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ORIGINAL RESEARCH

A Mendelian Randomization Study of the Association Between Polycystic Ovary Syndrome and Serum Urea Levels

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Background: Polycystic Ovary Syndrome (PCOS) is a common endocrine and metabolic disorder affecting the reproductive function of women of reproductive age. Its clinical features include irregular menstruation, obesity, insulin resistance, hyperandrogenism, and polycystic ovarian morphology. Elevated serum urea levels may be related to the pathogenesis of PCOS. However, existing observational studies have not been able to clarify the causal relationship between serum urea levels and PCOS.

Methods: This study employed a two-sample Mendelian randomization (MR) approach to evaluate the genetic causal relationship between serum urea levels and PCOS. We utilized summary data from genome-wide association studies (GWAS) from the UK Biobank for serum urea levels as the exposure variable, and from the FinnGen consortium for PCOS. Causal association analyses were conducted using inverse-variance weighting (IVW), MR Egger, weighted median, and simple mode methods. Additionally, Cochrane's Q test was applied to assess heterogeneity in the MR results, and potential horizontal pleiotropy was evaluated using the MR-Egger intercept test and the MR-PRESSO method.

Results: IVW analysis revealed a statistically significant causal relationship between serum urea levels and PCOS(OR = 1.623,95% CI=1.015–2.597,P=0.043). Further analysis found no significant evidence of horizontal pleiotropy (P=0.674),and leave-one-out analysis confirmed the robustness of the causal association.

Conclusion: In this two-sample MR analysis, we present the evidence of a genetic causal relationship between serum urea levels and PCOS, thereby offering a novel perspective on the pathogenesis of this disease.

Keywords: Mendelian randomization, serum urea levels, polycystic ovary syndrome, genome-wide association studies

Introduction

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine and metabolic disorders among premenopausal women, with clinical features primarily characterized by hirsutism, obesity, hyperandrogenism, and insulin resistance,[1–3] affecting 5% to 18% of women of reproductive age.[4] According to the 2003 Rotterdam criteria, PCOS is diagnosed by fulfilling any two of the following three criteria: hyperandrogenism (clinical or biochemical), oligo-ovulation, and polycystic ovarian morphology. This diagnostic standard is also recognized by the international evidence-based guidelines for the assessment and management of PCOS.[5] PCOS is increasingly considered a complex trait resulting from the interplay of multiple genetic and environmental factors.[6] As the most prevalent endocrine-metabolic disease among women of reproductive age worldwide,[7] the condition increases the risk of type 2 diabetes, gestational diabetes, and other pregnancy-related complications, as well as venous thromboembolism, cerebrovascular, and cardiovascular events,[8–10] severely impacting the quality of life of affected individuals. Therefore, investigating the etiological factors associated with PCOS has become a focal point of research.

Recent studies have increasingly focused on the role of metabolic indicators in the pathophysiology of PCOS. Serum urea levels are a crucial indicator of nitrogen metabolism in the human body and are commonly used to assess kidney function.[11,12]

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Previous studies have found that disruptions in serum urea levels can trigger related gynecological conditions.[13–16] Gao et al observed that monitoring serum urea levels during pregnancy is significant for predicting gestational kidney disease.[13] An RCT study by Gao et al found that metabolic indicators such as serum urea levels and creatinine were significantly higher in non-obese PCOS patients compared to non-obese controls, providing a reference for the diagnosis and treatment of non-obese PCOS patients in clinical practice.[14] A meta-analysis by Widjanarko et al on polycystic ovary syndrome and kidney function impairment indicators revealed a correlation between PCOS and elevated kidney metabolic markers.[15] Aubuchon et al discovered through a randomized double-blind trial that treatment with metformin or clomiphene in PCOS patients significantly reduced serum urea levels, improved kidney function, and alleviated PCOS symptoms, indicating a correlation between these factors.[7]

Although studies have suggested a potential association between serum urea levels and PCOS, and given the strong genetic component of PCOS where certain genetic variants may concurrently influence both urea levels and the risk of PCOS,[6] the underlying pathogenesis remains unclear.[16] Serum urea levels, among other metabolic indicators, can help identify insulin resistance and dyslipidemia in patients with PCOS, which are crucial for developing long-term disease management plans and improving patients' quality of life. Therefore, it is essential to investigate the genetic associations and causal relationships between the two-sample.

