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Original Research

Association of serum uric acid with male sexual hormones and erectile dysfunction: a bidirectional 2-sample Mendelian randomization analysis

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Abstract

Background: Observational studies indicated that serum uric acid (SUA) was associated with male sexual hormones and erectile dysfunction (ED). However, their relationship was still heterogeneous.
Aim: This study conducted 2-sample univariate mendelian randomization (UVMR) and multivariate mendelian randomization (MVMR) to explore the causal relationship between SUA and sexual hormones as well as ED.
Methods: Genetic variants associated with SUA were derived from the UK Biobank database (N = 437 354). Outcomes from the IEU Open GWAS and summary data sets were sexual hormones (sex hormone–binding globulin [SHBG], testosterone, estradiol [E2], follicle-stimulating hormone, luteinizing hormone) and ED, with 3301 to 625 650 participants. UVMR analysis primarily utilized the inverse variance weighted method, complemented by MVMR analysis. Thorough sensitivity analyses were carried out to ensure the reliability of results. Moreover, mediation analysis was conducted to estimate the mediated effect between SUA and outcomes.
Outcomes: The primary outcomes included results of UVMR and MVMR analysis and mediation analysis, along with sensitivity analyses involving the Cochran *Q* test, the MR Egger intercept test, leave-1-out analysis, and the MR-PRESSO method (mendelian randomization pleiotropy residual sum and outlier).
Results: UVMR analysis revealed that an elevated SUA level could decrease levels of SHBG ($\beta = -0.10$, $P = 1.70 \times 10^{-7}$) and testosterone ($\beta = -0.10$, $P = 5.94 \times 10^{-3}$) and had a positive causal effect on ED (odds ratio, 1.10; $P = .018$). According to reverse mendelian randomization results, increased levels of SHBG ($\beta = -0.06$, $P = 4.82 \times 10^{-4}$) and E2 ($\beta = -0.04$, $P = .037$) could also reduce SUA levels. As shown by MVMR analysis, SUA had a negative effect on SHBG and testosterone levels ($P < .05$), while the significant causal relationship between SUA and ED disappeared. Furthermore, SHBG mediated 98.1% of the effect of SUA on testosterone levels. Results of other mendelian randomization analyses were not statistically significant. No pleiotropy was found by sensitivity analysis in this study.
Clinical Implications: Given the causal relationship between SUA and sexual hormones, we must focus on SUA and E2 levels in men, especially patients with hypogonadism and ED.
Strengths and Limitations: This study evaluated the causal effect of SUA on male sexual hormones and ED genetically for the first time, clarifying the common biases in observational studies and confirming the negative relationship between SUA and testosterone level. Limitations include a population based on European ancestry, some crossover of the samples, and unobserved confounding factors.
Conclusion: Genetic studies provide evidence for the causal relationship between SUA and male sexual hormones (SHBG, testosterone, E2), while the relationship between SUA and ED should be further evaluated.

Keywords: mendelian randomization; serum uric acid; sex hormone–binding globulin; testosterone; estradiol; erectile dysfunction.

Introduction

Erectile dysfunction (ED) refers to the disease where men cannot get or keep an penile erection hard enough for satisfactory sexual intercourse.[1] ED is influenced by multiple factors, severely affecting men's physical and mental health. It is estimated that the overall prevalence of ED was 0.9% to 52% in European men aged <60 years, which was even higher in men aged >60 years (8.3%-88.8%).[2]

Researchers have recently found that changes in levels of sex hormone–binding globulin (SHBG) and male hormones—testosterone, estradiol (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH)—may lead to various sexual dysfunctions, including ED.[3] SHBG has a high affinity for androgen and transports testosterone in the body.[4] Testosterone affects the synthesis of cyclic guanosine monophosphate as a second messenger, reducing intracellular calcium ions and relaxing smooth muscle.[5] At the same time, testosterone regulates the expression and activity of phosphodiesterase 5 inhibitors, which together participate in the process of penile erection.[6] E2 negatively regulates the secretion of gonadotropins, reducing the testosterone level.[7] However, E2 could increase the activity of nitric oxide synthase, accelerating the synthesis of endothelial nitric oxide.[8] In addition, FSH and LH stimulate the testes to produce testosterone, and testosterone negatively regulates the secretion of FSH and LH.[9]

