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Mendelian randomization study of urolithiasis: exploration of risk factors using human blood metabolites

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Abstract

Background Urolithiasis is a highly prevalent global disease closely associated with metabolic factors; however, the causal relationship between blood metabolites and urolithiasis remains poorly understood.

Method In our study, we employed a bi-directional two-sample Mendelian randomization (MR) analysis to investigate the causal associations between urolithiasis and metabolites. The random-effects inverse-variance weighted (IVW) estimation method was utilized as the primary approach, complemented by several other estimators including MR-Egger, weighted median, colocalization and MR-PRESSO. Furthermore, the study included replication and meta-analysis. Finally, we conducted metabolic pathway analysis to elucidate potential metabolic pathways.

Results After conducting multiple tests for correction, glycerol might contribute to the urolithiasis and dehydroisoandrosterone sulfate (DHEA-S) might inhibit this process. Furthermore, several blood metabolites had shown potential associations with a causal relationship. Among the protective metabolites were lipids (dehydroisoandrosterone sulfate and 1-stearoylglycerol (1-monostearin)), amino acids (isobutyrylcarnitine and 2-aminobutyrate), a keto acid (acetoacetate) and a carbohydrate (mannose). The risk metabolites included lipids (1-palmitoylglycerophosphoethanolamine, glycerol and cortisone), a carbohydrate (erythronate), a peptide (pro-hydroxy-pro) and a fatty acid (eicosenoate). In reverse MR analysis, urolithiasis demonstrated a statistically significant causal relationship with butyrylcarnitine, 3-methyl-2-oxobutyrate, scyllo-inositol, leucylleucine and leucylalanine. However, it was worth noting that none of the blood metabolites exhibited statistical significance after multiple corrections. Additionally, we identified one metabolic pathway associated with urolithiasis.

Conclusion The results we obtained demonstrate the causal relevance between two metabolites and urolithiasis, as well as identify one metabolic pathway potentially associated with its development. Given the high prevalence of urolithiasis, further investigations are encouraged to elucidate the mechanisms of these metabolites and explore novel therapeutic strategies.

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Keywords Urolithiasis, Metabolites, Mendelian randomization study, Genetic epidemiology

Introduction

Urolithiasis is common in urologic diseases, with a continually increasing prevalence and incidence [1, 2]. Approximately 10% of the global population experiences kidney stone occurrence at least once during their lifetime, with a recurrence rate of 2% among affected individuals [3]. The metabolic risk factors associated with urinary stones are receiving increasing attention as our understanding of the etiology of urinary stones continues to deepen [4]. In order to evaluate the metabolic disorder associated with stone formation, some studies have applied metabolomics to urolithiasis. Through preliminary metabolic analysis of urine in renal stone patients, Duan et al. [5]. have found that four metabolic pathways, namely acetic acid and dicarboxylic acid metabolism, glycine, serine, and threonine metabolism, phenylalanine metabolism, and citric acid cycle, are closely associated with urolithiasis. Lately, Zhang et al. [6]. applied metabolomics technologies to discover the role of succinate in combating stone formation. In Agudelo et al.'s study [7], the significant enrichment of metabolites in the stone-forming group suggested that lithogenic metabolites in the urinary tract might be a crucial driver of stone formation. These studies are indeed promising to contribute to the targeted exploration of certain metabolites or metabolic pathways to identify biomarkers for urolithiasis. However, their analysis was limited to investigating the association between urolithiasis and urine metabolomics. In comparison to urinary metabolomics, blood metabolites offer the advantages of being easily obtainable in large quantities with good stability. Moreover, they provide a wealth of information [8], making them a promising option for early disease detection [9]. However, the detailed pathophysiological mechanisms of blood metabolites in urolithiasis have not yet been elucidated. Therefore, to clarify the causal relationship of blood metabolites in the pathogenesis of urolithiasis, a comprehensive and complete analysis is urgently needed. The best methods to investigate causality are randomized controlled trials (RCTs) due to their ability to mitigate reverse causality and residual confounding through randomization. However, the lengthy duration and high cost of RCTs pose significant challenges. Under this background, Mendelian randomization (MR) is a new way which can examine the causality between exposure and outcome, using single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) [10]. Additionally, the results of traditional observational studies are biased in the estimation of causal effects due to reverse causality and residual confounders whereas MR studies are generally unlikely impacted by confounders because the genotypes assignment from parents to offspring is random. MR studies are generally unlikely impacted by confounders because the genotypes assignment from parents to offspring is random [11]. Here, we use MR methods to analyze to determine the potential causal associations of metabolites with the risk of urolithiasis.

