Original Article

A Mendelian randomization study on associations between plasma lipidome, circulating inflammatory proteins, and erectile dysfunction

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Background: Some studies suggest a potential association between plasma lipidome and erectile dysfunction (ED), but the underlying mechanism and whether circulating inflammatory proteins act as mediators remain unclear. The purpose of this study was to investigate the potential causal relationships between plasma lipidome, inflammatory proteins, and ED.

Methods: Plasma lipidome, circulating inflammatory proteins, and ED cases were identified based on the summary data from several large-scale genome-wide association studies (GWAS). The causal relationships of plasma lipidome and circulating inflammatory proteins with ED were explored by a bidirectional two-sample, two-sample Mendelian randomization (MR) method. The inverse variance weighted (IVW) method was used as the primary analytical method. MR-Egger and the weighted median (IVW) methods were utilized as supplementary analytical techniques. Sensitivity analyses including MR-Pleiotropy RESidual Sum and Outlier method (PRESSO), Cochran's Q test, and MR-Egger intercept test were conducted to address heterogeneity and horizontal pleiotropy.

Results: Ceramide (d42:2) and triacylglycerol (56:3) were found to be associated with an increased risk of ED, while phosphatidylethanolamine (O-18:1_18:2) and phosphatidylinositol (18:1_18:1) were linked to a decreased risk of ED. Interleukin-1α (IL-1α), IL-7, IL-17C, and the tumor necrosis factor (TNF) receptor superfamily member 9 (TNFRSF9) positively affected ED. Conversely, leukemia inhibitory factor and urokinase-type plasminogen activator (uPA) showed a negative impact. Mediation analysis indicated that the uPA mediated between Triacylglycerol (56:3) and ED, accounting for a mediation proportion of –14.71%.

Conclusions: There was a causal relationship between plasma lipidome and circulating inflammatory proteins with ED. Circulating inflammatory proteins appeared to mediate between triacylglycerol (56:3) levels and ED.

Keywords: Mendelian randomization (MR); erectile dysfunction (ED); plasma lipidome; circulating inflammatory proteins

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Introduction

Erectile dysfunction (ED) or impotence is a common type of male sexual dysfunction, defined by the American Urological Association (AUA) as the inability of a man to achieve and maintain sufficient penile erection for satisfactory sexual intercourse (1). As the population

ages, the prevalence of ED increases. An epidemiological survey found that among men under 40 years of age, the prevalence of ED ranges from 1–9%. Among men over 40 years of age, the prevalence of ED increases with advancing age (2,3). ED not only undermines the psychosomatic health of the patient but also significantly disrupts family stability and marital harmony (4). This poses an increasing burden on global healthcare, economic, and social systems. Therefore, identifying the potential risk factors of ED and implementing early prevention measures hold significant clinical importance.

ED can be classified into organic, psychogenic, and mixed types based on etiology. In recent years, many scholars believe that ED is a manifestation of various diseases or causes influenced by numerous risk factors. In addition to some established risk factors (5), there is limited literature on the relationship between plasma lipidome and ED. Lipids are a diverse group of organic compounds that are insoluble in water but soluble in organic solvents. They not only serve as a source of energy but also play crucial roles in cell membrane structure, energy storage, and signal transduction in various cells (6). Many studies have reported an association between the plasma lipid and cardiovascular disease, obesity and metabolic disorders, which are recognized as risk factors for ED (7-9). An observational study enrolling 813 eligible male patients with type 2 diabetes mellitus (T2DM) revealed that the probability of developing dyslipidemia in T2DM patients was 2.3 times of that in those without ED (10), suggesting that there may be a relationship between abnormal plasma lipidome levels and ED. With the advancement and application of lipidomics sequencing technologies, our understanding of the variability and breadth of circulating lipids has expanded, enabling us to uncover a more intricate relationship between plasma lipid components and ED. A previous prospective study found that the high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) ratio could serve as the predictor of ED (11). In addition, existing studies have indicated a relationship between plasma lipidome and inflammation (12,13).