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Serum uric acid (SUA) is the metabolite of purine, which is associated with metabolic diseases such as metabolic syndrome, hypertension, and diabetes.[10] A high SUA level could cause damage to vascular endothelium and inhibit endothelial repair, making it an independent risk factor for cardiovascular disease.[11] It is confirmed that ED has several risk factors similar to cardiovascular disease, including smoking, diabetes, hypertension, dyslipidemia, and obesity; thus, we considered SUA a potential risk factor for ED.[12] Moreover, Long et al found that high SUA might cause the increase of reactive oxygen species and the decrease of nitric oxide in hyperuricemia rats, which were associated with the occurrence of ED.[13]

Epidemiologic studies have revealed the associations between SUA and sexual hormone levels as well as ED, but studies from different populations in different regions are still heterogeneous. A study for Russian gout patients found that high SUA could inhibit the secretion of testosterone and E2.[14] However, Wang and Charchar reported no significant association between SUA and E2 in the US adolescent population.[15] At present, the effect of SUA on male sexual hormones as well as ED is mostly reported by studies of patients with specific diseases, such as hypertension and diabetes, which limits the generalization of the findings. To the best of our knowledge, no previous study has investigated the causal relationships between SUA and male sexual hormones as well as ED using genetic data.

Mendelian randomization (MR) uses genetic variants randomly distributed in population, which mirror the different disease risk due to exposure factors.[16] The principle of MR is based on Mendel's second law of independent assortment, when DNA is transmitted from parents to offspring at gamete formation.[17] Individuals with or without some genetic variants were followed up to observe the relevant health outcomes and analyze the influence of genetic variants on the disease risk, which is similar to random assignment in randomized controlled trials.[18]

Hence, we could select certain genetic variants as instrument variables (IVs), such as single-nucleotide polymorphisms (SNPs) highly associated with exposure factors, and assess the risk of outcomes in individuals possessing these IVs. The causal estimates could be obtained from dividing the IVs-outcome association by the IVs-exposure association, which is also called *Wald estimates*.[17] By summarizing multiple Wald estimates from different SNPs via specific methods, we could infer the causal relationship between exposure and outcome. As compared with observational studies, MR studies have significant advantages, including the large sample size and the ability to minimize the impact of confounding factors, thus providing convincing evidence about the causal effect of risk factors on diseases from genetic data. In this study, we conducted a bidirectional 2-sample MR analysis on large-scale genome-wide association studies (GWASs) to investigate the causal associations between SUA and male sexual hormones as well as ED. In addition, we performed multivariate MR (MVMR) and mediation analysis to minimize bias due to potential confounders and investigate whether any factors mediated the causal effect.

Methods

Study design

In this study, we used a 2-sample MR analysis to explore the relationship between SUA and male sexual hormones as well as ED. In MR analysis, SNPs associated with exposure were selected as IVs, and 3 assumptions should be fulfilled: (1) IVs are highly associated with exposure ($P < 5 \times 10^{-8}$); (2) IVs are not associated with confounders of outcomes; (3) IVs are not themselves associated with outcomes.[19]

First, univariate MR (UVMR) analysis was used to estimate the causal effects of SUA on male sexual hormones (SHBG, testosterone, E2, FSH, LH) and ED. Second, bidirectional UVMR analysis was performed to evaluate the reverse causation effect of male sexual hormones and ED on SUA. Third, MVMR analysis was conducted to adjust for confounding factors on the causal relationship. Finally, we performed 2-step MR analysis to investigate if any mediator causally mediated the connection. A detailed flowchart summarizes the study design (Figure 1). All data were publicly available and from populations of European ancestry. The study followed the STROBE-MR reporting guidelines (Strengthening the Reporting of Observational Studies in Epidemiology–Mendelian Randomization).[20]

Data source

Genetic variants associated with SUA were obtained by the IEU Open GWAS data sets (https://gwas.mrcieu.ac.uk) of 437 354 individuals with 4 231 909 SNPs. Summary data sets for SHBG and testosterone were from the study by Leinonen et al, with individuals from the UK Biobank and FinnGen (N = 625 650) and SNPs of 17 239 131.[21] GWAS data on E2 were derived by Pott et al, with populations from the LIFE-Adult and LIFE-Heart cohorts, with a sample size of 13 369 and a number of SNPs of 1 037 249.[22] The genetic data of FSH and LH were derived from healthy blood donors in the INTERVAL study, which could be obtained by the IEU Open GWAS data sets.

Data related to ED were from a recent GWAS meta-analysis of 3 cohorts (the Partners HealthCare Biobank, Estonian Genome Centre of the University of Tartu, and the UK Biobank), with a total of 223 805 individuals.[23] The details are presented in Table S1.

