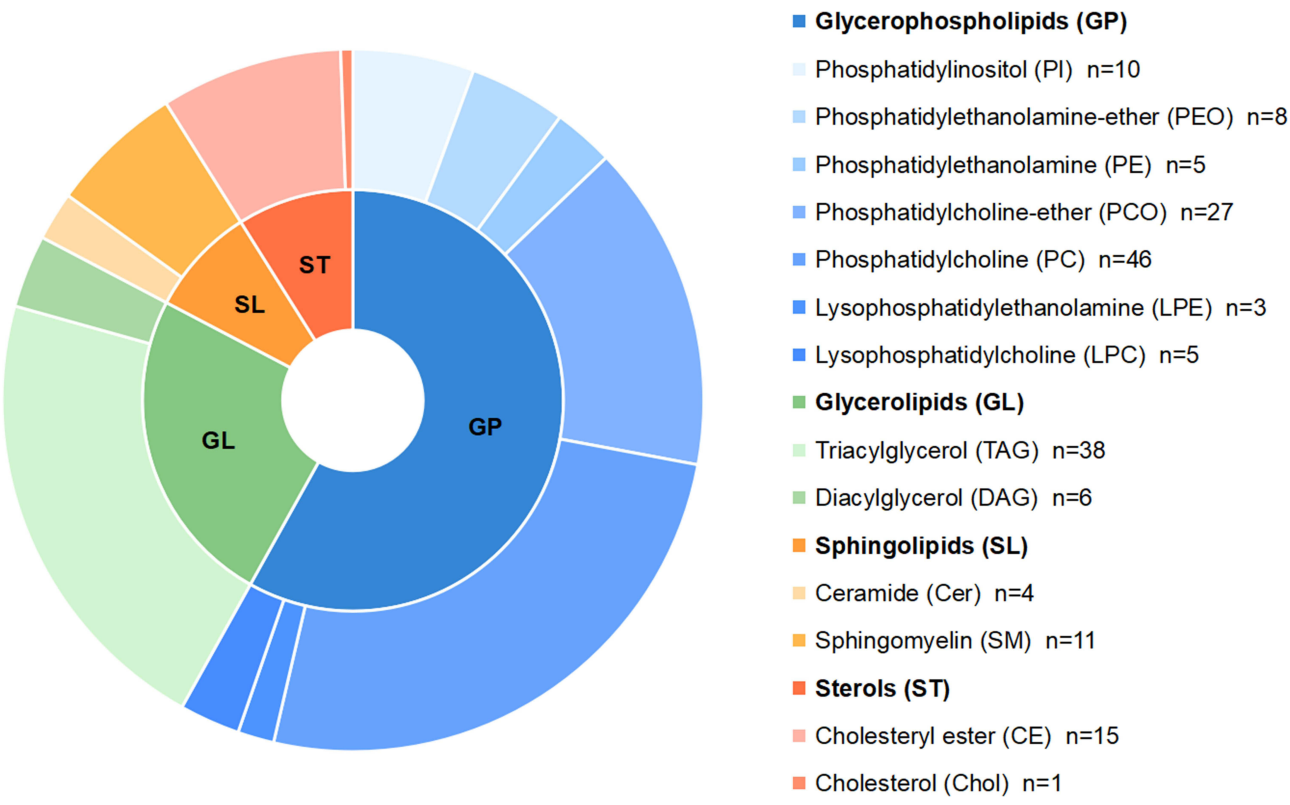

Figure 2 Categories and quantities of 179 plasma lipid species: An in-depth circular plot analysis.

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Selection of Instrumental Variables

The study applied stringent genetic selection criteria to identify SNPs significantly associated with 179 lipid species from the GWAS database, which were then used as genetic instruments. A threshold of $P < 1e{-}5$ was set to ensure a strong association between the selected SNPs and the exposure variable.[20,21] To minimize potential pleiotropic effects, SNPs significantly associated with confounding factors were excluded, retaining only those with an F-statistic > 10.[22] A linkage disequilibrium (LD) analysis was performed within a 500 kb window for the remaining SNPs, excluding those with $r^2 > 0.1$ to preserve the independence of the IVs and ensure the accuracy of the results.[23] Additionally, a false discovery rate (FDR) threshold of < 0.2 was applied as a measure of causality, and multiple comparisons and heterogeneity effects were controlled for using FDR correction.[24]