Inflammatory proteins play a crucial role in the pathogenesis of ED. Inflammation is a risk factor for ED, as it can impair endothelial function, leading to ED, and indirectly increase the risk of ED through metabolic syndrome and cardiovascular diseases (14,15). Meanwhile, the relationship between the plasma lipidome and inflammation has also been substantiated by related research. In the study on triglycerides (TG) and pancreatitis, Zhang *et al.* found that the hydrolysis of unsaturated fatty acids (UFA) in TG produces unsaturated non-esterified fatty acids (NEFA), which can result in lipotoxic inflammation and organ dysfunction. Excessive UFA can exacerbate chemokine and cytokine-mediated inflammatory cascades. Additionally, the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) can also be increased by excessive UFA levels (16). IL-10 is a key anti-inflammatory cytokine. Phosphatidylcholine and phosphatidylethanolamine are positively correlated with the anti-inflammatory cytokine IL-10 (17). Saturated very long chain ceramides played a crucial role in mediating the increased inflammatory gene expression in IL-10-deficient macrophages (18). Currently, it appears that both plasma lipidome and circulating inflammatory proteins can influence the development of ED, there is a close connection between the two. We hypothesize that circulating inflammatory proteins may act as mediating factors in the pathway from plasma lipidome to ED.

Mendelian randomization (MR) employs single nucleotide polymorphisms (SNPs) derived from genome-wide association studies (GWAS) as instrumental variables (IVs) to explore the causal relationship between exposure and outcome (19). GWAS determine associations between

Highlight box

Key findings

- There was a causal relationship between plasma lipidome and circulating inflammatory proteins with erectile dysfunction (ED). Circulating inflammatory proteins appeared to mediate between Triacylglycerol (56:3) levels and ED.

What is known and what is new?

- Many studies have reported an association between the plasma lipid and cardiovascular disease, obesity and metabolic disorders, which are recognized as risk factors for ED.
- With the advancement and application of lipidomics sequencing technologies, our understanding of the variability and breadth of circulating lipids has expanded, enabling us to uncover a more intricate relationship between plasma lipid components and ED. Meanwhile, the relationship between the plasma lipidome and inflammation has also been substantiated by related research. We hypothesize that circulating inflammatory proteins may act as mediating factors in the pathway from plasma lipidome to ED.

What is the implication, and what should change now?

- It is our hope that the results could provide useful clues for preventing or delaying the onset and progression of ED.

genotypes and phenotypes, profoundly impacting the field of complex disease genetics by testing millions of genetic variations across individual genomes (20). Compared with most randomized controlled trials, in two-sample MR analysis, by leveraging genetic information from large-scale GWAS, MR analysis can minimize the impact of confounding factors and provide reliable evidence for the causal relationship between exposure factors and outcomes before the onset of the disease. In research on ED, scientists have discovered that plasma lipids may increase the risk of ED by affecting factors such as metabolic syndrome, cardiovascular diseases, and obesity. Concurrently, inflammatory proteins could directly damage endothelial cells and impair vascular function. Moreover, inflammatory proteins may also lead to ED indirectly by exacerbating cardiovascular diseases. By investigating the relationship between the plasma lipidome, inflammatory proteins, and ED, scientists can gain a deeper understanding of the underlying biological mechanisms of ED. The aim of the present study was to explore the potential causal effects between plasma lipidome, inflammatory protein factors and ED through two-sample MR analysis and mediation analysis, determine whether inflammatory protein factors act as mediators in the pathway from plasma lipidome to ED, and examine whether genetic susceptibility to ED risk influences plasma lipids and inflammatory protein factors through bidirectional MR analysis. It is our hope that the results could provide useful clues for preventing or delaying the onset and progression of ED. We present this article in accordance with the STROBE-MR reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-378/rc).

Methods

Study design

This study consisted of three main parts. Step 1: analyzing the causal effect of 179 plasma lipidome components on ED; Step 2: analyzing the causal impact of 91 inflammatory proteins on ED; Step 3: mediation analysis of inflammatory proteins in the pathway from plasma lipidome to ED. To ensure the validity of our research findings, MR analysis was used to satisfy three core assumptions: (I) genetic variations were closely related to the exposure factor (plasma lipidome); (II) genetic variations were not causally related to potential confounding factors; (III) genetic variations did not directly affect the ED outcome. The specific research process is illustrated in *Figure 1*.

Data source

Genetic data related to plasma lipidome were extracted from the prospective GeneRISK cohort's GWAS summary data, which included 7,266 participants (4,642 females, 2,624 males). Participants' plasma, serum, and DNA samples were collected for lipid analysis. The GWAS summary data comprised 179 lipid species across 13 lipid categories, covering four main lipid classes: glycerolipids (GL), glycerophospholipids (GP), sphingolipids (SL), and sterols (ST) (21). The genetic information of circulating inflammatory proteins was obtained from a recent study that recruited 11 cohorts, ultimately including a total of 14,736 participants and measuring 91 inflammation-related proteins (22).