IV selection

The study first selected SNPs highly associated with SUA level based on the threshold of $P < 5 \times 10^{-8}$ to reach genome-wide significance. When the reverse analysis was conducted, a more liberal P value threshold of 5×10^{-5} was applied for the IV selection for E2, FSH, LH, and ED, since there were few SNPs highly associated with them.[24] Subsequently, aggregation was performed with stringent criteria ($r^2 < 0.001$, kb = 10 000) to screen out SNPs containing linkage disequilibrium. Then we excluded SNPs pleiotropically associated with the common confounding factors (type 2 diabetes, hypertension, hyperlipemia, obesity, and smoking) through PhenoScanner Pheno Scanner V2.[20] In addition, the F statistics of all SNPs were calculated to evaluate the validity of IVs, with the formula $F = R^2 \times (N - 2) / (1 - R^2)$.[25]

Before the MR analysis, radial MR and MR-PRESSO (MR pleiotropy residual sum and outlier) were applied to test and exclude possible outlier SNPs. Finally, the exposure and outcome data sets were merged for the MR analysis.[19]

Statistical analysis

This study used 5 methods to investigate the relationship between SUA and male sexual hormones as well as ED: inverse variance weighted (IVW), MR Egger, weighted median,

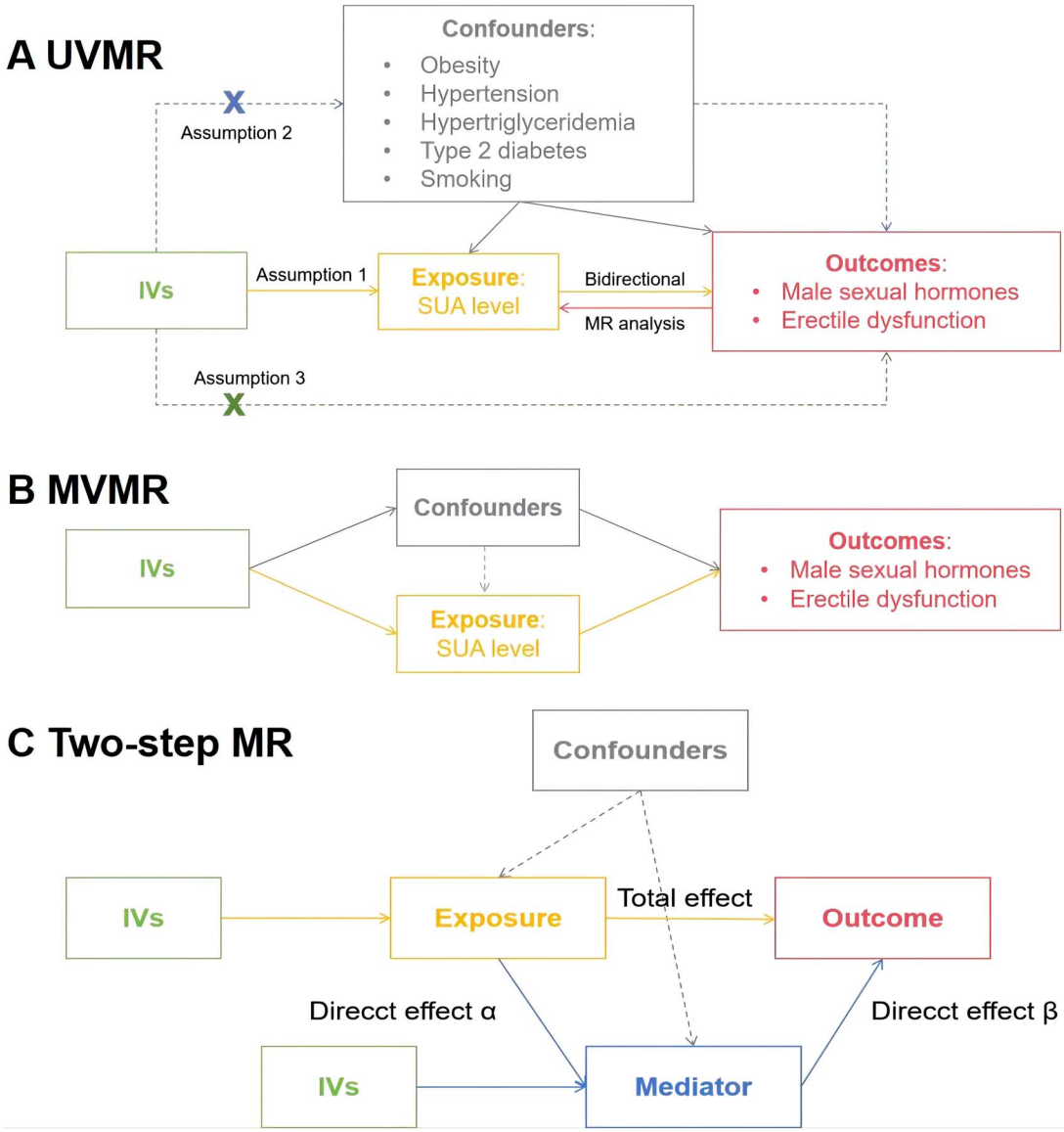

Figure 1. Study flow graph. Schematic representations: (A) univariate mendelian randomization analysis, (B) multivariate mendelian randomization analysis, and (C) 2-step mendelian randomization analysis. IVs, instrumental variables.