Methods

Data sets

Human blood metabolome genome-wide association study (GWAS) dataset was obtained from IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/) [12, 13]. It's worth noting that this study identified 2.1 million SNPs for 486 metabolites from 7,824 European which was conducted by Shin et al [14]. In addition, we also analyzed GWAS dataset from 24,925 European which was conducted by Kettumen et al [15].

Urolithiasis GWAS summary statistics data released FinnGen consortium (URL: https://r8.finngen.fi/pheno/N14_CALCUKIDUR), which included 4,969 cases and 213,445 controls [16]. The summary of data sources was presented in Supplementary Table S1.

Mendelian randomization analysis

The MR flowchart is shown in Fig. 1. In order to reduce the deviation caused by genetic variables, IVs should rely on three essential assumptions, which are elucidated in Fig. 1: (1) the SNPs should be closely associated with metabolites; (2) the SNPs are independent with any confounders; (3) the SNPs should affect the risk of urolithiasis only via metabolites and not through any other pathway [17, 18]. The Inverse Variance Weighted (IVW) method was widely acknowledged as a more quick, convenient and common approach for analysis, thus we adopted IVW as the primary analytical method. In cases where heterogeneity existed among causal estimates of different variants (as demonstrated in this article), the random effects model became more appropriate [19]. Furthermore, two additional methods were used to complement the analysis presented in this study. Specifically, MR egger [20] was employed for the identification and adjustment of pleiotropy effects, while weighted median [21] analysis was utilized to mitigate potential biases in strong hypotheses that hold true for all instrumental variables (IVs) in IVW. Firstly, we relaxed standards and chose IVs with the significance threshold ($p<1\times10^{-5}$) given that the scarcity of SNPs reaching genome-wide significance [22], and we used the clumping method ($r^2<0.001$ and clump distance$<$10,000 kb) to exclude SNPs based on European lineage reference data from the 1000 Genome Project, refraining from biased results