The GWAS datasets related to ED was extracted from a study by Bovijn *et al.* (23), which included samples from the Partners HealthCare Biobank, the University of Tartu Estonian Genome Center, and the UK Biobank, comprising 6,175 cases and 217,630 controls. Cases of ED were identified through self-reports, clinical diagnoses, administration of oral ED medications, or records of ED surgeries. Detailed information is provided in Table S1. To avoid overlap between samples for exposure and outcomes, data on plasma lipidome, circulating inflammatory proteins, and ED were sourced from distinct GWAS databases.

Given the genetic differences between populations of different ethnicities, participants in the aforementioned GWAS datasets were of European descent. This study involved secondary analysis of publicly available GWAS summary data, with each original GWAS study obtaining ethical approval. As individual-level data were not used in this study, no additional ethical approval was required.

IV selection

In MR studies, extracting a sufficient number of SNPs is a prerequisite for ensuring reliable results. When we strictly use 5×10^{-8} as the threshold, the number of obtained SNPs is limited, which cannot ensure the reliability of the analysis results. To maximize the instruments available for each plasma lipid and circulating inflammatory protein, we first chose a threshold of SNP P value at 1×10^{-5} for plasma lipids and circulating inflammatory proteins (24). To exclude SNPs in linkage disequilibrium during analysis, SNPs closely associated with plasma lipidome and circulating

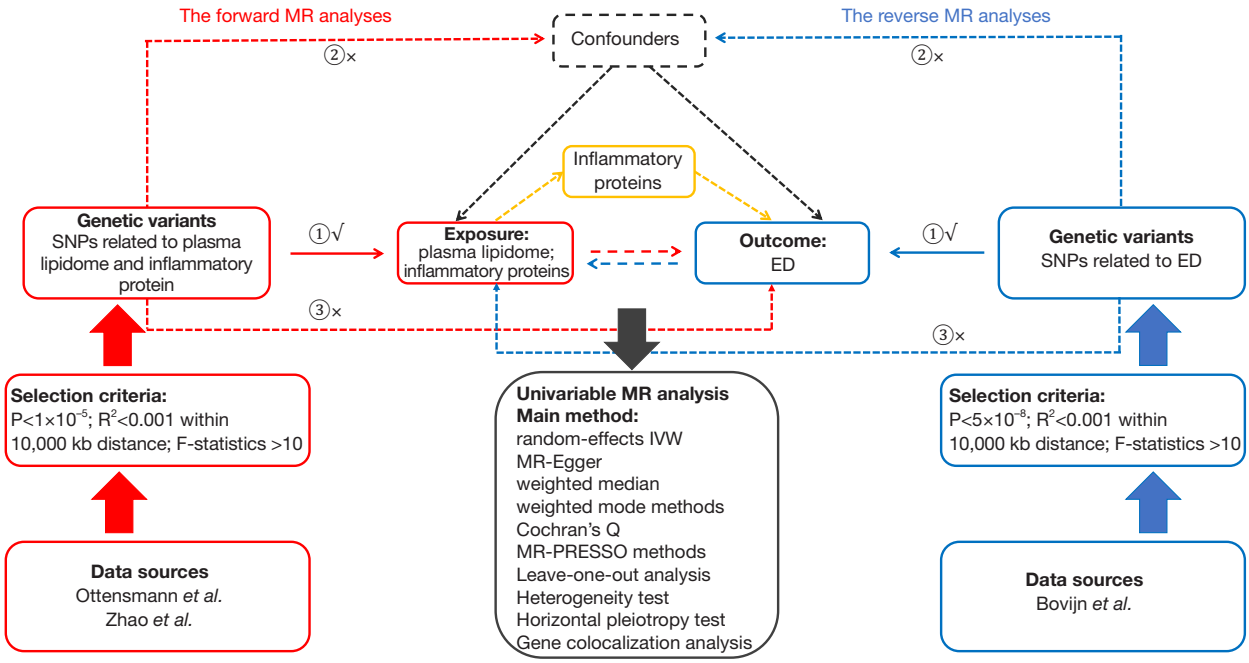

Figure 1 The workflow of this study. ①, ②, ③, correspond to the three core assumptions of MR analysis. ED, erectile dysfunction; SNP, single nucleotide polymorphism; MR, Mendelian randomization; IVW, inverse variance-weighted; PRESSO, Pleiotropy RESidual Sum and Outlier method.