Statistical Analysis

This study utilized the TwoSampleMR (v0.5.7) and MendelianRandomization (v0.10.0) packages in R software for all analyses to ensure rigor and reproducibility. By integrating multiple MR methods, the accuracy and stability of causal effect estimates were enhanced. The inverse variance weighted (IVW) method was employed as the primary approach for reliable causal inference,[25] while sensitivity analyses were conducted using MR-Egger regression and weighted median method to examine the genetic associations between lipid metabolism and female reproductive disorders. MR-Egger regression was used to detect and correct horizontal pleiotropy, with a significant deviation of the intercept from zero ($P < 0.05$) indicating pleiotropy.[26] The weighted median method offers greater robustness when a large proportion of instrumental variables are invalid.[27] Additionally, Cochran's Q test ($P < 0.05$) was employed to assess heterogeneity, and the MR-PRESSO method was applied to identify and correct outliers, thereby reducing biases due to pleiotropy.[25,28] To further ensure the robustness of the analysis, a leave-one-out method was conducted to exclude individual SNPs and confirm that the results were not reliant on any single genetic variant.[29]

Results

Causal Effects of Plasma Lipids on PCOS

Through two-sample MR analysis, this study assessed the potential causal effects of the plasma lipids on the risk of PCOS (Figure 3A). The results indicated that glycerides, glycerophospholipids, and sphingolipids may influence the risk of PCOS. Specifically, lipid species such as diacylglycerol, triacylglycerol, phosphatidylcholine, phosphatidylinositol, and phosphatidylethanolamine were identified as risk factors for PCOS. Among these, triacylglycerol (48:2) emerged as the most significant risk factor, with a higher level associated with a 29% increased risk of PCOS (OR = 1.291, 95% CI: 1.097–1.518, P = 0.0020). In contrast, sphingomyelin (d38:2) from the sphingolipid family served as a protective factor, with an elevated level linked to a 9% decreased risk of PCOS (OR = 0.909, 95% CI: 0.835–0.990, P = 0.0277).

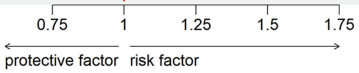
Causal Effects of Plasma Lipids on Infertility

The two-sample MR analysis revealed potential causal effects of glycerophospholipids, glycerolipids, sphingolipids, and sterols on infertility (Figure 3B). Consistent with the findings in PCOS, triacylglycerol, phosphatidylcholine, and phosphatidylethanolamine were also identified as risk factors for infertility. Among these, triacylglycerol (48:2) exhibited the most significant effect on infertility risk, with higher levels associated with approximately a 12% increase in risk (OR = 1.122, 95% CI: 1.059–1.188, P < 0.0001). Additionally, an elevated level of sterol ester (27:1/16:1) level was linked to a higher infertility risk (OR = 1.082, 95% CI: 1.021–1.147, P = 0.0075). Notably, although both sphingomyelin and ceramide are sphingolipids, their effects on infertility are divergent. All four sphingomyelin forms demonstrated a protective effect, particularly sphingomyelin (d36:2), with an increased level corresponding to a 7% reduction in infertility risk (OR = 0.926, 95% CI: 0.888–0.966, P = 0.0003). In contrast, an elevated level of ceramide (d40:1) was associated with a modest 5% rise in infertility risk (OR = 1.054, 95% CI: 1.010–1.100, P = 0.0165).

