Lipids in Health and Disease

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The causal relationship between 179 lipid species and urolithiasis: a bidirectional and multivariable Mendelian randomization study combined with meta-analysis

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Abstract

Background Previous research has suggested a potential link between urolithiasis and lipid species levels. A Mendelian randomization (MR) study was conducted to investigate whether a causal relationship exists between genetic susceptibility to plasma lipids and the risk of urolithiasis.

Methods Data on lipid species were collected from genome-wide association (GWAS) analyses of plasma lipidomes. For the initial analysis, GWAS data on urolithiasis were extracted using the GWAS ID ebi-a-GCST90018935. The inverse variance weighted (IVW) approach was utilized as the main method for MR analysis. Multivariable MR, multiple supplementary analyses, and comprehensive sensitivity analyses were also conducted. Additional independent datasets were utilized for replication analysis and meta-analysis.

Results Findings from the IVW method, repeated analyses, and meta-analysis revealed six significant causal effects of lipid species on urolithiasis. The specific lipid species identified were: phosphatidylcholine (PC; 16:1_20:4) levels [OR: 0.92; 95%CI: 0.87, 0.96; $P=6\times10^{-4}$], PC (16:0_20:4) levels [OR: 0.94; 95%CI: 0.90, 0.98; $P=0.0017$], phosphatidylethanolamine (PE; 18:2_0:0) levels [OR: 1.10; 95%CI: 1.04, 1.15; $P=4\times10^{-4}$], PE (16:0_20:4) levels [OR: 1.05; 95%CI: 1.01, 1.09; $P=0.0028$], PE (18:1_18:1) levels [OR: 1.06; 95%CI: 1.01, 1.11; $P=0.0136$], and sterol ester (SE; 27:1/20:4) levels [OR: 0.93; 95%CI: 0.89, 0.96; $P=1.5\times10^{-4}$].

Conclusion The MR study proposes a potential causal link between six plasma lipids and urolithiasis. Particularly, SEs (27:1/20:4), PC (16:0_20:4), and PC (16:1_20:4) may serve as potential inhibitors of calcium-containing urolithiasis growth. The integration of genomics and lipidomics in MR analysis holds promise for early screening, prevention, and treatment of urinary tract stones.

Keywords Lipids, Urolithiasis, Mendelian randomization analysis, Meta-analysis

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Introduction

Urolithiasis is a common disease worldwide, affecting people of all ages [1]. Urinary stones are formed due to the accumulation of inorganic and organic substances in the renal parenchyma [2]. Approximately 10% of the world's population suffers from urinary stone disease [3]. Of note, the incidence of urolithiasis is on the rise, and the recurrence rate is alarmingly high, with studies showing a 10-year recurrence rate of up to 50%. Data from the National Health and Nutrition Examination Survey in the United States showed that the self-reported prevalence of urolithiasis increased from 3.2% between 1976 and 1980 to 8.8% in 2014 [3]. The occurrence of urolithiasis is associated with a variety of factors, including dietary habits, genetic factors, and chronic kidney disease.

The etiology of urinary stones is very complex, involving metabolic disorders, atypical anatomical structures, infections and other factors. Recent studies have shown that abnormal lipid metabolism is closely related to stone formation [4]. Eric N's team found that the formation of urinary stones is closely related to metabolic syndrome (MetS) in the body, including abnormal lipid metabolism, hyperglycemia, hypertension, obesity and insulin resistance [4].

The global rise in kidney stone prevalence has paralleled an epidemic of metabolic disorders, suggesting a potential pathophysiological link between the two. Metabolic syndrome, characterized by obesity, insulin resistance, dyslipidemia, and hypertension, has emerged as an important risk factor for kidney stones. Emerging evidence suggests that comorbidities associated with metabolic syndrome, such as polycystic ovary syndrome (PCOS), obesity, and cardiovascular disease, may jointly contribute to stone formation through common mechanisms, including chronic inflammation, oxidative stress, and altered urine biochemistry.

Obesity is a hallmark of MetS and is closely associated with hypercalciuria and hypocitraturia, both of which are major risk factors for calcium oxalate stone formation. Adipose tissue-derived inflammatory cytokines (e.g., TNF-α, IL-6) may further impair tubular function and exacerbate urolithiasis [5]. Similarly, insulin resistance in MetS drives urine acidification through impaired ammonia production, favoring uric acid crystallization [6]. Notably, PCOS, a condition intertwined with insulin resistance and hyperandrogenism, is associated with a 1.5-fold increased risk of kidney stones in women, which may be mediated by androgen-driven hyperoxaluria and metabolic dysregulation [7].

Cardiovascular comorbidity is another aspect of MetS that may indirectly increase stone risk. Hypertension and endothelial dysfunction reduce renal blood flow and enhance tubular reabsorption of calcium and sodium—a pathway that has been confirmed in cohort studies showing that hypertensive patients have a higher rate of stone recurrence [8]. In addition, dyslipidemia in MetS increases urinary oxalate excretion through a peroxisome proliferator-activated receptor (PPAR)-mediated pathway, as shown in a mouse model [9].

Despite these associations, the synergistic effects of MetS components on stone pathogenesis remain underexplored. This study aimed to elucidate the combined effects of metabolic disturbances on the characteristics of urinary stone formation and provide insights into personalized prevention strategies. In addition, lipid metabolism disturbances have been reported to be an independent risk factor for urinary stones [10].

Metabolic syndrome and obesity are significant risk factors for the development of urinary stones [11]. Patients with these conditions often present with dyslipidemia [12]. Measuring plasma lipid levels through lipoprotein assessment is a standard clinical method [13]. Recent advancements in plasma lipidomics analysis have greatly enhanced the specificity and accuracy of lipid measurements [14]. Medical researchers have made substantial progress in understanding lipid metabolism and its relationship with cardiovascular diseases by uncovering the genetic architecture of the plasma lipidome. In recent years, the rapid development of plasma lipidomics has significantly extended our comprehension of plasma lipids [15], offering better opportunities to investigate the relationships and underlying mechanisms between plasma lipids and various diseases.

Plasma lipids are typically classified based on their chemical structure into sterol esters (SEs), ceramides, diacylglycerols, lysophosphatidylcholine, phosphatidylcholine (PC), PC ether, phosphatidylethanolamine (PE) ether, sphingomyelin, and triacylglycerol [14, 16, 17]. A study of the Korean population found that patients with kidney stones tend to have higher triglyceride levels and lower cholesterol levels [18]. Another cross-sectional study indicated that a higher triglyceride-glucose index increases the incidence of kidney stones through insulin resistance [19]. Furthermore, several studies have reported that dyslipidemia contributes to an increased risk of nephrolithiasis [20, 21]. However, observational studies such as these generally provide unreliable estimates of causal relationships [22].

Additionally, confounding factors (i.e., variables that influence both the exposure and the outcome) along with other forms of bias, can lead to misleading conclusions in observational epidemiology. Previous research has demonstrated a negative correlation between statin drug use and the incidence of urolithiasis [23]. However, this study is limited as it does not address lipid levels [23].

The findings from prior observational studies are inconsistent, with small sample sizes, varying study populations, and designs that have not been conducted under

standardized conditions. These limitations highlight the need for further data integration through systematic, well-designed studies to confirm the potential causal relationship between genetic susceptibility to plasma lipids and the risk of urolithiasis.