inflammatory proteins should meet the following criteria: r^2<0.001 and distance >10,000 kb (25). Palindromic SNPs were removed after matching the results. Relevant information such as SNPs, chromosome, effect allele (EA), other allele (OA), EA frequency (EAF), effect sizes (β), standard error (SE), and P value were extracted. Data from SNPs with reverse causation were screened by Steiger test, where a Steiger test statistic P value less than 0.05 indicates no reverse causation (26). Finally, F-statistic parameter was calculated using the equation: [F = (beta/se)^2], and IVs with the F-statistic parameter <10 were excluded to ensure that the identified IVs were closely related to the exposure (27). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

Univariable MR analysis

To estimate the causal effect of plasma lipidome and circulating inflammatory proteins on ED, we conducted a two-sample MR analysis (28), and examined the causal relationships between genetically predicted plasma lipidome, circulating inflammatory proteins, and ED by the inverse variance weighted (IVW) method, whereby the mean effect of all IVs was used to estimate the causal effect, assuming all IVs are valid without heterogeneity or pleiotropy. To account for potential heterogeneity and pleiotropy in the SNPs, we also utilized the MR-Egger method, the simple mode method, the weighted median method, and the weighted mode method to assess the IVs (29,30). The MR-Egger method estimates the causal effect between exposure and outcome while considering the pleiotropy of IVs. The MR-Egger regression intercept reflects the extent to which IVs influence factors beyond exposure and outcome. If the intercept is non-zero (MR-Egger's statistical P value <0.05), horizontal pleiotropy exists (31). To evaluate heterogeneity between IVs related to each plasma lipidome and circulating inflammatory protein, we conducted Cochran's *Q* test (32). Furthermore, we used MR-Pleiotropy RESidual Sum and Outlier method (MR-PRESSO) to test for horizontal pleiotropy between the IVs, and mitigated its impact by detecting and removing outliers (33). Results were considered statistically significant when the P value of the aforementioned MR analysis methods was <0.05, the direction of beta was consistent, the Egger intercept and MR-PRESSO indicated no horizontal pleiotropy, and

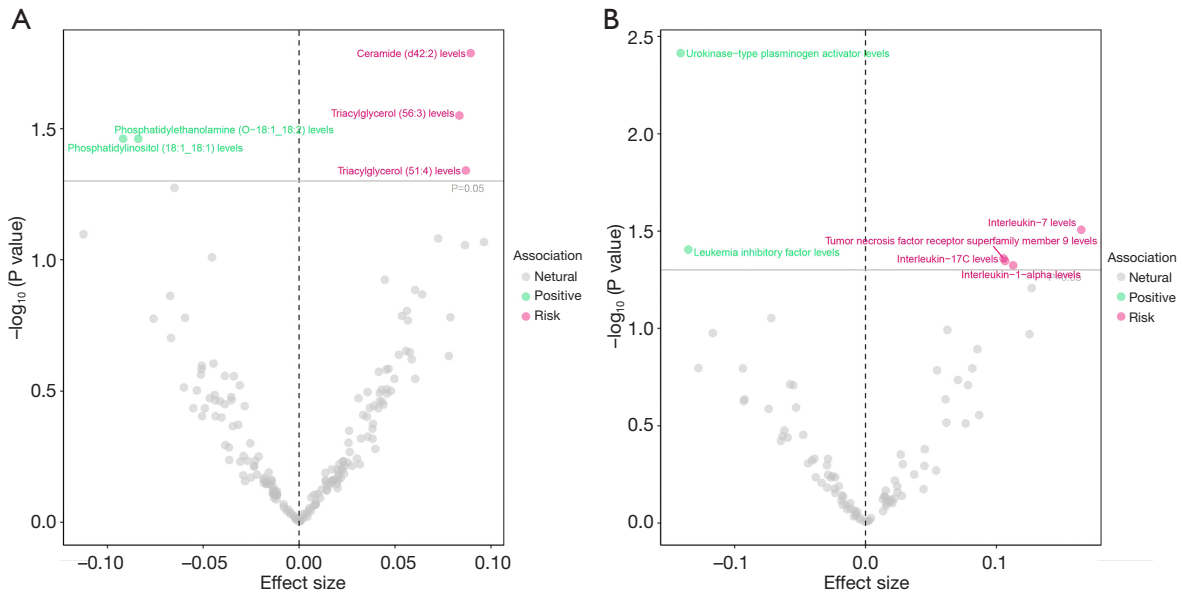

Figure 2 Volcano map of Mendelian randomization analysis between plasma lipidome, inflammatory proteins and erectile dysfunction. (A) Mendelian randomization analysis between plasma lipidome and ED; (B) Mendelian randomization analysis between inflammatory proteins and ED. ED, erectile dysfunction.