(A) PCOS

Traits	Method	P-value	nSNP	PFDR	OR(95%CI)
Diacylglycerol (18:1_18:1) levels	Inverse variance weighted	0.022830048	28	0.18037038	1.182(1.023 to 1.364)
Phosphatidylcholine (17:0_18:2) levels	Inverse variance weighted	0.023176083	40	0.18037038	1.144(1.019 to 1.284)
Phosphatidylcholine (18:0_18:1) levels	Inverse variance weighted	0.003552927	32	0.07949675	1.259(1.078 to 1.470)
Phosphatidylcholine (18:0_20:3) levels	Inverse variance weighted	0.009269959	38	0.13118751	1.180(1.042 to 1.337)
Phosphatidylcholine (O-16:0_16:1) levels	Inverse variance weighted	0.019208470	19	0.16469373	1.230(1.034 to 1.462)
Phosphatidylcholine (O-16:0_20:3) levels	Inverse variance weighted	0.002416888	22	0.06180328	1.277(1.090 to 1.495)
Phosphatidylcholine (O-18:2_18:2) levels	Inverse variance weighted	0.019321611	23	0.16469373	1.226(1.034 to 1.453)
Phosphatidylethanolamine (16:0_18:2) levels	Inverse variance weighted	0.014223523	67	0.15884423	1.092(1.018 to 1.172)
Phosphatidylethanolamine (18:0_18:2) levels	Inverse variance weighted	0.000543955	102	0.05005189	1.120(1.050 to 1.194)
Phosphatidylethanolamine (18:1_18:1) levels	Inverse variance weighted	0.001414274	51	0.06072859	1.168(1.062 to 1.284)
Phosphatidylethanolamine (O-16:1_22:5) levels	Inverse variance weighted	0.026293940	17	0.18826461	1.243(1.026 to 1.506)
Phosphatidylinositol (16:0_18:2) levels	Inverse variance weighted	0.016525288	35	0.16433481	1.163(1.028 to 1.315)
Sphingomyelin (d38:2) levels	Inverse variance weighted	0.027664138	68	0.19045695	0.909(0.835 to 0.990)
Triacylglycerol (48:1) levels	Inverse variance weighted	0.006365775	28	0.11394736	1.255(1.066 to 1.478)
Triacylglycerol (48:2) levels	Inverse variance weighted	0.002035595	27	0.06072859	1.291(1.097 to 1.518)
Triacylglycerol (49:1) levels	Inverse variance weighted	0.001718585	27	0.06072859	1.284(1.098 to 1.502)
Triacylglycerol (50:3) levels	Inverse variance weighted	0.000948326	42	0.05658344	1.240(1.092 to 1.409)

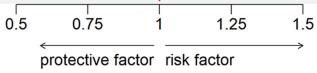
P<0.05 was considered statistically significant



(B) Infertility

Traits	Method	P-value	nSNP	PFDR	OR(95%CI)
Sterol ester (27:1/16:1) levels	Inverse variance weighted	0.007535786	27	0.073131373	1.082(1.021 to 1.147)
Ceramide (d40:1) levels	Inverse variance weighted	0.016523454	39	0.134440833	1.054(1.010 to 1.100)
Phosphatidylcholine (16:1_18:1) levels	Inverse variance weighted	0.021277340	37	0.158693496	1.055(1.008 to 1.105)
Phosphatidylethanolamine (16:0_18:2) levels	Inverse variance weighted	0.000107709	67	0.004241234	1.050(1.025 to 1.077)
Phosphatidylethanolamine (18:0_20:4) levels	Inverse variance weighted	0.000216524	87	0.005753985	1.045(1.021 to 1.070)
Phosphatidylethanolamine (18:1_18:1) levels	Inverse variance weighted	0.004263158	51	0.054507524	1.050(1.016 to 1.086)
Sphingomyelin (d36:1) levels	Inverse variance weighted	0.026782572	57	0.182556349	0.960(0.926 to 0.995)
Sphingomyelin (d36:2) levels	Inverse variance weighted	0.000335394	39	0.007504435	0.926(0.888 to 0.966)
Sphingomyelin (d38:1) levels	Inverse variance weighted	0.001439320	74	0.026193919	0.954(0.927 to 0.982)
Sphingomyelin (d40:1) levels	Inverse variance weighted	0.006991383	77	0.073131373	0.961(0.933 to 0.989)
Triacylglycerol (46:2) levels	Inverse variance weighted	0.014710671	24	0.125390955	1.070(1.013 to 1.129)
Triacylglycerol (48:2) levels	Inverse variance weighted	0.000084628	27	0.004241234	1.122(1.059 to 1.188)
Triacylglycerol (50:4) levels	Inverse variance weighted	0.000003325	40	0.000595122	1.114(1.065 to 1.166)
Triacylglycerol (52:3) levels	Inverse variance weighted	0.001613509	37	0.026256192	1.073(1.027 to 1.121)
Triacylglycerol (54:5) levels	Inverse variance weighted	0.026881463	35	0.182556349	1.055(1.006 to 1.107)