weighted mode, and simple mode. The IVW method is the primary one for MR analysis, which combines the Wald ratio estimates for all IVs. If heterogeneity exists, a random effect model is used; otherwise, a fixed effect model is adopted.[26] The MR Egger and weighted median methods are used to supplement the IVW method, testing the robustness of the conclusions when pleiotropy exists. In addition, we adopted the weighted mode method to obtain the smaller bias under a limited sample size. The simple mode method could group SNPs based on whether the estimated causal effect is similar.

The MVMR analysis was conducted to confirm the causal relationship between SUA and male sexual hormones as well as ED.[27] In addition, mediation analysis was conducted to investigate if any mediator causally mediated the association. Three estimates were performed for mediation analysis: the total effect of SUA on the outcome, the direct effect α of SUA on the mediator, and the direct effect β of the mediator on the outcome. Mediation effect could be calculated by the following equation: mediation effect = $\alpha \times \beta$. The proportion of the mediation effect was also estimated as the total causal effect of SUA on the outcome divided by the mediation effect.

The heterogeneity test of IVs is implemented through the Cochran Q test, and the pleiotropy is tested via the MR Egger intercept method. In addition, the leave-1-out method is used as a sensitivity analysis to check whether the results are robust by calculating the combined effect of the remaining SNPs after excluding each SNP in turn. In addition, the symmetry of the funnel plot is observed to check the stability of the results.

All statistical analysis was performed with R (version 4.1.2). The R packages "TwoSampleMR" and "MendelianRandomization" were used for MR analysis and plotting. The significance level α was set at 0.05.

Results

IV selection

The study first found 325 SNPs strongly associated with SUA from the GWAS database as the exposure. Subsequently, 9