Cochran's *Q* test suggested no heterogeneity. The value less than 0.05 is suggestive of an association.

Bi-directional causality analysis

To assess the bidirectional causal effect between plasma lipids, inflammatory proteins and ED, we selected ED as the exposure and considered plasma lipidome and circulating inflammatory proteins as outcomes. We used SNPs closely associated with ED as IVs and chose a threshold of SNP P value at 5×10^{-8}.

Mediation analysis

Through the utilization of two-sample MR analysis, plasma lipidome and circulating inflammatory protein phenotypes with significant causal effects on ED were included in the mediation analysis to determine whether there is a causal effect between plasma lipidome and circulating inflammatory proteins. If so, we would conduct a mediation analysis to investigate whether circulating inflammatory proteins acted as mediators in the pathway from plasma lipidome to ED. All analyses were conducted using the TwoSampleMR (version 0.5.10), MendelianRandomization (version 0.8.0), and MRPRESSO package (1.0) in R Software 4.3.2 (https://www.R-project.org). And the study protocol and detail hadn't been pre-registered.

Results

IV selection

After excluding SNPs in linkage disequilibrium and those with F-statistic values less than 10, we included 104 SNPs ($P<1\times10^{-5}$) related to 179 plasma lipidome traits. These 104 SNPs were selected as IVs for the 179 plasma lipidome traits (Table S2). Subsequently, we included 199 SNPs ($P<1\times10^{-5}$) associated with 91 circulating inflammatory proteins (Table S3).

Causal effects of plasma lipidome on ED

Four categories of plasma lipids were found to be associated with ED. Information on 104 SNPs related to the four plasma lipidome categories is displayed in *Figures 2,3* (Table S4). Detailed 104 SNPs information for 4 plasma lipids is shown in Table S5. As shown by MR analysis in *Figure 2*, the genetic predisposition to two plasma lipidome categories (SL and GL) was associated with an increased risk of ED. Ceramide (d42:2) [odds ratio (OR) =1.093, 95% confidence interval (CI): 1.017–1.176, P=0.02] and triacylglycerol (56:3) (OR =1.09, 95% CI: 1.01–1.17, P=0.03) significantly increased the risk of ED. On the other hand, the genetic predisposition to GP was associated with

Exposure	Outcomne	Method	nSNP	P.value	OR(95%CI)	Heterogeneity.Test.P	MR.Egger.Intercept.P	MR.PRESSO.Global.Test.P
Ceramide (d42:2) levels	Erectile dysfunction	Inverse variance weighted	30	0.020	1.09(1.02 to 1.18)	0.82	0.85	0.88
Phosphatidylethanolamine (O-18:1_18:2) levels	Erectile dysfunction	Inverse variance weighted	27	0.040	0.91(0.84 to 0.99)	0.76	0.46	0.80
Phosphatidylinositol (18:1_18:1) levels	Erectile dysfunction	Inverse variance weighted	23	0.040	0.92(0.85 to 0.99)	0.62	0.35	0.62
Triacylglycerol (56:3) levels	Erectile dysfunction	Inverse variance weighted	24	0.030	1.09(1.01 to 1.17)	0.48	0.73	0.54
Interleukin-1-alpha levels	Erectile dysfunction	Inverse variance weighted	25	0.048	1.12(1.00 to 1.25)	0.67	0.62	0.73
Interleukin-7 levels	Erectile dysfunction	Inverse variance weighted	26	0.030	1.18(1.02 to 1.37)	0.30	0.63	0.35
Leukemia inhibitory factor levels	Erectile dysfunction	Inverse variance weighted	29	0.040	0.87(0.77 to 0.99)	0.34	0.78	0.38
Tumor necrosis factor receptor superfamily member 9 levels	Erectile dysfunction	Inverse variance weighted	36	0.044	1.11(1.00 to 1.23)	0.92	0.94	0.93
Interleukin-17C levels	Erectile dysfunction	Inverse variance weighted	39	0.045	1.11(1.00 to 1.24)	0.58	0.17	0.60
Urokinase-type plasminogen activator levels	Erectile dysfunction	Inverse variance weighted	44	0.004	0.87(0.80 to 0.96)	0.40	0.09	0.32