To address the methodological limitations in previous investigations, an innovative analytical framework was developed that integrates two-sample MR (TSMR) with meta-analytic methodologies. This approach enables a systematic examination of causal associations between specific lipid classes and the pathogenesis of urolithiasis.

As a widely used epidemiological method for instrumental variable (IV) analysis, MR employs single nucleotide polymorphisms (SNPs) related with both the exposure and the outcome as IVs to evaluate the causal relation between the two [24]. MR analysis overcomes the observational studies' limitations by reliably estimating causal relationships. Genetic variants are typically not influenced by the outcome and, therefore, are not subject to reverse causation. Since genetic variation is unaffected by the outcome or confounders, MR methods can address concealed confounding effects and reverse causality in the relationship between outcome and exposure. TSMR allows for the examination of instrument-exposure and instrument-outcome relationships using two independent samples, thereby enhancing the efficacy of the analysis [25]. In this study, extensive published data was gathered from large genetic studies to examine whether there is a causal relation between plasma lipid levels and urolithiasis risk utilizing TSMR analysis.

Materials and methods

Data sources and study design

In the current study, SNPs associated with plasma lipids were selected from genome-wide association (GWAS) analyses of plasma lipidomes conducted in 2023 [26]. These analyses found new lipid-associated variants and revealed 495 genome-trait associations across 56 genetic loci, such as 8 novel loci, with a significant contribution from the multivariate analysis [26]. The study included 179 lipid species from 7,174 Finnish individuals, including 377,277 FinnGen participants [26]. Notably, this report identified 495 genome-wide associations across 56 genetic loci and revealed associations with 40 lipid loci for 953 disease endpoints in a comprehensive GWAS analysis. The study also established reliable genetic links between lipid species and various diseases. For the outcome datasets, SNPs related to urolithiasis were found from the IEU OPEN GWAS PROJECT, with the GWAS ID ebi-a-GCST90018935, comprising 6,223 cases and 482,123 controls [27]. Urolithiasis diagnosis in the inpatient registry was defined as the presence of stones within the urinary tract, with reported traits including: ICD10 N20, N21 (kidney stones with CNV U-shape model); ICD10 N20, N21 (kidney stones with CNV deletion-only model); ICD10 N20, N21 (kidney stones with CNV duplication-only model); ICD10 N20, N21 (kidney stones with CNV mirror model); ICD10 N20 (kidney, ureter, or bladder stones); ICD10 N20 (kidney, ureter, or bladder stones with Gene-based burden); and other variations of kidney, ureter, or bladder stones, as well as urolithiasis. All participants in both the outcome and exposure datasets were of European ancestry.

3 key assumptions underlie MR analysis: (a) The chosen SNPs must be strongly related to the exposure [28]. The evaluation of the instrument–exposure association strength was conducted using the F-statistic [29]. The formula for F is given by $R^2(n - k - 1) / [k(1 - R^2)]$, where R^2 denotes the chosen SNPs' cumulative explained variance on circulating lipid levels, k is the number of chosen SNPs, and n is the sample size. If the F-statistic was > 10, this indicated no bias due to weak SNPs; (b) The included genetic variants should be related with the risk of the outcome only through the exposure, but not through confounding factors [30]. MR–Egger regression was utilized to identify any horizontal pleiotropy between the genetic variant and the outcome; (c) The SNPs should be independent of confounders. Figure 1 overviews the study design.

Selection of instrumental genetic variables

To extract additional IVs, all genetic variants related with plasma lipids ($P < 1 \times 10^{-5}$) were considered as IVs [31]. Two thresholds, R^2 and F-statistics, were utilized to select the IVs in order to mitigate potential biases from strong linkage disequilibrium (LD) [29]. For the selected SNPs, F-statistics and R^2 were employed to assess the strength of the IVs and minimize weak-tool bias. The most recent and rigorous calculation method was applied, where the F-statistic formula is given by $R^2(n - k - 1) / [k(1 - R^2)]$ [32]. Where, R^2 denotes the cumulative explained variance of the chosen SNPs on circulating lipid levels, k denotes the number of chosen SNPs, and n represents the sample size. If the F-statistic was > 10, this indicated no bias from weak SNPs [33].

The SNPs related to plasma lipids were required to meet the criteria of $R^2 < 0.001$ and to be located at least 10,000 kb apart from each other. To exclude potential pleiotropic effects, a thorough search was conducted for potentially related traits (secondary phenotypes) related with every SNP utilizing the LDtrait Tool from the GWAS Catalog (https://ldlink.nih.gov/?tab=home) up to March 2024 [34, 35]. This was done to evaluate whether the IVs were related to common confounders of urolithiasis. A *P*-value less than 1×10^{-5} was considered indicative of no confounding factors. After removing SNPs corresponding to phenotypes related to the outcomes, the remaining SNPs were retained and MR

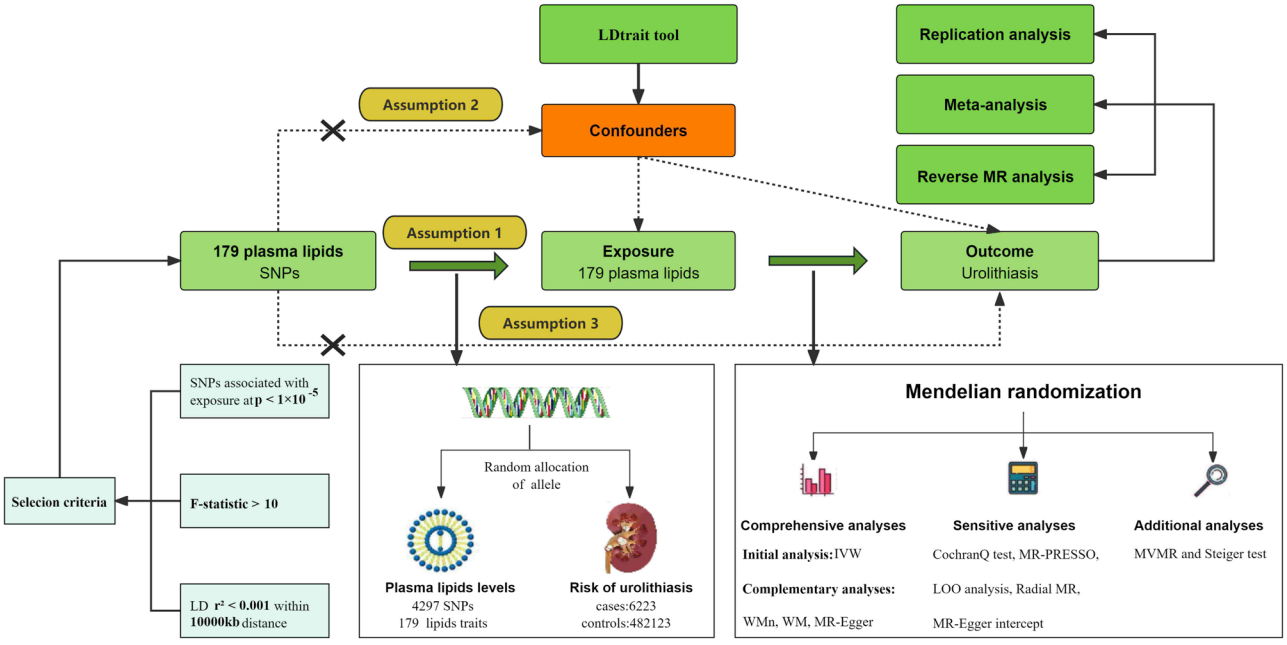

Fig. 1 A flowchart illustrating the study design process of Mendelian randomization. (**a**) The selected SNPs must be strongly related to the exposure; (**b**) The included genetic variant must be associated with the risk of the outcome solely through the exposure, not by confounding factors; (**c**) The SNPs should be independent of confounders. IVW: Inverse-variance weighted; WMn: Weighted median; WM: Weighted mode; LOO analysis: Leave-one-out sensitivity analysis

analysis was reconducted to verify the results' reliability. In the reverse MR analysis, independent SNPs with genome-wide significance ($P < 1 \times 10^{-5}$, $R^2 < 0.001$, and distance > 10,000 kb) were chosen as IVs for urolithiasis.