Mendelian randomization(MR) is an analysis method based on genetic variables that utilizes the random distribution properties of genetic variants. This approach reduces the interference of confounding variables and avoids the issue of reverse causality because genetic variants are determined at conception and do not change with disease progression. This method provides stronger evidence for causal relationships.[17] In this study, we explored the causal relationship between serum urea levels and PCOS through two-sample MR analysis based on large-scale genome-wide association study (GWAS) data.

Methods

Study Design and Data Sources

This study employed a two-sample MR analysis to investigate the causal relationship between urea levels and PCOS. We used GWAS data from independent cohorts to enhance the strength of causal inference. Single nucleotide polymorphisms (SNPs) were selected as instrumental variables (IVs) for further analysis. In this study, serum urea levels were considered as exposure data, which were derived from the UK Biobank (https://www.ukbiobank.ac.uk/), comprising 13,586,012 SNPs. The data included in this study are limited to females only. PCOS was considered as outcome data, sourced from the FinnGen database (https://www.finngen.fi/en), with a total of 642 cases and 118,228 controls. Similarly, this is restricted to female individuals only. This choice was made because polycystic ovary syndrome (PCOS) occurs exclusively in the female population, and our research aims to investigate the causal relationship between serum urea levels and PCOS. The GWAS data used in this study were publicly released by the hosting research institutions. Therefore, no further ethical approval was required.

Selection of Instrumental Variables

To perform MR analysis, three assumptions must be followed: relevance, independence, and exclusion restriction. Therefore, all IVs used for further analysis were rigorously screened. First, we selected SNPs strongly associated with the exposure ($P < 5\times10^{-8}$) and excluded SNPs with an F-statistic less than 10 to ensure significance and avoid weak IV bias. The formula for the F-statistic used in this study was $F = R^2 \times (N-2)/(1-R^2)$, where R^2 is the proportion of variance in the exposure explained by each IV. $R^2 = 2\times EAF\times(1-EAF)\times Beta^2$, where Beta is the effect size of the allele and EAF is the effect allele frequency. Second, to avoid bias due to strong linkage disequilibrium among the selected SNPs, a clumping process ($r^2 < 0.001$, physical window = 10,000 kb) was performed to ensure the independence of IVs. Third, SNPs associated with confounders and outcomes were excluded using the LDtrait tool (Figure 1).

Statistical Analysis

Five different methods were used to explore the genetic association between serum urea levels and PCOS: MR-Egger regression, weighted median, inverse-variance weighting (IVW), simple mode, and weighted mode methods. IVW assumes