P<0.05 was considered statistically significant



(C) RSA

Traits	Method	P-value	nSNP	PFDR	OR(95%CI)
Phosphatidylinositol (18:0_20:4) levels	Inverse variance weighted	0.000419742	71	0.07513381	0.790(0.693 to 0.900)
Sphingomyelin (d42:2) levels	Inverse variance weighted	0.000915114	68	0.08190271	0.779(0.672 to 0.903)

P<0.05 was considered statistically significant

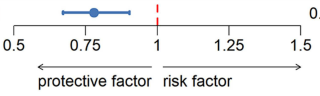


Figure 3 Forest plots of causal effect estimates of lipid species on the risk of female reproductive disorders. (**A**) PCOS. (**B**) Infertility. (**C**) RSA.

Causal Effects of Plasma Lipids on RSA

According to two-sample MR analysis, glycerophospholipids and sphingolipids may have significant causal relationships with the occurrence of RSA (Figure 3C). Notably, the effect of phosphatidylinositol in the glycerophospholipid category on RSA differs from its role in PCOS. An elevated level of phosphatidylinositol (18:0_20:4) was associated with a 21% reduction in RSA risk (OR = 0.790, 95% CI: 0.693–0.900, P = 0.0004). Additionally, an increased sphingomyelin level within the sphingolipid family demonstrated a significant protective effect, with a higher level of sphingomyelin (d42:2) linked to a 22% reduction in RSA risk (OR = 0.779, 95% CI: 0.672–0.903, P = 0.0009).

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Sensitivity Analysis

This study assessed the robustness of the results using several sensitivity analysis methods, including Cochran's Q test, MR-Egger regression, the weighted median method, and leave-one-out analysis. The IVW analysis showed no significant heterogeneity in studies examining PCOS, infertility, and RSA, supporting the consistency of the findings. In MR-Egger regression, the P-values for the intercepts were all greater than 0.05, indicating the absence of horizontal pleiotropy. Additionally, the MR-PRESSO testing failed to detect pleiotropic bias, further confirming the reliability of the results. Details can be found in STables 2–4. Scatter plots depicted the causal relationships between the plasma lipids and the risks of the three reproductive disorders, while funnel plot analysis showed no significant heterogeneity. Furthermore, leave-one-out analysis demonstrated that excluding any individual SNP did not substantially alter the MR results, reinforcing the robustness of the causal inference.

Discussion

PCOS, infertility, and RSA are common female reproductive disorders. Although their etiologies are complex and multifactorial, all three are influenced by lipid metabolism and share certain pathophysiological intersections. Disruption of lipid metabolism may represent one of the common pathogenic mechanisms underlying these disorders. This study is the first to systematically investigate the causal relationships between 179 plasma lipid species and female reproductive disorders, offering a comprehensive data-driven perspective on this field. We utilized 179 plasma lipids as exposure variables and PCOS, infertility, and RSA as outcome variables, conducting an in-depth analysis of the complex causal mechanisms linking the lipidome to these diseases.

In PCOS, glycerophospholipids (phosphatidylcholine, phosphatidylinositol, phosphatidylethanolamine) and glycerolipids (diacylglycerol, triacylglycerol) were identified as risk factors, whereas sphingomyelin, a sphingolipid, demonstrated a protective effect. In infertility, glycerophospholipids (phosphatidylcholine, phosphatidylethanolamine), glycerolipid (triacylglycerol), and sterol (cholesteryl ester) were similarly associated with increased risk, while the role of sphingolipids was more complex. Specifically, sphingomyelin exhibited a protective effect, whereas ceramide increased the risk, underscoring the dual role of lipid metabolism in infertility. In RSA, both phosphatidylinositol and sphingomyelin acted as protective factors, with elevated levels significantly linked to a reduced RSA risk. Notably, phosphatidylinositol exhibited divergent effects in PCOS and RSA: the elevated level of phosphatidylinositol was associated with an increased risk of PCOS, while significantly reducing the risk of RSA. In contrast, sphingomyelin consistently demonstrated a protective effect across all three disorders.