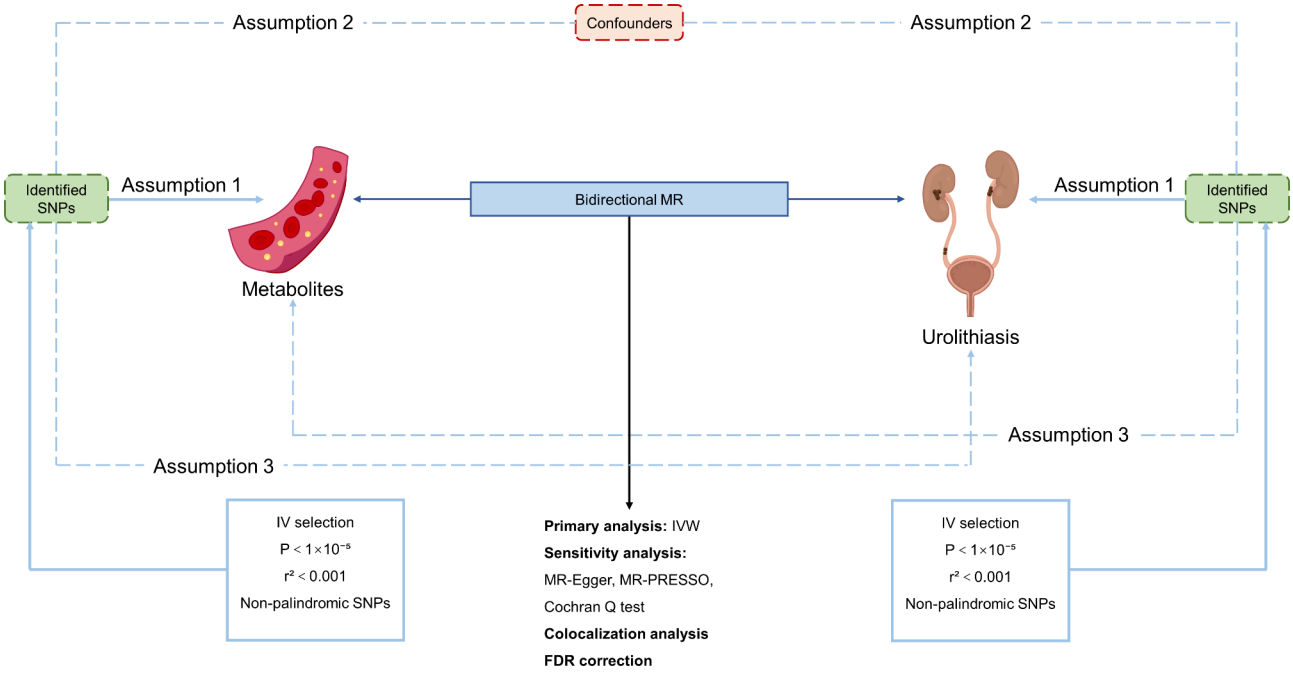

Fig. 1 Overview of the present MR study design. SNP, single-nucleotide polymorphism; IV, instrumental variable; MR, Mendelian randomization

originated from strong linkage disequilibrium (LD) [23, 24]. Another important point is that during the harmonizing process, palindromic SNPs were excluded to ensure the effects of SNPs on exposure accorded with the same allele as the effects of SNPs on the outcome.

Compared with two sample MR analysis, bidirectional MR analysis can solve the potential problem of causal entanglement. By conducting two-sample MR analysis from both directions to ascertain the direction of causal relationships, we were able to mitigate confusion arising from reverse causality and achieve a more comprehensive understanding of causal pathways. Therefore, we also performed reverse MR analysis on urolithiasis to assess its potential impact on blood metabolites. During this stage, we applied a P-value threshold of $P<5\times10^{-8}$, which aligns with the approach employed in forward MR analysis.

Sensitivity analysis

Sensitivity analysis includes Cochran's Q test and the MR-Egger test in order to assess the significance of our results. Cochran's Q statistic was applied to estimate the heterogeneity among SNPs associated with each metabolite [25]. We used MR-Egger regression and MR-Presso tests to evaluate whether genetic instruments had made pleiotropic effects on the outcome [20]. In addition, we excluded IVs with F statistics<10, the F-statistic was defined as the ratio of the model's mean square to that of the error: $\mathrm{F}=\frac{R^2(n-1-k)}{(1-R^2)k}$, in accordance with its academic and professional significance [26]. We implemented all MR analyses in R (version 4.2.1) using R package TwoSampleMR [13] to detect the causal effects of different blood metabolites on the risk of urolithiasis. The statistical significance was considered when the P-value was less than 0.05. In addition, the OR value was calculated based on the results obtained from IVW, and if it exceeded 1 and the P-value was less than 0.05, it indicated a significant risk factor for urolithiasis; conversely, if it was below 1 and the P-value was less than 0.05, it suggested a protective factor against urolithiasis.

Multiple-testing correction

The FDR (False Discovery Rate) was utilized for the correction of all P-values. The significance threshold, denoted as q, was adjusted to be less than 0.05. When a correlation between urolithiasis and blood metabolites was observed with P-values below 0.05 and q-values greater than or equal to 0.05, it suggests a potential association.

Power calculation

We employed a specialized online tool (https://shiny.cnsgenomics.com/mRnd/) [27], which utilizes asymptotic theory to estimate power values for detecting causal effects derived from IVs, to assess the statistical power of MR. We conducted power calculations at a type I error rate of 0.05, considering factors such as OR obtained from MR analyses utilizing the IVW approach, R^2 of IVs and the proportion of cases of urolithiasis GWAS.