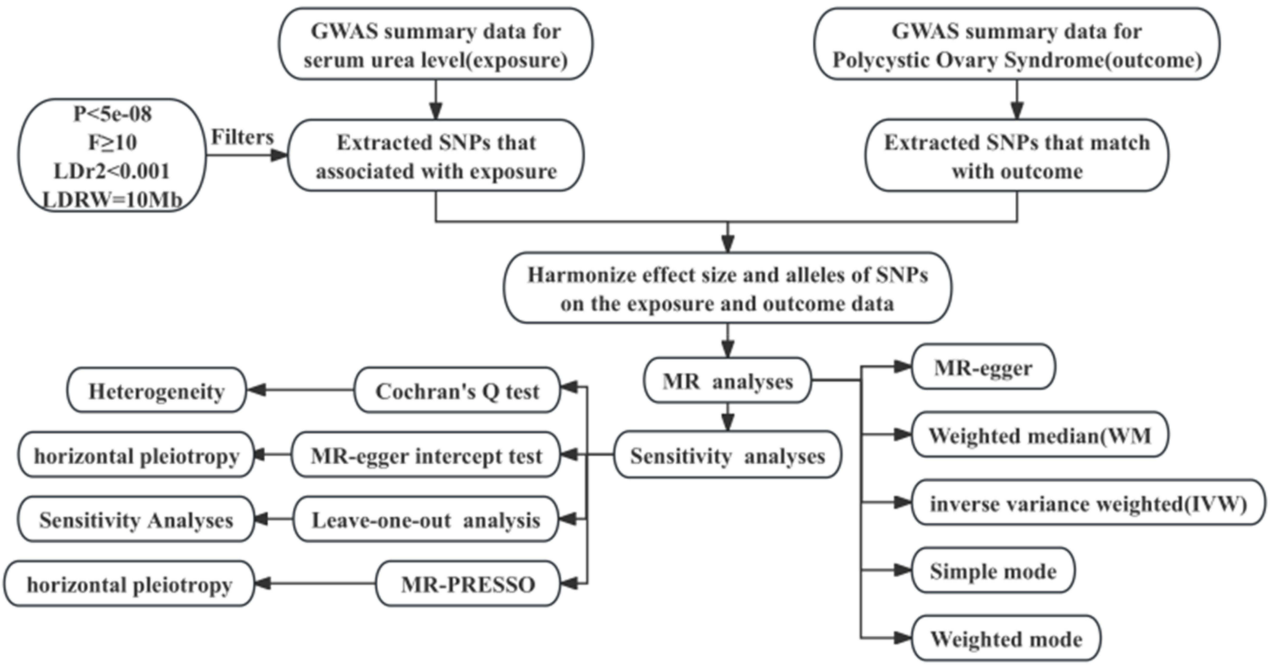

Figure 1 Two-sample Mendelian randomization between serum urea level and PCOS.SNP: single nucleotide polymorphism.

that all SNPs used for analysis are valid; thus, it may yield the most precise estimates. Therefore, IVW was considered the primary analysis method in this study. The formula for calculating R^2 has been mentioned above. Various tests were conducted to ensure the reliability of the results. Cochrane's Q test was used to reveal heterogeneity in the associations. Additionally, funnel plots were used to display heterogeneity through symmetry. The MR-Egger intercept test and the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) global test[18] were used to test for pleiotropy. MR-PRESSO can also detect outliers in the associations and provide estimates after excluding the outliers. Finally, sensitivity analyses were performed to test the stability of the results. By sequentially excluding SNPs, this method explored whether the association could be influenced by a single influential SNP. Statistical analyses were conducted using R software (version 4.3.3) and the TwoSampleMR package.[19] A P-value of < 0.05 was considered statistically significant.

Results

Instrumental Variable Selection

After filtering SNPs that were strongly associated with exposure data ($P < 5 \times 10^{-8}$, F-value > 10) and independent ($r2 < 0.001$, physical window = 10,000 kb), 172 SNPs were considered as preliminary IVs, with the lowest F-value being 27.06575. Detailed information on the F-values is listed in Supplementary Table 1. Although we used the LDtrait tool to exclude SNPs associated with the outcomes and confounding factors ($P < 1 \times 10^{-5}$), no SNPs were excluded at this step. After harmonizing the exposure and outcome data, 162 SNPs were selected for further MR analysis, excluding incompatible alleles rs12476098 and rs3991792, as well as SNPs with intermediate allele frequency palindromes rs13240042, rs2505284, rs4940994, rs9482771, and rs9823691. Finally, 155 SNPs were selected as IVs.

Mendelian Randomization Analysis

The random effects IVW method was used as the primary approach to explore the genetic association between urea levels and PCOS, and the results indicated that urea levels are an independent risk factor for PCOS(P = 0.043, OR = 1.623, 95% CI = 1.015–2.597) (Supplementary Table 1). Additionally, the weighted median method also supported the existence of a genetic causal relationship between urea levels and PCOS. Supplementary Table 1 presents the five methods and results of our MR analysis.