Statistical analysis and sensitivity analysis

The TSMR method effectively addresses the issue of sample overlap. TSMR analysis was performed to assess the causal relation between genetic susceptibility to lipid levels and urolithiasis risk. The assessments were carried out using standard MR methods, including the IVW, MR-Egger regression, weighted median (WMn), and weighted mode (WM). The estimates from the IVW method are derived from a summary analysis of the Wald ratios for all genetic variants, providing the accurate valuation of causal effects under the assumption that all SNPs are independently valid [25]. Thus, IVW was adopted as the main MR method for causal inference, as it needs all chosen SNPs to be valid IVs. The IVW method assumes that all IVs jointly impact the outcome via the exposure [36]. In contrast, weighted median, MR-Egger regression, and WM were utilized as supplementary analyses.

Sensitivity analysis is crucial for verifying the certainty and stability of causal effects, as well as for examining heterogeneity and horizontal pleiotropy. MR-Egger regression was employed to assess bias from horizontal pleiotropic effects and invalid IVs among the included SNPs [37]. MR-Egger regression, weighted median, and WM can provide more reliable causal estimates even in the invalid SNPs' presence [30, 37, 38]. Under a moderately loose condition ($P < 1 \times 10^{-5}$), these three methods ensure more robust estimates. MR-Egger regression generates an intercept that indicates horizontal pleiotropy (where IVs impact the outcome via channels other than the exposure), offering more reliable estimates even when some IVs may be invalid [37]. The WMn method uses an inverse-variance weighted ratio to estimate the median [30, 39]. Compared to IVW and MR-Egger, this approach is more robust to outliers, providing consistent estimates when at least 50% of the weights come from genetic variations of valid instruments [30]. The WM method, which also uses an inverse-variance weighted ratio to estimate the mode [38, 39], is stronger than MR-Egger but inferior to IVW and the WMn method [38], providing consistent estimates when the largest weight comes from effective genetic variations [38].

The MR-PRESSO method automatically detects outliers in IVW linear regression and removes them to correct MR estimation [40]. Radial MR [41] was conducted to identify abnormal outliers, and MR analysis was repeated after removing heterogeneous SNPs. Outliers were also removed using the radial MR and global test of MR-PRESSO [40, 41]. The aggregated exposure and outcome datasets were harmonized to ensure consistency in alleles for each SNP between plasma lipids and urolithiasis risk. Heterogeneity among estimates from each SNP was evaluated using Cochran's Q statistic [31]. A leave-one-out sensitivity analysis was conducted by sequentially

removing each SNP and applying the IVW method to the remaining SNPs [42]. This analysis assessed the stability of effect sizes and identified specific SNPs that disproportionately influenced the association.

Additionally, the threshold for estimates ($P < 0.05$) was adjusted based on the number of exposures using the Bonferroni correction to reduce the false positive rate in multiple comparisons. The significance level for each comparison was calculated using the Bonferroni formula: $\alpha = 2.8 \times 10^{-4}$ (0.05/179). For each comparison, this adjusted significance level ($P < 2.8 \times 10^{-4}$) was applied to determine the results' significance.

All statistical analyses were conducted utilizing the "TwoSampleMR," "MR-PRESSO," and "Radial MR" packages in R software, Version 4.2.1. Unless otherwise stated, statistical significance was set at a two-sided *P*-value < 0.05.

Replication and meta-analysis

The majority of participants in current genetic studies are of European descent. To investigate whether the MR results are applicable to a broader range of populations, a GWAS dataset was selected from East Asian populations for further validation, thereby strengthening the stability and accuracy of the existing estimates. The IVW analysis was replicated in an additional urolithiasis cohort that included 6,638 East Asian cases and 205,815 East Asian ancestry controls [43]. The urolithiasis dataset for the replication analysis was also got from the GWAS Catalog. Additionally, a meta-analysis, combining this dataset with the existing study on plasma lipids, was performed to provide complementary results. Specifically, data with GWAS ID ebi-a-GCST90018935 was used in the preliminary analysis, while for the replication analysis, the dataset with GWAS ID bbj-a-155 was utilized. The data were analyzed utilizing Review Manager software (version 5.4).

Multivariable mendelian randomization analysis

Multivariable MR (MVMR) allows for the comparison of interactions among multiple exposures, adjusting for genetic interactions between exposures and ensuring that genetic variation is associated with a single risk factor [44]. MVMR can independently assess the direct impact of each exposure on outcomes. MVMR was conducted on the identified lipid species to adjust for their interactions utilizing the IVW and MR-PRESSO approaches. In multivariable MR, the IVW method regresses all SNPs associated with exposures against outcomes, weighting them by the inverse variance of the outcomes [45]. MR-PRESSO can eliminate outliers to correct for IV pleiotropy [46].

Results

Initial analysis

Qualified IVs were first identified from a correlated lipidomics dataset based on both univariate and multivariate genome-wide analyses ($P < 1 \times 10^{-5}$). The clumped IVs contained SNPs ranging from 13 to 34. Specifically, the genetically proxied PC (O-16:2_18:0) levels had the least number of SNPs (13), while triacylglycerol (53:4) levels had the most (34). When the F-statistic was greater than 10, the correlation was considered free from bias due to weak SNPs. After harmonization, the outcome data extracted via IVs were ultimately included in the MR analysis (Table S1).

To minimize the influence of horizontal pleiotropy, Radial plots and Radial regression were used to exclude unqualified SNPs, presenting detailed information on outliers in Table S2. The screened plasma lipidomes were then categorized into three groups based on chemical structure attributes: glycerolipids, glycerophospholipids, and sterol lipids. Using the IVW approach, underlying causal relationships between 27 plasma lipids were initially identified across these three categories and urolithiasis (Figs. 2 and 3).

Further screening of the initially identified plasma lipids was conducted through sensitivity analysis, horizontal pleiotropy analysis, and supplementary analysis. Ultimately, 21 types of plasma lipids met the screening criteria (Table S3). The direction and magnitude of MR-Egger, WMn, and WM estimates were consistent with the IVW estimates (Figure S1). Subsequently, outliers identified in the global test of MR-PRESSO were removed. The reanalysis revealed no evidence of horizontal pleiotropy (Table S4). The results from the leave-one-out analysis corroborated that the presence of a single SNP did not introduce bias into the MR estimation (Figure S2).