This study identified phosphatidylcholine (17:0_18:2, 18:0_18:1, 18:0_20:3), diacylglycerol (18:1_18:1), and triacylglycerol (48:1, 48:2, 49:1, 50:3) as potential contributors to an increased risk of PCOS. Additionally, phosphatidylcholine (16:1_18:1) and triacylglycerol (46:2, 48:2, 50:4, 52:3, 54:5) were closely associated with infertility, suggesting their role as risk factors. Phosphatidylcholine, a key component of cell membranes, is essential for maintaining membrane fluidity and functionality, thereby modulating insulin receptor activity and inflammatory responses.[9,10] Excessive accumulation of phosphatidylcholine can induce oxidative stress in oocytes, while elevated phosphatidylcholine levels in follicular fluid have been linked to reduced embryo quality on the third day post-fertilization.[30] These findings highlight critical mechanisms underlying the pathological progression of PCOS and infertility, offering compelling evidence of their shared pathogenic pathways.

Dysregulation of phosphatidylcholine metabolism typically results in its conversion into diacylglycerol and triacylglycerol through the action of phosphatidylcholine hydrolase or other metabolic pathways. Diacylglycerol, a critical lipid signaling molecule, activates protein kinase C and its downstream pathways, promoting insulin resistance and disrupting glucose and lipid metabolism.[31] In PCOS, diacylglycerol exacerbates insulin resistance and lipid accumulation by modulating insulin signaling and lipid metabolism, further aggravating metabolic disturbances within the follicles.[32] Triacylglycerol, the primary form of intracellular fat storage, provides energy support for oocytes under normal physiological conditions.[32,33] However, in PCOS patients, abnormal triacylglycerol accumulation leads to energy metabolism imbalances and elevated free fatty acid levels, triggering oxidative stress and inflammatory responses.[34] These metabolic disturbances alter the follicular microenvironment, impair oocyte maturation and quality, and result in ovulatory dysfunction and hormonal imbalances, significantly increasing the risk of PCOS and infertility.[35] Additionally,

elevated free fatty acids and inflammation disrupt the uterine endometrial environment, impairing embryo implantation and further exacerbating infertility.

This study suggested that phosphatidylethanolamine (16:0_18:2, 18:0_18:2, 18:1_18:1) served as risk factors for PCOS, with its specific subtypes (16:0_18:2, 18:0_20:4, 18:1_18:1) also playing a promotive role in infertility. Previous research has shown that the oxidation of phosphatidylethanolamine induces ferroptosis via the ACSL4/GPX4 pathway.[36] In PCOS patients, iron overload promotes oxidative stress and ferroptosis, exacerbates insulin resistance, impairs ovarian function, and disrupts the ovulation process.[37,38] Furthermore, ferroptosis damages immune cell function and triggers local inflammatory responses, thereby impairing the endometrial microenvironment and affecting embryo implantation, ultimately increasing the risk of infertility.[39] These findings provide important biological insights into the potential detrimental effects of phosphatidylethanolamine in PCOS and infertility.

Ether lipids are a distinct class of phospholipids linked by ether bonds between fatty acids or fatty alcohols and glycerol, with phosphatidylethanolamine ether and phosphatidylcholine ether being common types. Due to their unique ether bond structure, ether lipids play a crucial role in maintaining cell membrane stability and antioxidant functions.[40] This study demonstrated that phosphatidylcholine (O-16:0_16:1, O-16:0_20:3, O-18:2_18:2) and phosphatidylethanolamine (O-16:1_22:5), were associated with an increased risk of PCOS. Based on these findings, we hypothesize that in the pathological state of PCOS, elevated levels of phosphatidylethanolamine ether and phosphatidylcholine ether may act as an adaptive response to oxidative stress and membrane damage. By enhancing membrane stability, reducing oxidative burden, and regulating lipid metabolism, these ether lipids could help mitigate oxidative stress and inflammation, thereby improving metabolic dysfunction and promoting cellular function.