P<0.05 was considered statistically significant

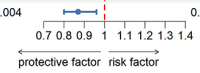

Figure 3 Mendelian randomization results of causal effects between plasma lipidome, circulating inflammatory proteins and erectile dysfunction. nSNP, number of single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization; PRESSO, Pleiotropy RESidual Sum and Outlier method.

a reduced risk of ED, while phosphatidylethanolamine (O-18:1_18:2) (OR =0.91, 95% CI: 0.84–0.99, P=0.04) and phosphatidylinositol (18:1_18:1) (OR =0.92, 95% CI: 0.85–0.99, P=0.04) significantly lowered the risk of ED.

Causal effects of circulating inflammatory proteins on ED

Furthermore, four circulating inflammatory proteins were found to be associated with ED (Table S6). IL-1α (OR =1.12, 95% CI: 1.00–1.25, P=0.048), IL-7 (OR =1.18, 95% CI: 1.02–1.37, P=0.03), IL-17C (OR =1.11, 95% CI: 1.00–1.24, P=0.045), and TNF receptor superfamily member 9 (TNFRSF9) (OR =1.11, 95% CI: 1.00–1.23, P=0.044) significantly increased the risk of ED. Conversely, leukemia inhibitory factor (OR =0.87, 95% CI: 0.77–0.99, P=0.04) and urokinase-type plasminogen activator (uPA) (OR =0.87, 95% CI: 0.80–0.96, P=0.004) significantly decreased the risk of ED.

Mediation analysis

Our analysis results demonstrated that both plasma lipidome categories and circulating inflammatory proteins were causally related to ED. Inflammatory proteins may serve as mediators between plasma lipidome categories and the pathway leading to ED. A fundamental requirement of Mediation analysis is that plasma lipidome categories associated with ED and the circulating inflammatory proteins associated with ED should also show a significant relationship (Table S7). Our research found that the elevated uPA levels mediate the causal pathway from Triacylglycerol (56:3) to ED (*Figure 4*). The mediation effect of uPA accounted for −14.71% of the total effect of ED, with a mediated proportion from −0.289 to −0.005 (Table S8). We also observed that phosphatidylinositol (18:1_18:1) levels related to ED and IL-17C levels related to ED show a significant relationship (OR =1.118, 95% CI: 1.026–1.218, P=0.01). Unfortunately, mediation analysis revealed that IL-17C does not mediate this relationship.

Bi-directional causal effects of ED on plasma lipidome and circulating inflammatory proteins

To determine whether ED exerted a reverse causal effect on plasma lipidome and circulating inflammatory proteins, we conducted a reverse MR analysis using the IVW method as the primary approach. To ensure the specificity of the results, we set the threshold for the P-statistic value at 5×10^{-8}. In the reverse MR analysis, we did not find any causal effect between ED and plasma lipidome. Regarding the relationship between ED and circulating inflammatory proteins, we did not include sufficient numbers of SNPs for MR analysis (Table S9).

Sensitivity analysis

Our MR-PRESSO analysis of MR study demonstrated the absence of horizontal pleiotropy (P>0.05, Table S10), and the MR-Egger regression intercept method showed no bias due to genetic pleiotropy, nor did Cochran's *Q* test show significant heterogeneity (P>0.05, Table S10). The Leave-one-out analysis results confirmed the reliability of the MR analysis, for the total CI of SNP does not cross zero (Figures S1,S2). The overall effects between plasma lipidome, circulating inflammatory proteins and ED are shown by the scatter plot, where the horizontal axis represents the IV-exposure effect and the vertical axis represents the IV-outcome effect (Figures S3,S4). The effect sizes of each SNP and the causal relationships between plasma lipidome, circulating inflammatory proteins and ED