All *P*-values for the IVW Cochran's Q statistics and MR-Egger intercept test exceeded 0.05, indicating no heterogeneity or pleiotropy among the SNPs (Table S3). The remaining 21 plasma lipids were considered as candidates for further analysis. Bonferroni-corrected results identified three lipid species with causal effects associated with urolithiasis: PC (16:1_18:0) levels (OR: 1.14; 95%CI: 1.07, 1.22; P_IVW = 1×10^{-4}), PC (18:0_20:4) levels (OR: 0.93; 95%CI: 0.90, 0.96; P_IVW = 1.9×10^{-5}), and SE (27:1/20:4) levels (OR: 0.93; 95%CI: 0.89, 0.96; P_IVW = 1.5×10^{-4}) (Tables S5–S7). The Cochran's Q test and MR-Egger intercept test strongly suggested no heterogeneity or pleiotropy among the three lipid species (Table 1). Notably, in the complementary analyses of SE (27:1/20:4), consistent results were observed in the WMn analysis (OR: 0.932, 95%CI: 0.901–0.965, $P = 8.0 \times 10^{-5}$), MR-Egger analysis (OR: 0.946, 95%CI: 0.900–0.994, $P = 0.036$), and WM (OR: 0.930, 95%CI: 0.898–0.963, $P = 2.9 \times 10^{-4}$) (Table 1). Therefore, after rigorous screening, sufficient

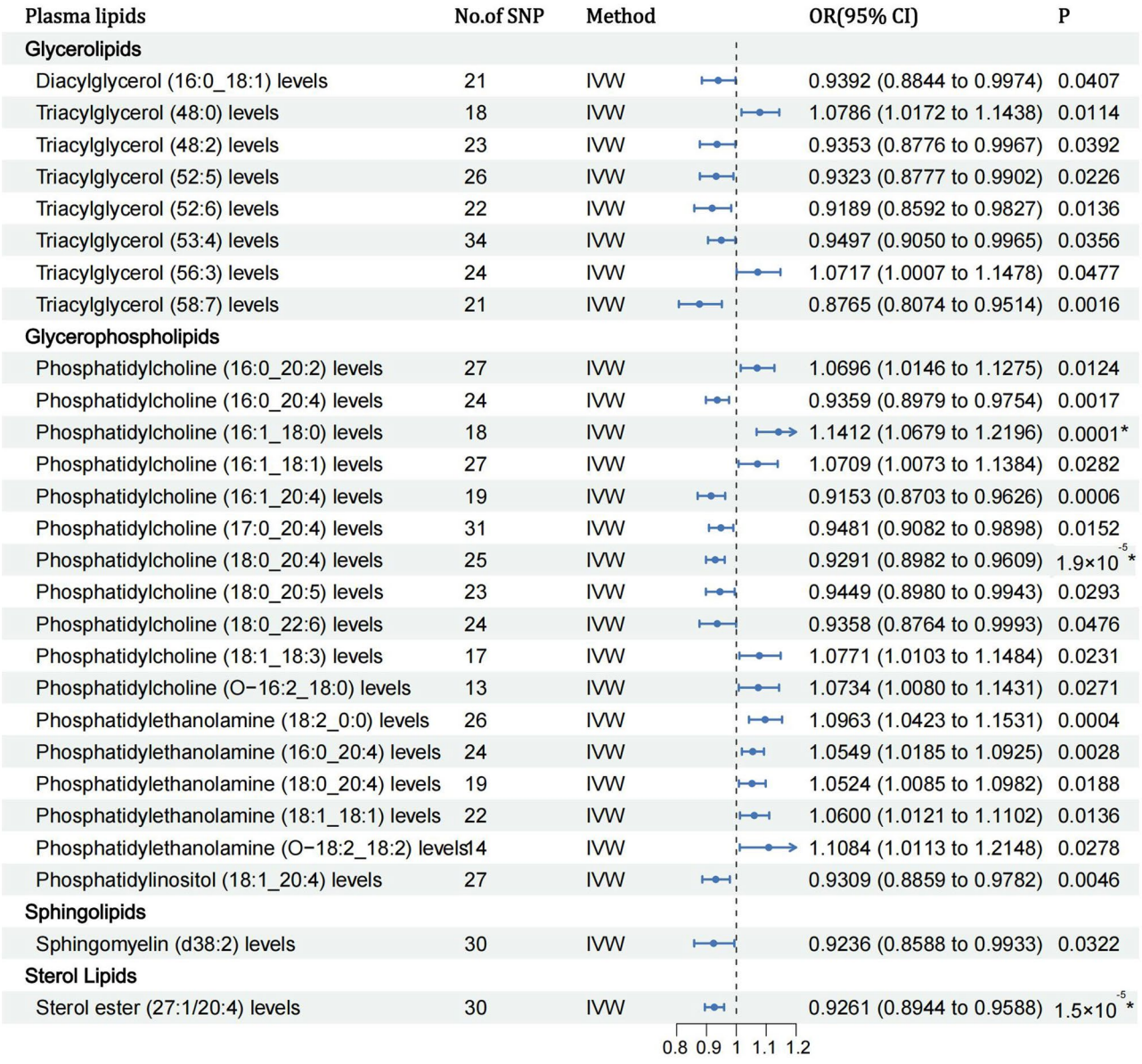

Fig. 2 Mendelian randomization IVW estimates of plasma lipids on the risk for urolithiasis. An asterisk (*) indicates the lipid species that has reached the significant threshold of Bonferroni correction($P < 2.8 \times 10^{-4}$). IVW: Inverse variance weighted; OR, odds ratio; SNP: single nucleotide polymorphism. CI: confidence interval

evidence suggest that SE (27:1/20:4) is associated with a lower risk of urolithiasis.

Additional validation and meta-analysis

To enhance the stability and accuracy of the existing estimates, an additional dataset was selected from the GWAS for further validation. Following the MR analysis conducted on individuals of European descent, the results were replicated using East Asian populations. The IVW analysis of the East Asian dataset revealed a similar trend to the original findings. Among the 21 preliminarily identified lipid species, six plasma lipids exhibited consistent patterns. Specifically, the levels of SE (27:1/20:4) [OR: 0.926; 95%CI: 0.893, 0.960; $P = 2.6 \times 10^{-5}$], PC (16:0_20:4) [OR: 0.934; 95%CI: 0.897, 0.972; $P = 8.13 \times 10^{-4}$], and PC (16:1_20:4) [OR: 0.911; 95%CI: 0.872, 0.951; $P = 2.22 \times 10^{-5}$] were associated with a decreased genetic susceptibility to urinary stones in both the replicated and meta-analysis results.