Replication and meta-analysis

In order to strengthen the robustness of our results, the replication and meta-analysis of MR were expanded by integrating additional GWAS datasets. The GWAS datasets were accessible through the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/). The GWAS datasets information could be found in Supplementary Table S1. The IVW method was the main methods for the replication and meta-analysis was utilized for combining the outcomes from these GWAS datasets.

Colocalization analysis

In order to determine whether the associations of the identified blood metabolites with urolithiasis were influenced by a shared causal variant, we utilized the R package coloc (v5.2.3) to complete this step, which employed Bayesian colocalization analysis. This analysis assessed five corresponding posterior probabilities of its following hypotheses, including H0 (no correlation with either trait); H1 (solely associated with Trait 1); H2 (solely associated with Trait 2); H3 (two traits are associated but with different causal variations) and H4 (two traits are associated and share a causal variation) [28]. H4/(H3+H4) reveals the probability of colocalization given the presence of a causal variant for urolithiasis [29].

Metabolic pathway analysis

Using MetaboAnalyst 5.0 (https://www.metaboanalyst.ca/) to investigate the association of metabolic pathways with urolithiasis, the Kyoto Encyclopedia of Genes and Genomes (KEGG) [30] database was analyzed.

Results

A total of 296 SNPs ($P<1\times10^{-5}$) associated with 12 traits were identified for human blood metabolites. None of the F- statistics were less than 10, indicating a significant correlation between SNPs and metabolites (Supplementary Table S2).

MR analysis results of human blood metabolite

Firstly, we identified 12 human blood metabolites that were significantly associated with urolithiasis ($P<0.05$), including lipids, amino acids, fatty acids, carbohydrates, peptide and keto acid (Fig. 2; Table 1). Several significant findings regarding clinically relevant blood metabolites were found in our study. Specifically, cortisone (OR: 2.18 (95%CI: 1.05–4.52), $P=0.035$), glycerol (OR:1.38 (95%CI:

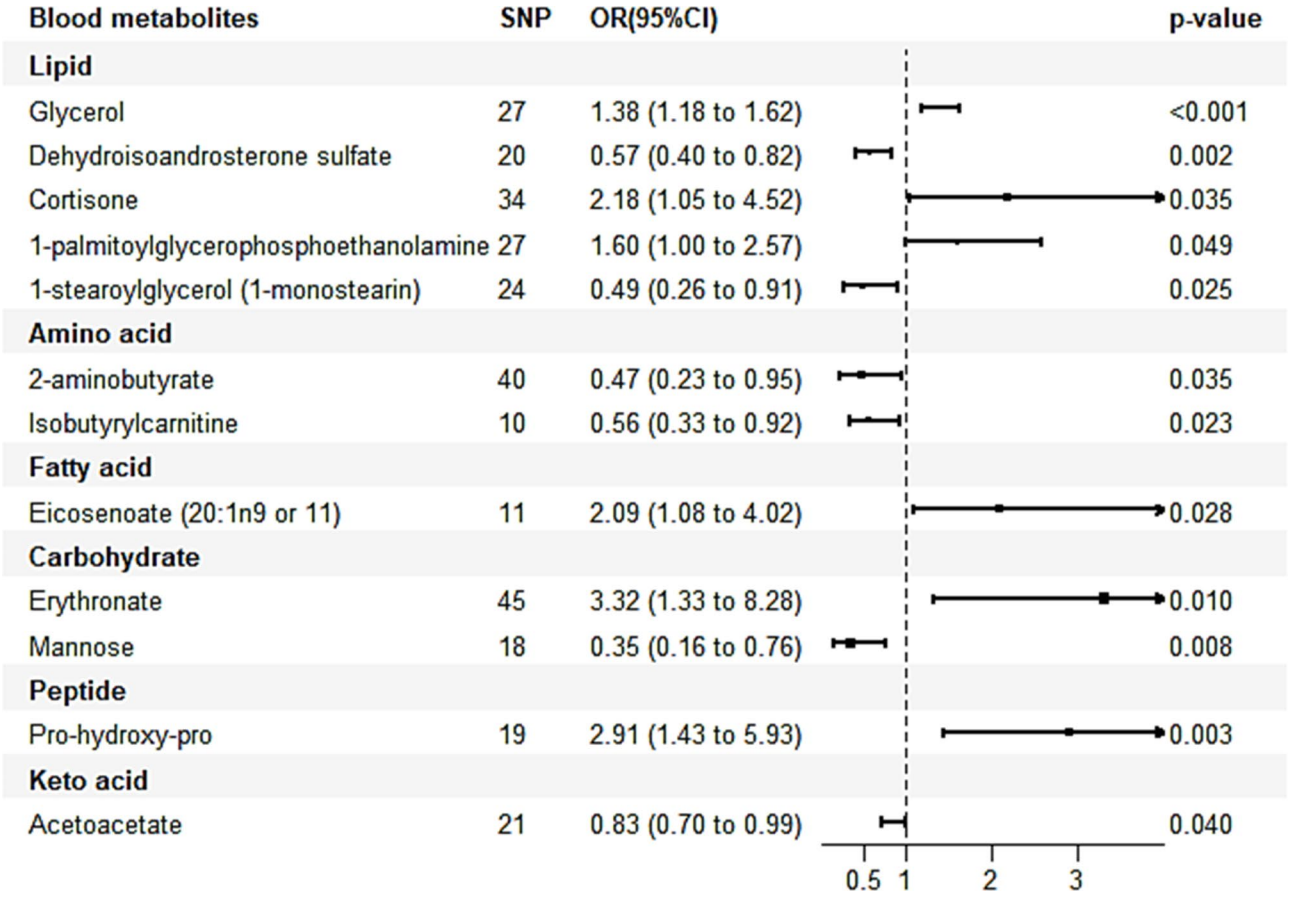

Fig. 2 Forest plot for evaluating the causal relationship between urolithiasis and blood metabolites based on the values obtained from the IVW method

Table 1 MR analysis for the association between blood metabolites and urolithiasis

Exposure	Outcome	SNP	Methods	OR	95% CI	*P*-value	q-value
2-aminobutyrate	Urolithiasis	40	MR Egger	0.64	0.07-5.64	0.694	0.988
			Weighted median	0.49	0.18-1.37	0.168	0.986
			IVW	0.47	0.23-0.95	**0.035***	0.423
Isobutyrylcarnitine	Urolithiasis	10	MR Egger	0.38	0.13-1.07	0.105	0.988
			Weighted median	0.52	0.27-0.98	0.051	0.986
			IVW	0.56	0.33-0.92	**0.023***	0.338
Eicosenoate (20:1n9 or 11)	Urolithiasis	11	MR Egger	1.43	0.26-7.89	0.693	0.988
			Weighted median	1.81	0.80-4.12	0.194	0.986
			IVW	2.09	1.08-4.02	**0.028***	0.352
Dehydroisoandrosterone sulfate (DHEA-S)	Urolithiasis	20	MR Egger	0.77	0.27-2.21	0.634	0.988
			Weighted median	0.58	0.35-0.95	**0.035***	0.986
			IVW	0.57	0.40-0.82	**0.002***	**0.045***
Mannose	Urolithiasis	18	MR Egger	0.29	0.06-1.56	0.169	0.988
			Weighted median	0.31	0.13-0.72	**0.007***	0.986
			IVW	0.35	0.16-0.76	**0.008***	0.134
Pro-hydroxy-pro	Urolithiasis	19	MR Egger	1.30	0.12-13.76	0.829	0.988
			Weighted median	3.33	1.20-9.26	**0.018***	0.986
			IVW	2.91	1.43-5.93	**0.003***	0.057
1-palmitoylglycerophosphoethanolamine	Urolithiasis	27	MR Egger	1.82	0.79-4.20	0.173	0.988
			Weighted median	1.82	0.95-3.48	0.060	0.986
			IVW	1.60	1.00-2.57	**0.049***	0.541
Erythronate*	Urolithiasis	45	MR Egger	1.64	0.03-94.60	0.813	0.988
			Weighted median	2.41	0.76-7.69	0.138	0.986
			IVW	3.32	1.33-8.28	**0.010***	0.162
Cortisone	Urolithiasis	34	MR Egger	2.66	0.56-12.71	0.229	0.988
			Weighted median	2.50	0.84-7.41	0.117	0.986
			IVW	2.18	1.05-4.52	**0.035***	0.423
1-stearoylglycerol (1-monostearin)	Urolithiasis	24	MR Egger	0.36	0.07-1.95	0.250	0.988
			Weighted median	0.43	0.17-1.06	0.067	0.986
			IVW	0.49	0.26-0.91	**0.025***	0.352
Glycerol	Urolithiasis	27	MR Egger	1.35	1.01-1.81	**0.053***	0.988
			Weighted median	1.33	1.07-1.65	**0.011***	0.986
			IVW	1.38	1.18-1.62	**0.000***	**0.001***
Acetoacetate	Urolithiasis	21	MR Egger	0.90	0.63-1.30	0.592	0.988
			Weighted median	0.85	0.67-1.07	0.160	0.986
			IVW	0.83	0.70-0.99	**0.040***	0.464