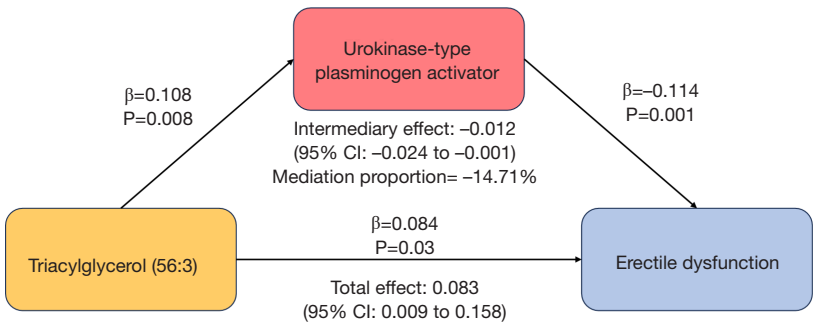

Figure 4 The mediation effect of urokinase-type plasminogen activator in the causal effect of triacylglycerol (56:3) on ED risk. ED, erectile dysfunction.

are displayed by the forest plot (Figures S5,S6).

Discussion

In this study, we used large amounts of publicly available genetic data to explore the causal relationship between 179 plasma lipidome categories and ED. To the best of our knowledge, this is the first MR analysis to investigate the causal relationship between multiple plasma lipid phenotypes and ED. Our study results revealed that elevated levels of SL [ceramide (d42:2)] and GL [triacylglycerol (56:3)] were associated with an increased risk of ED, while elevated levels of GP [phosphatidylethanolamine (O-18:1_18:2), phosphatidylinositol (18:1_18:1)] reduced the risk of ED.

SL are important bioactive lipids, playing crucial roles in cell proliferation, apoptosis, and disease progression (34,35). Our findings suggested that the risk of ED increased with higher levels of ceramide (d42:2). In a prospective cohort study that included 1,131 participants, patients within the highest quartile for ceramide scores were found to have nearly a 1.5-fold increased risk of major adverse cardiac events, with a hazard ratio of 1.47 (95% CI: 1.12–1.92) (36). Other studies have shown that endogenous ceramides facilitate the transcellular transport of oxidized low-density lipoprotein across endothelial cells, promoting the initial stages of atherosclerosis by retaining lipids beneath the vascular wall, which indicates that ceramides may increase the risk of ED by promoting atherosclerosis (35,37). Another study found that TNF-α level was elevated in patients with diabetes-related ED, and TNF-α induced the risk of ED by promoting reactive oxygen species (ROS) generation mediated by nicotinamide adenine dinucleotide phosphate oxidase in the corpus cavernosum (38), which aligns with our analysis results. However, our analysis suggests that TNF-α did not mediate the pathway from ceramides to ED (39). Additionally, ceramides are closely related to insulin resistance. Previous study has found that ceramide levels are directly associated with insulin resistance in obese patients with type 2 diabetes (40). Another study also found that pharmacological inhibition of ceramides can increase insulin sensitivity (41). Therefore, ceramides may contribute to ED through insulin resistance. Recent research has shown that inhibiting the notch pathway in fibroblasts of the corpus cavernosum can increase blood flow to the penis (42). Ceramide may reduce the action of TGF-β in fibroblasts by antagonizing Smad, with TGF-β inducing the expression of connective tissue growth factor (CTGF) in fibroblasts (43). Therefore, elevated levels of ceramide may inhibit fibroblast generation, leading to ED. It is important to note that research on neurotensin is still limited, especially ceramide (d42:2). There is currently no literature on the impact of ceramide levels on fibroblasts in the corpus cavernosum, indicating the need for further investigation in the future.

As important components of plasma lipids, GL have been implicated in increasing the risk of ED based on the results of MR analysis. Specifically, triacylglycerol (56:3) have been demonstrated to be associated with an increased risk of ED. A preliminary study suggested that the occurrence of ED is more prevalent among men suffering from severe hypertriglyceridemia compared with those with severe hyperlipidemia (42.9% *vs.* 29.4%), and also more prevalent than those with normal cholesterol levels (42.9% *vs.* 24.2%) (8). Numerous studies have shown that cardiovascular disease is a risk factor for ED, with triacylglycerol closely linked to cardiovascular disease. Prolonged high triacylglycerol intake can lead to obesity and metabolic disorders (9). Research

has indicated that the PI3K Akt pathway is activated in early obesity, with PI3K being negatively correlated with ED (44). Another study found that obese men may experience functional hypogonadism, leading to lower testosterone levels. Meanwhile, men with low testosterone levels tend to have their multipotent mesenchymal stem cells in adipose tissue preferentially differentiate into adipose tissue. This resulted in increased insulin resistance and the synthesis of pro-inflammatory adipokines, such as IL-1, IL-6, and TNF-α. The secretion of pro-inflammatory adipokines exacerbated inflammation and worsened tissue sensitivity to insulin, ultimately leading to the development of ED (45). Elevated plasma triacylglycerols can increase the risk of ED by promoting the progression of atherosclerosis (46,47).