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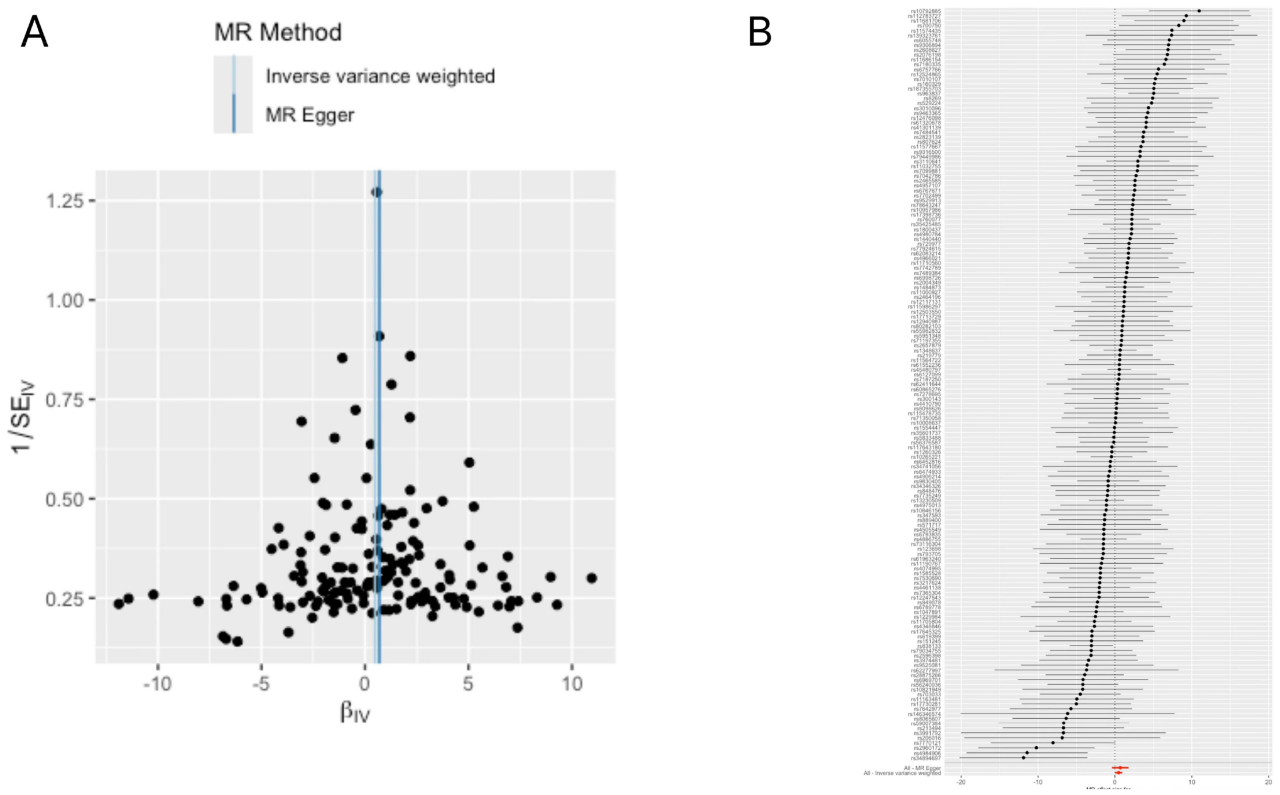

Figure 2 The association between serum urea levels and PCOS. (**A**) Forest plot of causal effects of serum urea levels and PCOS. (**B**) Scatter plot of causal effects of serum urea levels on PCOS. The slope of the line represents the causal effect of each method.