On the other hand, the levels of PE (18:2_0:0) [OR: 1.105; 95%CI: 1.058, 1.154; $P = 6 \times 10^{-6}$], PE (16:0_20:4) [OR: 1.052; 95%CI: 1.022, 1.083; $P = 6.17 \times 10^{-4}$], and PE (18:1_18:1) [OR: 1.095; 95%CI: 1.012, 1.184; $P = 0.0232$] were positively associated with the risk of urolithiasis. The direction of these associations was consistent across both analyses. Furthermore, the meta-analysis confirmed

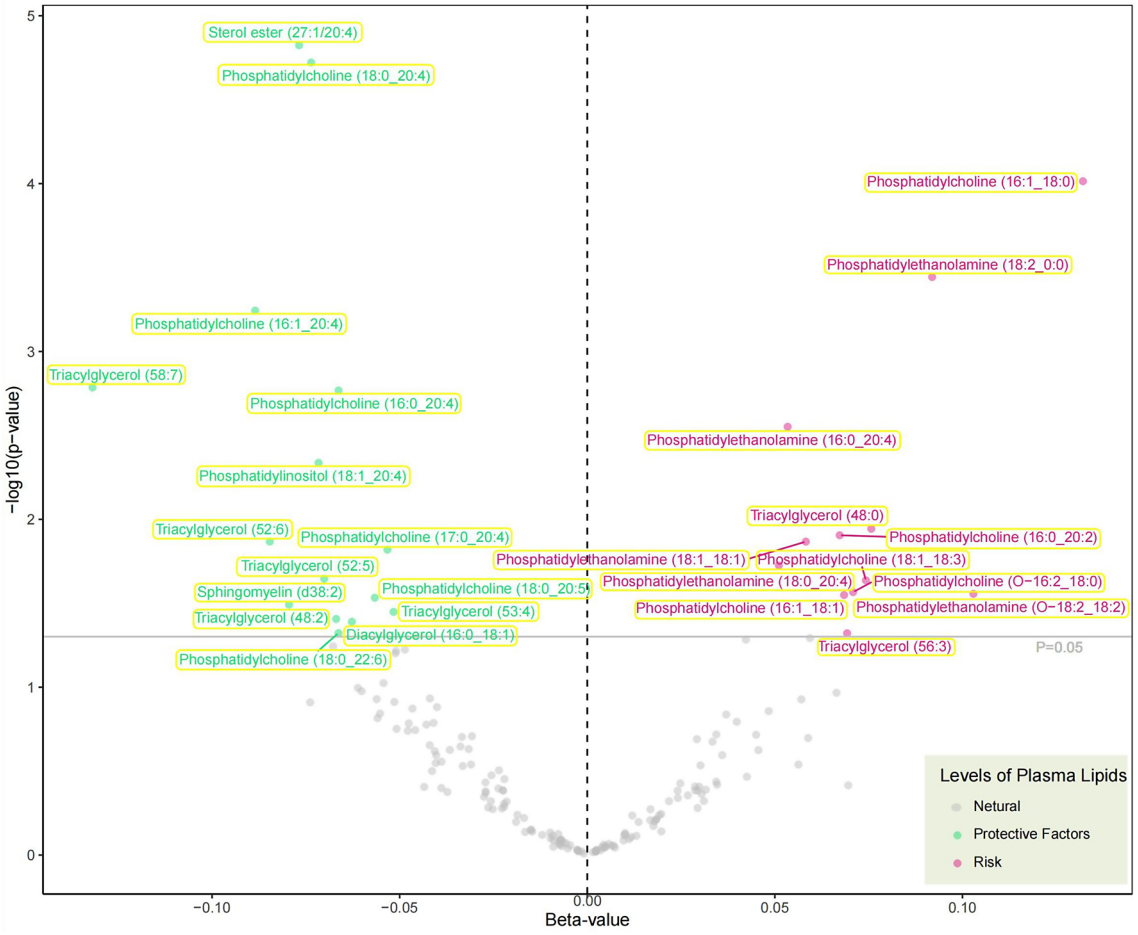

Fig. 3 The volcano plot demonstrates the association between 179 plasma lipid levels and urolithiasis risk. The X-axis represents the beta-value, and the Y-axis represents the logarithmic p-value with a base of 10. $P < 0.05$ is regarded as the statistically significant threshold. Green points represent the protective lipids species for urolithiasis, and red points represent risk

Table 1 Causality from plasma lipid on kidney stones via supplementary and sensitivity analysis. Abbreviations: CI, confidence interval; ME, MR-Egger; N: number of single nucleotide polymorphisms; OR: odds ratio; WMn: Weighted median; WM: Weighted mode

Plasma Lipid	*N*	MR analysis			Pleiotropy		Heterogeneity	
		Methods	OR(95% CI)	*p*	Intercept	*p*	Q	*p*
Phosphatidylcholine (16:1_18:0) levels	18	ME	1.100(0.955–1.267)	0.205	0.006	0.573	13.389	0.710
		WMn	1.133(1.014–1.267)	0.028				
		WM	1.134(1.019–1.261)	0.034				
Phosphatidylcholine (18:0_20:4) levels	25	ME	0.935(0.891–0.982)	0.013	-0.002	0.706	32.152	0.123
		WMn	0.935(0.904–0.966)	7.1×10^{-5}				
		WM	0.934(0.903–0.966)	0.001				
Sterol ester (27:1/20:4) levels	30	ME	0.946(0.900-0.994)	0.036	-0.007	0.261	41.839	0.058
		WMn	0.932(0.901–0.965)	0.000				
		WM	0.930(0.898–0.963)	0.000				

that these plasma lipids can influence the risk of urolithiasis (Fig. 4).

Confounding analysis and evaluation of genetic directionality

After excluding SNPs that did not meet the estimated values during sensitivity analysis, further assessment was conducted to determine whether all SNPs associated with the six plasma lipids were independent of common confounding factors. It was found that only the levels of PC (16:0_20:4) and PE (18:2_0:0) were unaffected by these confounders. For the other four plasma lipids, four confounding factors were identified: vitamin D measurement, metabolic syndrome, dietary measurement, and