*Values are statistically significant

1.18–1.62), $P<0.001$) were identified as risk factors for urolithiasis, whereas 2-aminobutyrate (OR: 0.47 (95%CI: 0.23–0.95), $P=0.035$), dehydroisoandrosterone sulfate (DHEA-S) (OR: 0.57 (95%CI: 0.40–0.82), $P=0.002$), mannose (OR: 0.35 (95%CI: 0.16–0.76), $P=0.008$) and acetoacetate (OR:0.83 (95%CI:0.70–0.99), $P=0.040$) were identified as protective factors for urolithiasis (Fig. 2; Table 1). After applying FDR correction, only dehydroisoandrosterone sulfonate (DHEA-S) (q=0.045) and glycerol (q=0.001) exhibited statistically significant differences. Pro-hydroxy-pro, Erythronate and Cortisone had a high statistical power of 1.00 (Supplementary Table S3). Furthermore, we conducted metabolite pathway analysis on all metabolites discovered by the IVW method ($P<0.05$). As shown in Table 2, one metabolic pathway was significantly causal with urolithiasis.

Sensitivity analysis results

Except for mannose ($P=0.044$) and erythronate ($P=0.011$), no significant heterogeneity of IVs was showed according to the results of Cochran's MR Egger Q test and Cochran's IVW Q test (Table 3). Through the MR-PRESSO test, the IV rs6860069 (Rssobs=0.0131, $P<0.015$) was identified as outlier and removed from the next analysis. In addition, according to the results of the MR-Egger intercept tests and the MR-Presso tests (Table 3), it suggested that erythronate has horizontal pleiotropy. However, the subsequent distortion test P-value was greater than 0.05, which indicated that it did

Table 2 Sensitivity analysis of the causal association between blood metabolites and urolithiasis

Exposure	Cochran's *Q* test		MR-Egger intercept	MR-PRESSO global test	
	Method	P-value	P-value	P-value	Distortion test P-value
2-aminobutyrate	MR Egger	0.618	0.760	0.657	
	IVW	0.657			
Isobutyrylcarnitine	MR Egger	0.364	0.426	0.468	
	IVW	0.392			
Eicosenoate (20:1n9 or 11)	MR Egger	0.884	0.649	0.932	
	IVW	0.916			
Dehydroisoandrosterone sulfate (DHEA-S)	MR Egger	0.850	0.560	0.856	
	IVW	0.873			
Mannose	MR Egger	**0.044**	0.813	0.114	
	IVW	0.060			
Pro-hydroxy-pro	MR Egger	0.938	0.493	0.925	
	IVW	0.945			
1-palmitoylglycerophosphoethanolamine	MR Egger	0.900	0.725	0.933	
	IVW	0.921			
Erythronate*	MR Egger	**0.009**	0.727	**0.014**	0.370
	IVW	**0.011**			
Cortisone	MR Egger	0.359	0.781	0.433	
	IVW	0.403			
1-stearoylglycerol (1-monostearin)	MR Egger	0.440	0.718	0.563	
	IVW	0.492			
Glycerol	MR Egger	0.231	0.869	0.310	
	IVW	0.273			
Acetoacetate	MR Egger	0.919	0.616	0.933	
	IVW	0.935			