In Supplementary Table 1, the IVW method is considered the primary analysis method, which indicates that urea levels are an independent risk factor for PCOS (OR = 1.623, 95% CI = 1.015–2.597,P = 0.043). Other results: MR Egger method:OR=2.000,95%Cl:0.679–5.896,P=0.211; weighted median method:OR=1.766,95%Cl:0.853–3.656,P=0.126; Simple model:OR=1.805,95%Cl:0.375–8.682,P=0.462; Weighted model:OR=2.024,95%Cl:0.697–5.800,P=0.197

Cochran's Q was calculated to quantify the heterogeneity of individual causal effects, showing the presence of heterogeneity in the association between urea levels and PCOS (P = 0.021) (Supplement Table 2). Therefore, a random-effects IVW MR analysis should be used. The funnel plot also indicates that the SNPs are symmetrically distributed (Figure 2A). As shown in the forest plot (Figure 2B) and the scatter plot (Figure 3A). The MR intercept and MR-PRESSO global test suggest that there is no horizontal pleiotropy in this association (P = 0.674) (Supplement Table 3). MR-PRESSO results show no outliers in the MR analysis. Additionally, the leave-one-out sensitivity test demonstrates that our MR analysis results are not influenced by any single SNP (Figure 3B); hence, the result is stable and reliable.

Discussion

Leveraging GWAS data, our MR analysis has, for the first time, unveiled a significant causal relationship between serum urea levels and PCOS. Our findings suggest that genetically elevated urea levels are associated with an increased risk of developing PCOS. This relationship implies that interventions aimed at reducing urea levels may help lower the incidence and severity of PCOS, thereby improving reproductive health and mitigating related long-term metabolic and reproductive complications.

An increasing body of evidence indicates that elevated urea levels are associated with the occurrence of PCOS. Elevated levels of serum urea may exacerbate insulin resistance by inhibiting insulin secretion and sensitivity, which is one of the core pathological mechanisms of PCOS. Accumulating experimental evidence has shown that urea can inhibit the insulin signaling pathway and promote abnormal glucose metabolism, which may indirectly contribute to the development of PCOS.[19,20]