This study revealed that phosphatidylinositol exerts opposing effects in PCOS and RSA. Specifically, elevated levels of phosphatidylinositol (16:0_18:2) were associated with an increased risk of PCOS, whereas the higher level of phosphatidylinositol (18:0_20:4) was linked to a reduced risk of RSA. This discrepancy may stem from the distinct pathological mechanisms underlying these conditions and the specific effects of different phosphatidylinositol subtypes. Phosphatidylinositol activates the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling pathway on the cell membrane through phosphorylation, which in turn regulates critical physiological processes such as cell proliferation, survival, metabolism, and immune responses.[41] Under normal conditions, activation of the PI3K/AKT pathway promotes follicular development and oocyte maturation. However, in PCOS, elevated phosphatidylinositol levels lead to excessive activation of the PI3K pathway, triggering insulin resistance and excessive androgen secretion.[42] These factors, in turn, disrupt follicular development and contribute to the formation of polycystic ovaries. Furthermore, excessive activation of the PI3K/AKT pathway impairs autophagy and apoptosis in ovarian cells, worsening ovarian dysfunction. Autophagic dysfunction results in metabolic abnormalities and hinders the clearance of damaged ovarian cells, further aggravating the progression of PCOS.[43] Previous studies have shown that moderate activation of the PI3K/AKT pathway promotes cell proliferation, migration, suppresses apoptosis, maintains immune tolerance, and supports placental development and angiogenesis, all contributing to normal pregnancy progression.[44–46] Based on these findings, we propose that in RSA, maintaining phosphatidylinositol (18:0_20:4) within an optimal concentration range may yield beneficial effects through the precise modulation of the PI3K/AKT pathway. This regulation prevents excessive activation, thereby ensuring proper cell function and supporting both endometrial and embryo development. Therefore, fine-tuning phosphatidylinositol levels is crucial for maintaining the functionality of both the endometrium and the embryo.

Sphingolipids are vital components of cell membranes, and alterations in the length and saturation of their fatty acyl chains can significantly affect biological functions and contribute to disease.[47] As key elements of the "sphingolipid cycle", sphingomyelin and ceramide participate in physiological processes such as signal transduction, cell proliferation, apoptosis, inflammation, and immune responses.[48] Elevated ceramide levels are closely associated with cellular stress, dyslipidemia, and insulin resistance, while increased sphingomyelin levels exert a counter-regulatory role in these processes.[11] Consequently, metabolic imbalances induced by ceramides may trigger ovarian stress responses, impair follicular maturation, decrease ovarian hormone secretion, and compromise normal ovulation. Additionally, ceramides activate pro-inflammatory signaling pathways, enhancing the expression of cytokines such as TNF-α and IL-6, which alter the uterine microenvironment and hinder embryo implantation, suggesting a potential mechanism of infertility.[49]

In contrast, sphingomyelin plays a protective role in mitigating these adverse physiological conditions by preserving the normal function of the ovaries and endometrium, thereby supporting proper pregnancy progression. This finding is consistent with our research on PCOS, infertility, and RSA. Previous studies have shown that the interaction between sphingomyelin and cholesterol ester significantly influences the fluidity and stability of cell membranes.[50,51] The accumulation of cholesterol esters may disrupt the structure of lipid raft structure, impair sphingolipid function, thus affecting membrane signaling, exacerbating lipid metabolic dysregulation, and compromising ovarian and endometrial function. This mechanism further emphasizes sterol ester (27:1/16:1) as a risk factor for infertility. While infertility shares common lipid metabolism dysregulation mechanisms with PCOS and RSA, ceramide and cholesterol ester may not be the primary drivers of their pathogenesis. These differences likely stem from distinct metabolic characteristics, biological functions, and the complex multifactorial interactions unique to each disease.

This study systematically investigates the potential role of plasma lipids in PCOS, infertility, and RSA for the first time, revealing that lipid metabolism dysregulation may represent a common pathological mechanism underlying these diseases. This provides new insights into the pathogenesis and progression of female reproductive disorders. The findings indicate that lipid metabolism abnormalities influence key biological pathways, including insulin signaling, oxidative stress, inflammation, and energy metabolism, which significantly affect ovulation, hormonal balance, and embryo implantation, thereby exacerbating disease onset and progression. Notably, certain lipids exhibit dual roles across different diseases, both promoting pathological processes and offering protective effects through specific mechanisms. Furthermore, the protective effects of lipids are concentration-dependent, with excessive accumulation or deficiency potentially leading to opposite effects, highlighting the importance of maintaining lipid metabolism dynamic balance in female reproductive health.