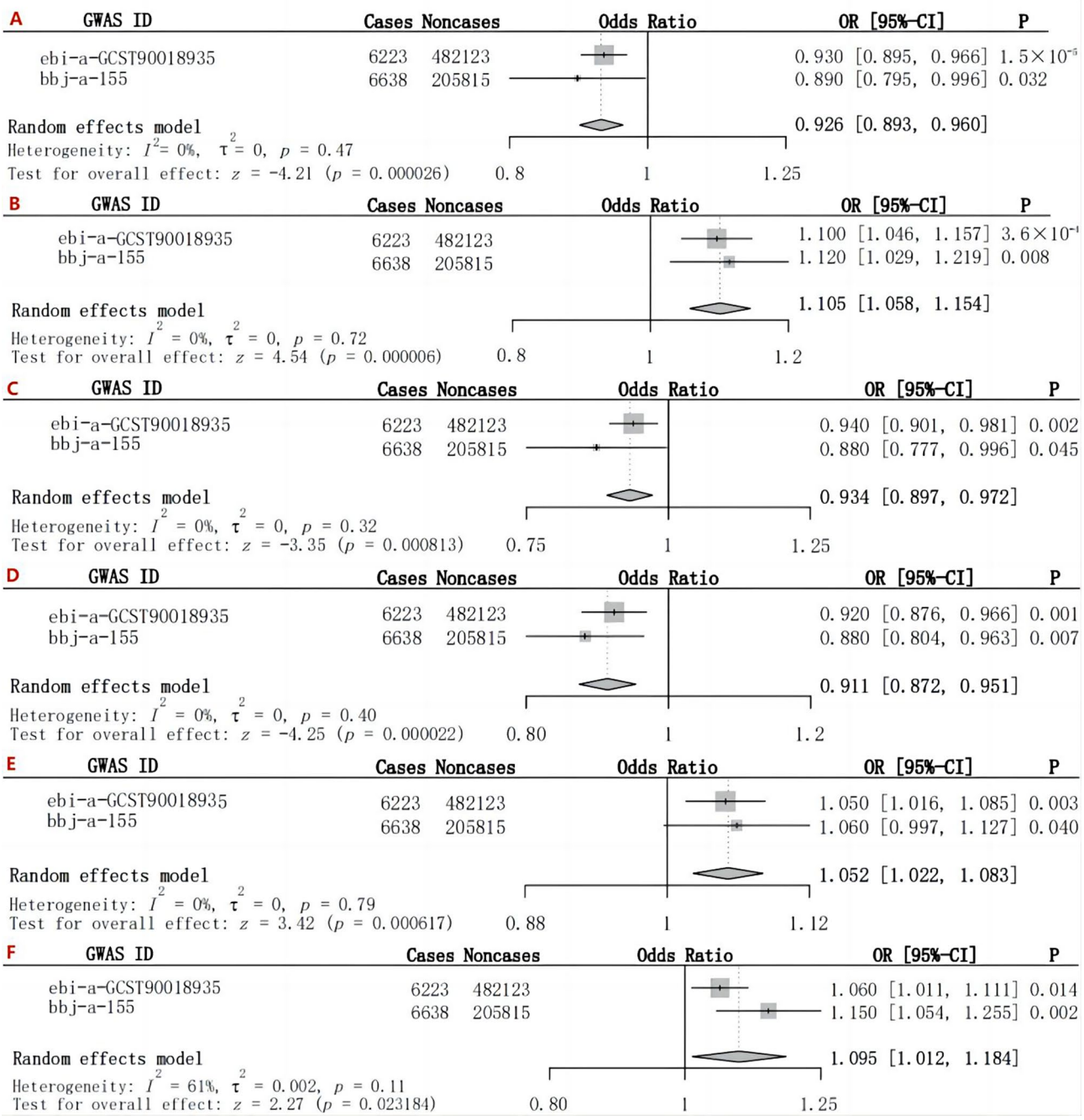

Fig. 4 Meta-analysis of significantly associated (IVW derived $P<0.05$) between plasma lipids and urolithiasis. A represents sterol ester (27:1/20:4) levels; B represents phosphatidylethanolamine (18:2_0:0) levels; C represents phosphatidylcholine (16:0_20:4) levels; D represents phosphatidylcholine (16:1_20:4) levels; E represents phosphatidylethanolamine (16:0_20:4) levels; F represents phosphatidylethanolamine (18:1_18:1) levels. OR, odds ratio. CI: confidence interval

type 2 diabetes mellitus (Table S8). This exclusion process was carried out using the LDtrait Tool retrieved from the GWAS Catalog.

After removing the confounding SNPs, the reanalysis still showed significant results as follows: SE (27:1/20:4) levels [OR: 0.926; 95%CI: 0.893, 0.961; $P=4.66\times10^{-5}$]; PE (16:0_20:4) levels [OR: 1.086; 95%CI: 1.022, 1.154; $P=0.0077$]; PE (18:1_18:1) levels [OR: 1.060; 95%CI: 1.006, 1.116; $P=0.0297$]; and PC (16:1_20:4) levels [OR: 0.903; 95%CI: 0.860, 0.949; $P=5.69\times10^{-5}$]. Additionally, the Steiger test indicated no reverse causal relationship between the genetically proxied IVs (Table S9).

Bidirectional mendelian randomization analyses

Reverse MR analyses were performed to confirm the robustness of the findings. This reverse analysis tested the causal effects of urolithiasis on the 21 lipid species identified in both the initial and complementary analyses. The filtered IVs included SNPs ranging from 34 to 50, with PE (16:0_20:4) levels being genetically proxied by the fewest SNPs (34) and SE (27:1/20:4) levels by the most (50 SNPs). Horizontal pleiotropy, heterogeneity, or weak instrument bias were not existed between IVs and urolithiasis (Table S10). Figure 5 presents the bidirectional MR results for urolithiasis and plasma lipid levels. The reverse MR IVW analysis showed no significant causal association between urolithiasis risk and lipid levels.

Multivariable Mendelian randomization analysis

MVMR analysis was performed to identify independent causal risk factors. After adjusting for interactions among plasma lipids, MVMR estimates using both the IVW and MR-PRESSO methods showed that genetically predicted higher levels of PE (18:2_0:0) [OR: 0.936; 95%CI: 0.887, 0.987; $P = 0.0149$], higher PC (16:0_20:4) levels [OR: 0.895; 95%CI: 0.810, 0.988; $P = 0.0284$], and lower PE (16:0_20:4) levels [OR: 1.084; 95%CI: 1.017, 1.154; $P = 0.0126$] were significant independent protective or risk factors for urolithiasis (Fig. 6).

Discussion

The elevated prevalence and recurrence rates of urolithiasis remain significant clinical concerns globally. Urinary tract stones can cause symptoms such as pain, hematuria, and fever. As the condition progresses, urolithiasis can lead to recurrent urinary tract infections, acute urinary tract obstruction, and even acute or chronic renal insufficiency [47]. Management typically involves surgical interventions like extracorporeal shock wave lithotripsy, percutaneous nephrolithotripsy, and transurethral lithotripsy [48, 49]. However, these procedures are complex, costly, and often fail to prevent stone recurrence [50], exacerbating the financial and psychological burdens on patients. Consequently, there has been increasing