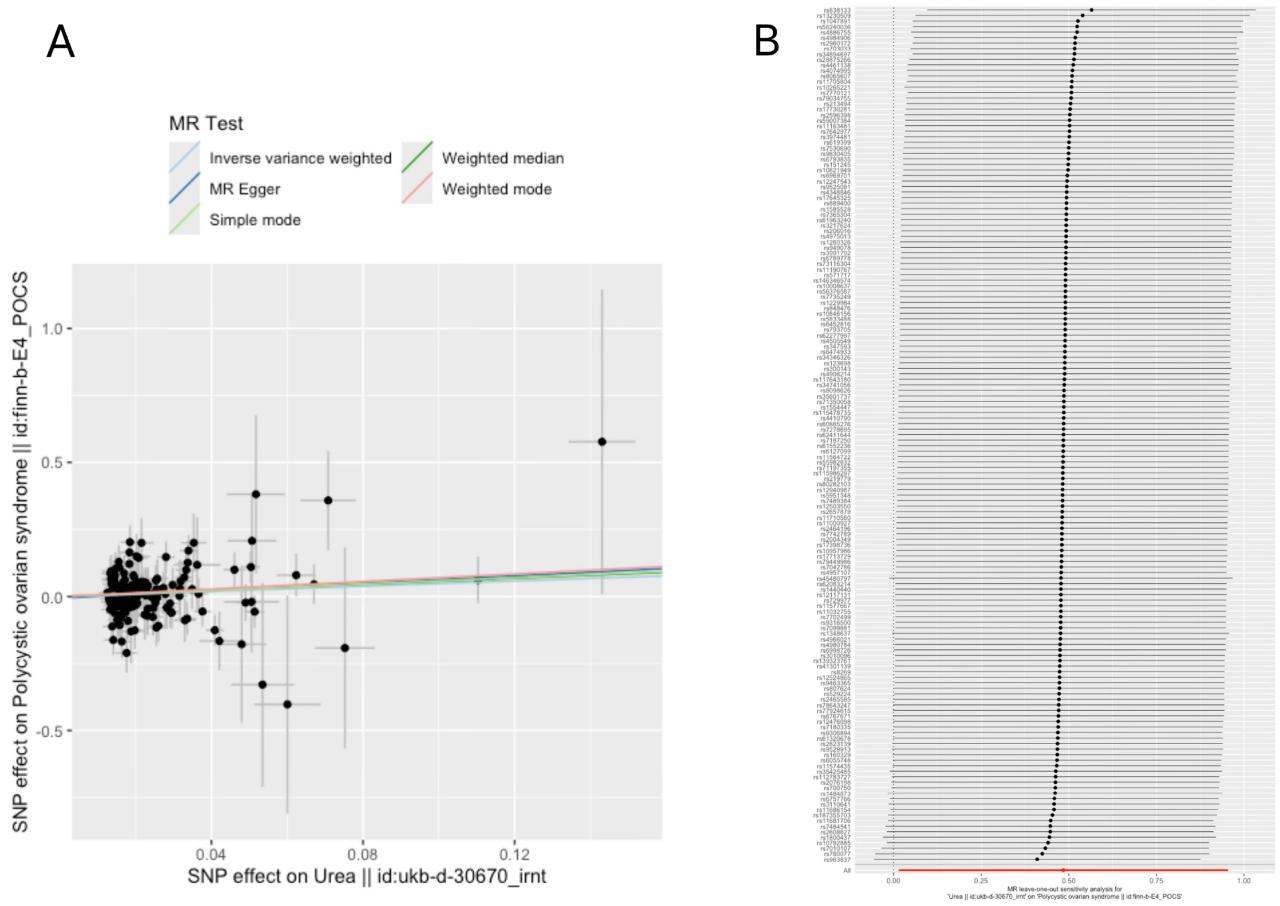

Figure 3 The effect size for serum urea levels and PCOS. (**A**) The funnel plot showed that the SNPs were symmetric, indicating that there was no heterogeneity in the association. (**B**) The leave-one-out test showed that the result was not affected by single influential SNP, so this association was stable.

Alahmadi et al revealed a potential link between PCOS and renal dysfunction through a rat model induced by injecting adult female rats with estradiol valerate (0.2 mg/rat × 2), finding that the development of PCOS was related to elevated urea levels.[21] PCOS is often accompanied by impaired follicular development. Kowsar et al found that elevated serum urea levels can disrupt the epidermal growth factor (EGF) system, thereby affecting the in vitro maturation of oocytes and leading to abnormal follicular development.[22] Lowering serum urea levels has been shown to improve PCOS; in a group study by treating PCOS rats induced by letrozole, it was found that the urea levels in the model rats increased, and treatment with Agaricus blazei, which has protective effects on the kidneys, confirmed this by reducing urea levels.[23] In a clinical study by Masaeli et al, 39 women with PCOS aged between 20–40 years who regularly took metformin were found to have improvements in metabolic indicators, including serum urea levels, contributing to the treatment of PCOS.[24] Oktanella et al studied renal function impairment in a PCOS animal model, suggesting that elevated serum urea levels and other indicators might be part of the pathogenesis of renal dysfunction in PCOS.[25]

Currently, the relationship between PCOS and chronic kidney disease (CKD) remains unclear and controversial. A recent Mendelian randomization study explored the causal relationship between certain biochemical indicators of CKD and PCOS, finding a positive causal relationship between PCOS and CKD (odds ratio [OR] = 1.180, 95% CI: 1.038–1.342; P = 0.010). Further analysis clarified that there is a causal relationship between PCOS and certain serological indicators of CKD, including fibroblast growth factor 23, creatinine, and cystatin C, demonstrating the necessity of regular renal function follow-up in PCOS patients for the early treatment of CKD.[26] Gateva et al also suggested that fibroblast growth factor 23 is significantly elevated in obese PCOS patients.[27] Elevated serum urea levels generally indicate a decline in the kidney's ability to clear waste from the blood, which is crucial for assessing kidney