These findings have significant clinical implications, breaking the traditional framework of studying single diseases and providing a new approach to exploring common pathological mechanisms across diseases. By identifying specific lipid species associated with PCOS, infertility, and RSA, this study offers potential biomarkers, aiding clinicians in early identification of high-risk populations and facilitating personalized interventions. Additionally, lipid metabolism-targeted therapies show great potential. Pharmacological interventions (such as the use of lipid-lowering drugs), dietary adjustments (such as increased Omega-3 fatty acid intake), and physical activity can not only improve lipid metabolism abnormalities but also indirectly modulate insulin sensitivity and inflammatory responses, thereby controlling disease progression and promoting reproductive health.

To validate the reliability of the results, multiple MR methods and sensitivity analyses were employed, providing strong causal inference evidence. These findings deepen the understanding of the nature of PCOS, infertility, and RSA, offering scientific support for the development of cross-disease diagnostic tools and therapeutic strategies. Future studies should further explore the molecular mechanisms underlying lipid metabolism dysregulation, with a focus on the dual roles of lipids and their complex manifestations in different diseases, while also validating the clinical efficacy of lipid-targeted therapies, advancing precision medicine in the field of reproductive health.

However, this study has several limitations. First, while the genetic homogeneity of the Finnish population enhances statistical power, it also limits the generalizability of the results. The research could include multi-ethnic cohorts to validate and extend these findings. Second, although horizontal pleiotropy analysis and sensitivity tests were conducted, genetic confounding may still not be fully eliminated, and covariates such as body mass index and reproductive history were not systematically adjusted, which may lead to residual confounding. Additionally, reliance on registry-based data may introduce misclassification bias, such as the potential underrepresentation of early miscarriages (<12 weeks) in the RSA cohort that did not require medical intervention. The effects of medications (eg, 23% of PCOS patients using metformin), lifestyle, environmental, and socioeconomic factors were also not fully considered. Furthermore, the cross-sectional design limits our ability to infer the temporal relationship between metabolic disturbances and reproductive outcomes. To address these limitations, future research could employ more advanced causal inference methods, such as MR-Clust or MR-LASSO, to optimize genetic confounding control, and integrate multivariable MR and mediation analysis to quantify direct and indirect effects. Additionally, incorporating multi-omics data and gene-environment interaction studies will provide a more comprehensive framework for advancing early interventions and precision

medicine. Furthermore, including longitudinal data will help better elucidate the causal relationship between metabolic disturbances and female reproductive outcomes.

Conclusion

In conclusion, this study is the first to use Mendelian randomization to examine causal links between 179 plasma lipids and female reproductive disorders (PCOS, infertility, RSA). Our findings highlight lipid metabolism dysregulation as a common pathological mechanism, significantly affecting reproductive function. Sphingomyelin protects against all three disorders, while phosphatidylinositol shows opposing effects in PCOS and RSA. These results underscore the importance of lipid balance in reproductive health and suggest specific lipid species as potential biomarkers for diagnosis and personalized intervention. Future research should validate these findings and explore their mechanisms to advance precision medicine in reproductive health.

Abbreviations

PCOS, polycystic ovary syndrome; RSA, recurrent spontaneous abortion; GWAS, genome-wide association study; MR, Mendelian randomization; IVW, inverse variance weighted; SNP, single nucleotide polymorphism; IV, instrumental variable; LD, linkage disequilibrium; FDR, false discovery rate; PI3K/AKT, phosphoinositide 3-kinase/protein kinase B.

Data Sharing Statement

The original contributions presented in this study are included in the article and its Supplementary Materials. For further inquiries, please contact the corresponding authors.

Ethics Statement

Since the GWAS data used in this study are entirely based on publicly available online GWAS summary-level statistics, no ethical approval is required. According to Article 32 of China's "Measures for the Ethical Review of Biomedical Research Involving Humans," which came into effect on February 18, 2023, the specific contents are as follows: Article 32: Biomedical research involving humans may be exempted from ethical review in the following circumstances: 1. Item 1: Research based on public databases that does not involve the identification or use of personal information. 2. Item 2: Analysis of collected data that does not involve the collection of new data or direct intervention in participants. These two provisions clarify that this article is exempt from ethical review when using public data and conducting data analysis.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests regarding this study.

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