*Values are statistically significant

Table 3 Significant metabolic pathways in the pathogenesis of urolithiasis

Metabolic pathway	Metabolites involved	*P* Value	Database
Steroid hormone biosynthesis	Dehydroepiandrosterone sulfate and Cortisone	**0.0176***	KEGG

*Values are statistically significant

not affect our results. Therefore, our process was consistent with MR assumptions.

Reverse MR analyses results

Furthermore, employing reverse MR analysis revealed a modest association among urolithiasis and butyrylcarnitine (β=0.04, *P*=0.029), 3-methyl-2-oxobutyrate (β = -0.02, *P*=0.043), scyllo-inositol (β=0.04, *P*=0.024), leucylleucine (β=0.05, *P*=0.007), x-14,304—leucylalanine (β=0.05, *P*=0.028); however, after implementing multiple corrections, none of the individual findings reached the threshold for statistical significance (Table 4).

Replication and meta-analysis

In order to strengthen the robustness of our results, the replication and meta-analysis of MR were expanded by integrating additional GWAS datasets for the positively identified metabolites after multiple-testing correction. The findings revealed that glycerol demonstrated similar trends of causal associations with urolithiasis in other GWAS datasets (Supplementary Figures S1-S2). However, the results of the replication and meta-analysis were not significant, possibly due to the broader heterogeneity across GWAS datasets (Heterogeneity: $P<0.01$) and including the heterogeneity statistics.

Colocalization analyses

Two metabolites with FDR significant MR associations with urolithiasis were performed colocalization analysis, and the results were presented in the Supplementary Table S4. The results of the colocalization analysis suggested that the connections between urolithiasis and the two established metabolites were not linked to shared causal variant sites. The regional associations identified in the colocalization results were illustrated on Supplementary Figures S3–S4.

Conclusion

By applying mendelian randomization and after applying FDR correction, only dehydroisoandrosterone sulfonate (DHEA-S) and glycerol exhibited statistically significant differences. 2-aminobutyrate, Isobutyrylcarnitine, mannose, acetoacetate and 1-stearoylglycerol

Table 4 Reverse MR analysis for the association between blood metabolites and urolithiasis

Exposure	Outcome	SNP	Methods	β	*P*-value	q-value
urolithiasis	Butyrylcarnitine	5	MR Egger	0.12	0.278	0.995
			Weighted median	0.03	0.112	0.998
			IVW	0.04	**0.029***	0.987
urolithiasis	3-methyl-2-oxobutyrate	5	MR Egger	-0.02	0.842	0.995
			Weighted median	-0.02	0.057	0.998
			IVW	-0.02	**0.043***	0.987
urolithiasis	Scyllo-inositol	5	MR Egger	0.08	0.488	0.995
			Weighted median	0.04	**0.044***	0.998
			IVW	0.04	**0.024***	0.987
urolithiasis	Leucylleucine	5	MR Egger	0.17	0.308	0.995
			Weighted median	0.05	0.085	0.998
			IVW	0.05	**0.007***	0.987
urolithiasis	X-14,304--leucylalanine	5	MR Egger	0.04	0.716	0.995
			Weighted median	0.05	0.124	0.998
			IVW	0.05	**0.028***	0.987

*Values are statistically significant

(1-monostearin) were detected to possess suggestive protective effects against urolithiasis. On the contrary, a number of metabolites, incorporating eicosenoate, pro-hydroxy-pro, erythronate, 1-palmitoylglycerophosphoethanolamine and cortisone had suggestive negative effects on urolithiasis. Given that the primary purpose of this study was to explore and discover as many potential significant metabolites as possible, we posited that metabolites with p-values less than 0.05 and q-values greater than 0.05 also warranted consideration. Nevertheless, it should be noted that these potential findings have not been subjected to FDR correction, thus necessitating cautious validation in larger sample sizes in future studies.