function and metabolic levels. Additionally, given the association between PCOS and certain serological indicators of CKD, increasing epidemiological evidence supports this correlation. For instance, uric acid (UA), the final metabolic product of purine metabolism, is elevated in the serum of PCOS patients.[28] It has been reported that women with PCOS have higher glomerular hyperfiltration (GH), which is an independent risk factor for deteriorating kidney function, as well as metabolic and cardiovascular diseases.[29] Serum urea level is a heritable trait and is commonly used as a diagnostic marker for kidney function. Thio et al conducted a two-stage meta-analysis of GWASs for serum urea in 13,312 participants and performed independent replication in 7,379 participants of European descent, identifying two novel SNPs (POU2AF1 and ADAMTS9-AS2) that are expression quantitative trait loci for genes highly expressed in kidney and gastrointestinal tissues. This provides insights into the genetic basis of urea metabolism, which may be related to kidney function.[30] This finding offers valuable ideas and insights for further research into endocrine and metabolic disorders such as PCOS. However, a recent questionnaire-based study found no significant correlation between serum urea levels and the skin-related quality of life index in patients with chronic kidney disease on hemodialysis. Given the controversy, further validation is needed through broader prospective multicenter studies.[31]

However, observational studies have not yet established a causal relationship between serum urea levels and PCOS. Since PCOS often coexists with metabolic diseases such as kidney disease, and serum urea levels are one of the important reference indicators for diagnosing kidney disease, this may contribute to the observed positive correlation. GWAS have become powerful tools for studying complex diseases, capable of identifying individual or genomic groups beyond single-gene association studies, validating previous research findings, and opening up new research perspectives.[32] Based on large-scale GWAS, our study provides genetic evidence for the causal relationship between serum urea levels and PCOS, explaining the potential causal link between these two conditions.

This study has several strengths. First, to our knowledge, this is the first study to explore the causal relationship between serum urea levels and PCOS using large-scale GWAS data. The two-sample MR approach overcomes some of the limitations of observational studies, such as reverse causality, confounding factors, and various biases. Second, all IVs used for MR analysis in this study were rigorously screened, with the lowest F-value of 27.066 exceeding the conventional standard, ensuring the accuracy and robustness of the results. Finally, we employed multiple methods to test the sensitivity, horizontal pleiotropy, and heterogeneity of the results. All these tests indicated that the association between serum urea levels and PCOS is stable and reliable.

However, this study also has some limitations. First, all participants involved in the GWAS were of European ancestry. Therefore, whether our findings can be generalized to other populations and regions requires further research and validation. Second, although we used the MR-intercept and MR-PRESSO global tests to detect and adjust for pleiotropy in genetic variations, there may still be some residual confounding factors, such as lifestyle, environmental exposures, and metabolic conditions, that cannot be entirely excluded and may introduce some bias into the study results. Third, since our MR analysis relies on information provided by the underlying GWAS meta-analysis, stratified analysis by different countries, ethnicities, or age groups was not possible. Therefore, the impact of serum urea levels on PCOS observed in this study may not be generalizable to groups with other specific characteristics, such as different ethnicities and ages.

Data Sharing Statement

Due to privacy restrictions, the cohort data used in this study are not publicly available but can be obtained from the corresponding author, Fang Lian (email: lianfangbangong@163.com), upon reasonable request. The genetic data used for the MR analysis were derived from publicly available GWAS datasets, and detailed information can be provided upon request.

Ethics Approval and Consent to Participate

All data utilized in this study were sourced from publicly available, de-identified international genomic databases. These databases had obtained prior ethical approval and informed consent in the original studies. The data were exclusively employed for statistical analysis in this study, without involving any personal privacy information or identifiable

individual data. Our research is exempt from ethical approval due to Items 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China.

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Author Contributions

In this study, Tingting Wang is the first author, and Fang Lian is the corresponding author. All authors have made substantial contributions to the work reported, whether in conception, study design, execution, data acquisition, analysis, and interpretation, or in all these areas; have been involved in drafting, revising, or critically reviewing the manuscript; have given final approval of the version to be published; have agreed to submit the article to this journal; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest.

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