Our study suggests that increased levels of phosphatidylethanolamine (O-18:1_18:2) and phosphatidylinositol (18:1_18:1) could reduce the risk of ED possibly. phosphatidylinositol may release the risk of ED by increasing the HDL-C levels (48). Unfortunately, there is limited research on phosphatidylinositol (18:1_18:1) in relation to ED. Similarly, researches on phosphatidylethanolamine (O-18:1_18:2) are scarce, with current study only showing its potential to reduce inflammation and treat atherosclerosis (49). Further research is needed to explore its potential in reducing the risk of ED. A study reported that GP metabolism played a key role in various metabolic syndromes, such as dyslipidemia, obesity, and insulin resistance.

In this study, we used MR experiments to explore the positive or negative relationship between plasma lipidome and ED. As the mechanisms by which plasma lipidome influences the onset of ED remain unclear, we propose that circulating inflammatory proteins may serve as mediators between the two. Our MR analysis results demonstrated that TNFRSF9, IL-1α, IL-7 and IL-17C levels were associated with an increased risk of ED. A study has shown that these proteins can modulate various systemic inflammatory responses, potentially increasing the risk of ED by affecting a range of diseases such as atherosclerosis, obesity, ischemic or hemorrhagic stroke, and rheumatoid arthritis (50). Recent studies found that Interleukin-17C may increase the risk of ED through its involvement in psoriasis and atherosclerosis (51,52). Our findings suggest a protective role of leukemia inhibitory factor levels and uPA levels against ED. The mechanism of this protective effect may be attributed to the anti-inflammatory actions and the preventive effect against obesity of leukemia inhibitory factor levels, knowing that inflammation and obesity are contributing factors of ED (53-55). uPA activator may reduce the risk of ED by releasing growth factors and pro-angiogenic molecules (56). This presents a potential therapeutic target for ED. Meanwhile, our findings indicate that uPA may act as mediators between plasma lipidome and ED. Unfortunately, no direct relationship had yet been identified between TG and uPA. Diets high in TG and elevated plasma TG levels often led to obesity, a high-risk factor for the development of triple-negative breast cancer (57), where elevated uPA levels are observed (58). Therefore, TG may indirectly increase uPA levels through breast cancer. Future research, including clinical trials and additional observational studies, is essential to validate and the outcomes of our present study.

This is the first large-scale MR analysis study on the causal relationship between plasma lipidome, circulating inflammatory proteins, and ED. Our study benefits from extensive data on plasma lipidome and circulating inflammatory proteins sourced from the latest published GWAS articles. However, there are some limitations in this study. First, the data on ED lacked sufficient cases and were not systematically categorized, such as organic ED, psychogenic ED, and mixed-type ED. Future research should focus on the relationship between plasma lipidome, inflammatory proteins, and different categories of ED. Second, our analysis only included the European population, which meant a lack of data from other ethnicities worldwide, necessitating the inclusion of diverse ethnic data and further validation of the results in the future. Third, the existing data on plasma lipidome and inflammatory proteins did not differentiate by gender, which might have affected the MR results. Including gender-specific analyses in future research could provide a deeper understanding of genetic associations. Finally, our mediation analysis suggests that circulating inflammatory proteins may act as mediators between plasma lipidome and the onset of ED, but we had not yet found sufficient literature to support the mediation analysis results. Therefore, further research is needed to elucidate the mechanisms by which plasma lipidome influences the development and progression of ED.

Conclusions

In this study, we comprehensively investigated the causal effects between plasma lipidome, circulating inflammatory proteins, and ED. There were two positive and two negative causal effects between plasma lipidome and ED.

Additionally, there were three positive correlations and one negative causal effect between circulating inflammatory proteins and ED. There was no evidence to support bidirectional causal relationships between plasma lipidome, circulating inflammatory proteins, and ED. Circulating inflammatory proteins appeared to act as mediators between plasma lipidome and ED.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-378/rc

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-378/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-378/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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