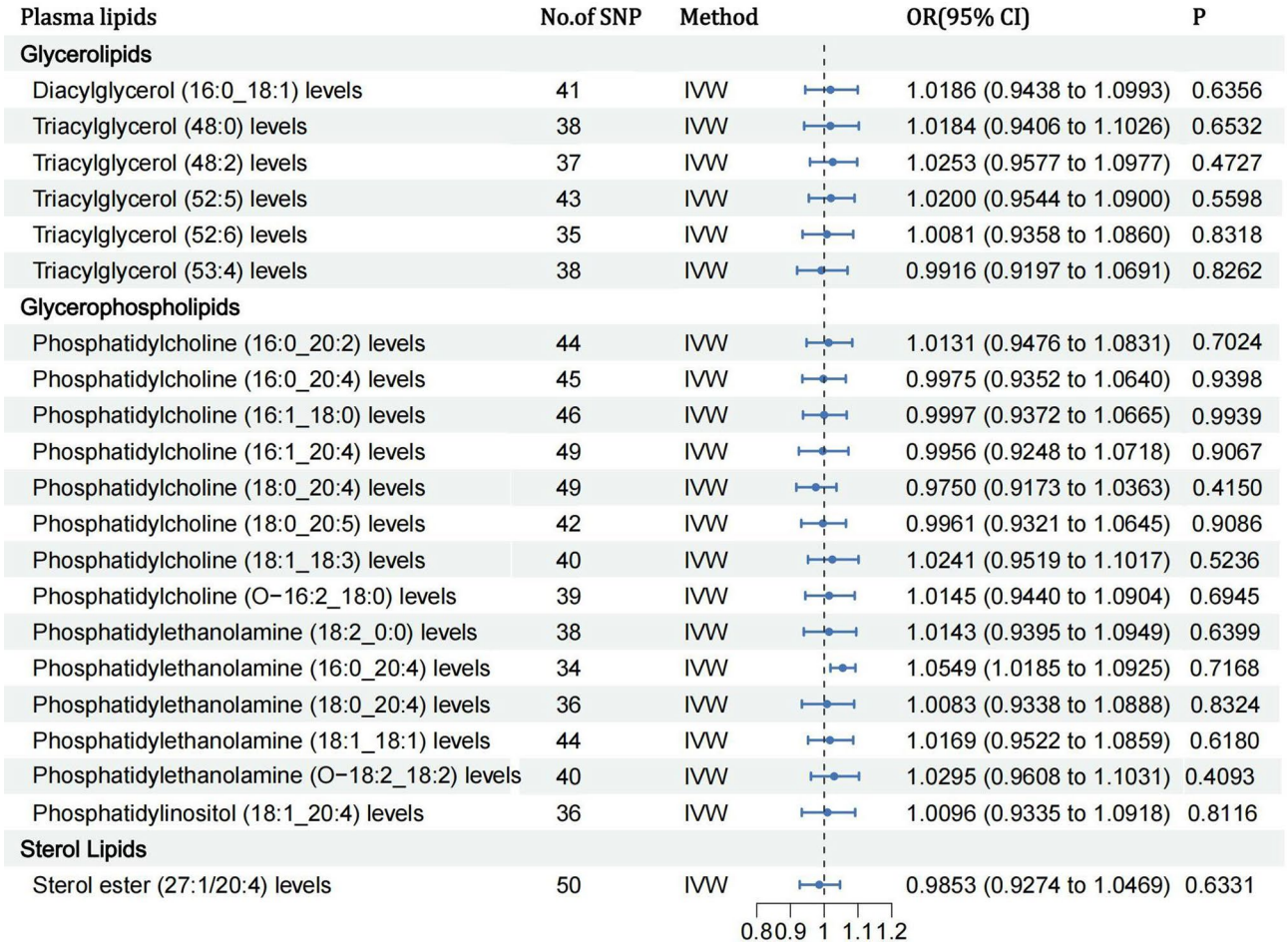

Fig. 5 Mendelian randomization IVW estimates of urolithiasis on the levels of initially identified plasma lipids. IVW: inverse variance weighted; OR, odds ratio; SNP: single nucleotide polymorphism

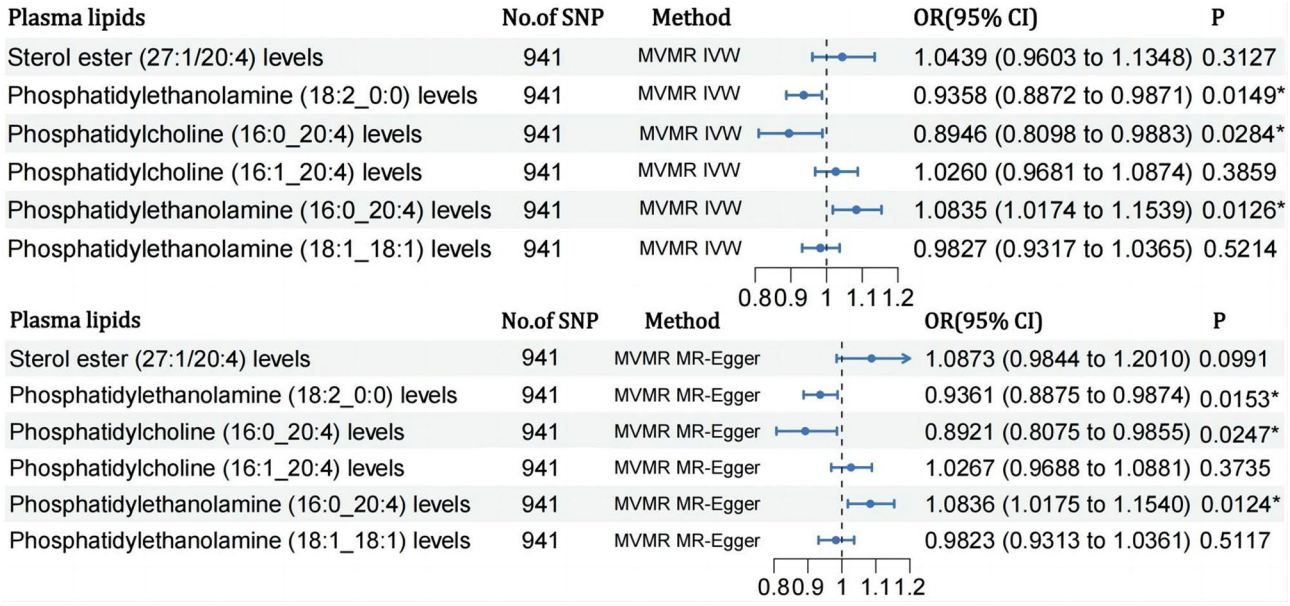

Fig. 6 Multivariable MR analysis of the final identified blood plasma lipids. An asterisk (*) indicates the lipid species that has reached the significant $P < 0.05$ threshold. CI: confidence interval; IVW: inverse variance weighted; MVMR: multivariable Mendelian randomization; OR: odds ratio; SNP: single nucleotide polymorphism

scholarly focus on elucidating the aetiology and preventive strategies for urinary tract stones.

This MR study investigated the causal relation between lipid species levels and urolithiasis risk using a comprehensive genetic dataset of 482,123 controls and 6,223 cases. Two large GWAS datasets were combined to systematically assess the causal effects of 179 lipid species on urolithiasis. The MR results provided compelling evidence that genetically predicted high levels of SE (27:1/20:4) are associated with a lower risk of urolithiasis [OR: 0.93; 95%CI: 0.89, 0.96; PIVW = 1.5×10^{-4}]. Replicated and meta-analysis results confirmed that genetically determined levels of SE (27:1/20:4), PC (16:0_20:4), and PC (16:1_20:4) were linked to a reduced genetic susceptibility to urinary stones. In contrast, higher levels of PE (18:2_0:0), PE (16:0_20:4), and PE (18:1_18:1) suggested an increased risk of urolithiasis. MVMR analysis showed that PE (18:2_0:0), PC (16:0_20:4), and PE (16:0_20:4) could independently influence the risk of stone disease, even after accounting for interactions with other plasma lipids.

SEs regulate cholesterol homeostasis and have a complex role in urolithiasis. SE (27:1/20:4) demonstrated a protective effect by enhancing cholesterol efflux mediated by ATP-binding cassette transporter A1, which may reduce the formation of small areas of stone formation membranes [9]. Conversely, the accumulation of SE in macrophages can promote the transformation of foam cells in the renal interstitium, release matrix metalloproteinases, and degrade the glycosaminoglycans that inhibit stone formation [9]. Plant SEs also have notable physiological functions, particularly their cholesterol-lowering effect [51]. The protective action of SE (27:1/20:4) may help reduce the solubility of urinary stone components by modulating lipid metabolism. SEs are involved in cholesterol esterification and incorporation into lipoproteins, potentially affecting crystal formation within the body [52]. Moreover, previous pharmacological reviews have suggested that SE extracts and bioactive compounds may have anti-urolithiasis properties [53]. However, these studies have not directly demonstrated the therapeutic effects of SEs on urinary calculi. The MR study addresses these gaps and provides valuable insights into the therapeutic potential of SE (27:1/20:4) for urolithiasis.

Glycerophospholipids play a dual role, with PC maintaining the integrity of the urinary tract epithelial barrier through membrane fluidity regulation [54]. The current MR study found that PC (16:0_20:4) was negatively correlated with urolithiasis risk. PC, the major phospholipid in cell membranes, is crucial for various cellular processes, such as inflammation and cell signaling. Elevated levels of PC can enhance membrane stability and improve cellular resistance to oxidative stress [55], both of which are associated with stone prevention.