In our study, we observed that DHEA-S exerted inhibitory effects on stone formation, highlighting its potential as a promising preventive agent in the field of urolithiasis. In an animal experiment, raising castrated rats with DHEA may directly modulate the hepatic enzyme activities of GRHPR and AGXT which subsequently regulate the endogenous oxalate production in the liver [31]. On the basis of it, Fuster et al [32]. conducted a cross-sectional analysis aiming to reveal the relationship between urinary sex hormones and excretion of urinary components in kidney stone formers. Of note, their result shown that DHEA had an inverse association with urinary oxalate excretion and supported our finding. Additionally, In Franca Serafini-Cessi et al.'s study, they described N-Glycans, which are rich in mannose, were capable to resist urological diseases [33]. S Proietti et al. assessed a D-mannose-containing product possessing protective effects against infection-related urinary stones [34]. Their experimental conclusions fully support the analysis results obtained in our MR analysis regarding the protective effect of mannose.

In parallel with these protective metabolites, it was of great interest to focus on the risk factors derived from our result. The most representative of these was cortisone, a glucocorticoid, which captured our attention. Several observational studies on hormone concentration in urine samples had indicated that glucocorticoids can mediate a negative impact on the excretion of inorganic salts and uric acid, even at normal physiological levels [35, 36]. Likewise, as an inactive precursor of glucocorticoids such as hydrocortisone, cortisone was a significant risk factor for stone formation in our analysis.

Apart from the metabolites mentioned, we found a significant relationship between steroid hormone biosynthesis and the formation of urolithiasis. In Wen et al.'s study [37], steroid biosynthesis was found to be altered in patients with urolithiasis. In addition, it was manifested that steroid derivatives are also potentially relevant to urolithiasis, which coincides with the protective and lithogenic effects of DHEA and cortisone, as concluded in our study, respectively. These metabolites and the altered metabolic pathway may collectively suggest the formation or compensatory onset of urolithiasis and may possess profound value as future biomarkers or therapeutic target sites for urolithiasis.

However, our study also had some limitations. Firstly, to address the issue of limited availability of SNPs for the exposure of interest at a genome-wide level, we had set a more relaxed threshold which was also commonly employed in other studies. Although relaxing the threshold might increase the likelihood of horizontal pleiotropy occurring, our findings confirmed the absence of any additional level of pleiotropy. In addition, the F-statistic value of selected SNPs all exceeded 10, indicating that our IVs were robust enough. Secondly, we did not prove our study in other populations such as Asians which may

affect the generalizability of the results. Moreover, it is significant that our study needs to be confirmed through careful basic research.

In general, the results we obtained show us the causal relevance between two metabolites and urolithiasis, and we also ascertained one metabolic pathway that may be related to the development of urolithiasis. Facing the high prevalence of urolithiasis, further investigations are encouraged to clarify the mechanisms of these metabolites and explore new therapeutic strategies.

Abbreviations

MR	Mendelian randomization
IVW	Inverse-variance weighted
RCTs	Randomized controlled trials
SNPs	Single nucleotide polymorphisms
GWAS	Genome-wide association study
IVs	Instrumental variables
LD	Linkage disequilibrium
KEGG	Kyoto Encyclopedia of Genes and Genomes
SMPDB	Small Molecular Pathways Database
OR	Odds ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12894-024-01568-8.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

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Author contributions
HZY designed the study. HDK collected and analyzed the data. DAQ and PJS prepared the manuscript and provided the figures. YR and GDF reviewed the manuscript. HBB revised the manuscript and HZY provided constructive suggestions. All authors read and approved the final manuscript.

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Data availability
All of the data analyzed in current research are available here: the FinnGen consortium (https://www.finngen.fi/en) and the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/).

Declarations

Ethics approval and consent to participate
Not applicable. Our study used available summary statistics.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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