In contrast, PE, a key component of membrane dynamics, influences vesicular transport and lipid bilayer composition [56]. Recent studies suggest that changes in PE levels can enhance inflammatory responses and oxidative stress, both contributors to renal calculi development [57–59]. Specifically, PE promotes crystal adhesion by exposing phosphatidylserine residues during oxidative

stress-induced membrane remodeling [60]. Higher PE levels may exacerbate crystallization by altering renal tubular cell function or modifying the local urinary microenvironment, increasing susceptibility to stone formation [61]. Furthermore, altered membrane phospholipids can promote face-selective nucleation and the retention of calcium oxalate and calcium phosphate crystals, which contribute to growing stones [62]. One study reported that phospholipid assemblies containing PC could catalyze calcium oxalate stone nucleation [63]. The MR findings in this study provide reliable evidence for causal inference, addressing the limitations of observational studies, such as small sample sizes and reverse causality.

The lipid-stone interface is also mediated by extracellular vesicles (EVs). Phosphatidylserine-enriched EVs from injured tubular cells act as nucleation sites for calcium oxalate crystals, while sphingomyelin-rich EVs inhibit aggregation by modulating surface charge [64]. This lipid-mediated crystal-matrix interaction is regulated by the balance between lithogenic (PEs, ceramide) and antilithogenic (PC, SE (27:1)) species.

While existing research suggests that lipid content and interactions regulate urinary stone formation in both directions, direct studies on the correlation between plasma lipids and urolithiasis remain limited. Moreover, these studies offer little in terms of early screening and prevention of urolithiasis, highlighting the significance of this MR analysis. This study provides new insights for drug development in stone disease prevention and improving dietary habits. Specifically, lipid-rich compounds like SEs (27:1/20:4), PC (16:0_20:4), and PC (16:1_20:4) may serve as active ingredients in inhibiting calcium stone growth.

This study has dual translational potential in clinical practice. First, the findings of this study offer critical insights for developing next-generation urolithiasis prevention strategies. From a therapeutic perspective, the observed risk-reducing effects of SEs, through modulation of cholesterol homeostasis and direct inhibition of calcium oxalate crystal aggregation, support their pharmaceutical development as nutraceutical agents or dietary supplements. From a diagnostic standpoint, the MR-identified biomarkers, such as serum/urinary SE (27:1/20:4), PC (16:0_20:4), and PC (16:1_20:4), could enable precision risk stratification for stone-prone populations. Systematically integrating SE profiles with genomic markers (e.g., CAV1 mutations) and metabolic signatures (oxalate/citrate ratio) could lead to a multidimensional predictive scoring system, advancing personalized recurrence-risk modeling and clinical decision algorithms.

Study strengths and limitations

The MR approach in this study has several strengths. Firstly, TSMR, radial MR, and Steiger test methods were employed to assess the impact of 179 types of plasma lipids on the occurrence of urinary calculi in patients. These approaches effectively minimize potential confounding factors and reverse causality. Secondly, horizontal pleiotropy was addressed through MR-PRESSO and MR-Egger regression intercept term tests. Thirdly, repeated analyses and meta-analyses were conducted using various methods, yielding consistent results that were supported by accurate data from large-scale GWAS meta-analyses.

This study has several limitations. Although sensitivity analyses were conducted to assess the assumptions of the MR study, it is important to acknowledge that the possibility of confounding bias or horizontal pleiotropy cannot be entirely excluded. To address these concerns, targeted sensitivity analyses were performed using WMn and WM estimators, which provide robust causal estimates even when up to 50% of the instruments are invalid. Additionally, negative control analyses using biologically unrelated phenotypes could help exclude systematic pleiotropic bias. The OR calculated by the IVW method in this study is close to 1, suggesting a relatively weak causal relation between exposure and outcome.

Furthermore, the GWAS data used in this research were primarily derived from individuals of European ancestry in the initial MR analysis. The analysis was performed with a population from East Asia in the replicated analysis and meta-analysis, meaning that the final results may be influenced by population genetic bias.

Additionally, post-translational modifications of lipids, such as oxidation and glycation, may play a crucial role in stone pathogenesis but were not captured in standard lipid GWAS datasets. This limitation could result in an underestimation of the true biological impact of lipids on urolithiasis. Therefore, it is important to note that GWAS-based lipid measurements primarily reflect static circulating levels rather than dynamic biochemical modifications. Future studies integrating metabolomics and proteomics approaches would be valuable for capturing a broader spectrum of lipid-related biochemical changes in stone formation.

Conclusion

This study offers robust evidence for a potential causal relationship between six plasma lipids and urolithiasis. In particular, SE (27:1/20:4), PC (16:0_20:4), and PC (16:1_20:4) appear to serve as protective factors, potentially inhibiting the growth of calcium-containing urinary stones. By integrating Mendelian randomization with genomics and lipidomics, this work highlights novel biomarkers that could significantly inform both clinical risk assessment and preventive strategies. Clinically,

these findings may aid in the development of lipid-based diagnostic panels for early identification of individuals at higher risk of stone formation. Moreover, they suggest that therapeutic modulation of specific lipid species, such as through dietary interventions or lipid-targeting nutraceuticals, could be a viable strategy for preventing stone recurrence in patients with a history of urolithiasis. For example, increasing circulating levels of SE (27:1/20:4) or PC (16:0_20:4) through targeted supplementation may offer a non-invasive adjunct to current management protocols. From a future perspective, integrating lipidomic profiling with genetic risk scores could support personalized prevention models, allowing clinicians to stratify patients based on their lipidomic-genomic risk and intervene accordingly. Additionally, identifying lipid signatures predictive of stone risk could reduce dependence on imaging in routine follow-up and improve long-term disease monitoring. Moreover, further investigation using the latest data from large-scale genetic studies and relevant clinical data is essential to validate and expand upon the findings of this MR study.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02573-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Acknowledgements

We thank the IEU OPEN GWAS PROJECT, and the BioBank Japan database for the shared research data.

Author contributions

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Funding

This work was supported by grants from the National Natural Science Foundation of China (Nos. 82370690, 82303813) and the Taishan Scholars Program of Shandong Province (No. tsqn202306403).

Data availability

In the primary analysis, data on urolithiasis can be available IEU OPEN GWAS PROJECT with the GWAS ID ebi-a-GCST90018935 (https://gwas.mrcieu.ac.uk/). In the repeated analysis, data on urolithiasis can be available IEU OPEN GWAS PROJECT with the GWAS ID bbj-a-155 (https://gwas.mrcieu.ac.uk/). Summary statistics for plasma lipids are retrieved from the EBI GWAS catalog (https://www.ebi.ac.uk/gwas/), with accession numbers GCST90277238 to GCST90277416. Data associated with plasma lipids can also be obtained from an univariate and multivariate genome-wide analyses. (https://pubmed.ncbi.nlm.nih.gov/37907536/; https://doi.org/10.1038/s41467-023-42532-8)

Declarations

Ethical approval

All analyses were based on previously published studies. Thus, no ethical approval and patient consent are required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 20 February 2025 / Accepted: 16 April 2025
Published online: 25 April 2025

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