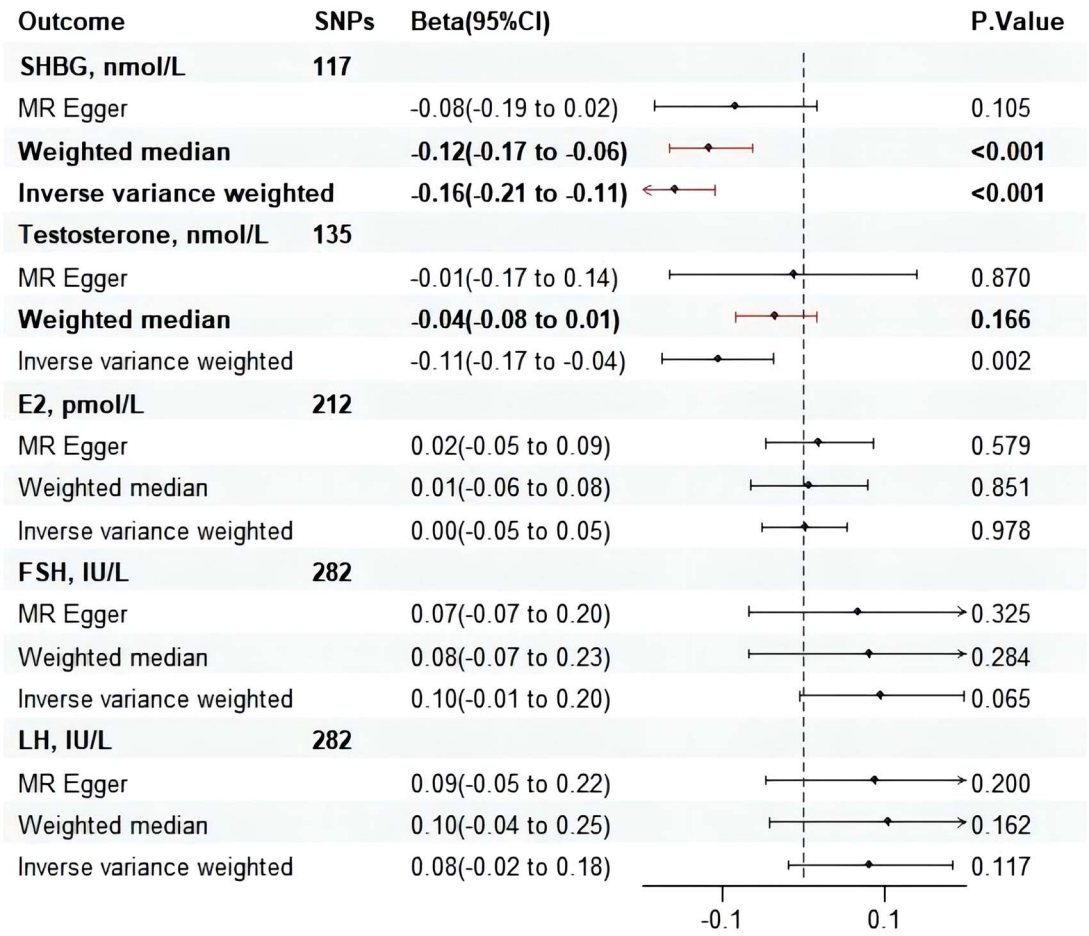

Figure 2. Causal relationship between serum uric acid and sexual hormone levels.

SNPs with linkage disequilibrium were screened out. After SNPs associated with the confounding factors as well as the outliers were excluded, the numbers of SNPs finally included were as follows: 117, 135, 212, 282, and 282 SNPs as IVs for SHBG, testosterone, E2, FSH, and LH, respectively, and 284 SNPs for ED. Furthermore, 87, 76, 15, 23, 39, and 25 SNPs strongly associated with SHBG, testosterone, E2, FSH, LH, and ED were identified as IVs for the reverse MR analysis (Tables S2-S8). All IVs had F values >10.

UVMR analysis

Overall, a negative causal relationship was found between SUA and SHBG as well as testosterone, while SUA had no significant causal effect on E2, FSH, and LH. As shown in Figure 2, results from the IVW method showed that SUA had a negative causal effect on SHBG levels ($\beta = -0.16$; 95% CI, −0.17 to −0.04; $P = 1.04 \times 10^{-10}$). The Cochran Q test yielded $P < .05$, indicating the presence of heterogeneity; thus, the random effect model was adopted. The MR Egger intercept test resulted in $P = .109 > .05$, which excluded the presence of pleiotropy. The other 4 methods were used to supplement the results of the IVW method (Figure S1). Results of the weighted median ($\beta = -0.12$, $P = 1.04 \times 10^{-5}$), simple mode ($\beta = -0.14$, $P = 6.34 \times 10^{-3}$), and weighted mode ($\beta = -0.10$, $P = 5.40 \times 10^{-4}$) were consistent with the IVW method, which further validated the causal relationship between SUA and SHBG levels (Table S9).

For testosterone levels, we found a negative causal relationship between SUA and testosterone levels ($\beta = -0.11$; 95% CI, −0.17 to −0.04; $P = 2.16 \times 10^{-3}$). The Cochran Q test indicated the presence of heterogeneity, and the MR Egger test showed that there was no horizontal pleiotropy in the study results ($P = .187$).

In addition, SUA displayed no significant causal association with E2, FSH, and LH levels (Figure 2). Results from the other 4 analysis methods also did not find a significant causal effect of SUA on the 3 hormones (Table S9). The Cochran Q test and MR Egger test yielded $P > .05$, indicating that there was no heterogeneity or pleiotropy in the MR analysis.

The leave-1-out analysis was used for sensitivity analysis (Table S10). No outliers were found to drive a significant impact on the causal association estimates. In addition, the funnel plot confirmed that there were no outliers leading to an increase in pleiotropy for the MR analysis (Figure S2).

Figure 3 showed a positive causal association between SUA and ED by MR analysis (odds ratio, 1.10; 95% CI, 1.02-1.19; $P = .018$). Heterogeneity and horizontal pleiotropy tests resulted in $P > .05$ (Table S9), and sensitivity analysis demonstrated that there were no SNPs with a significant impact on the results among 284 IVs included (Figure S2).

Reverse MR analysis

We conducted a reverse MR analysis to assess the causal effect of male sexual hormones and ED on SUA levels (Figure 4).

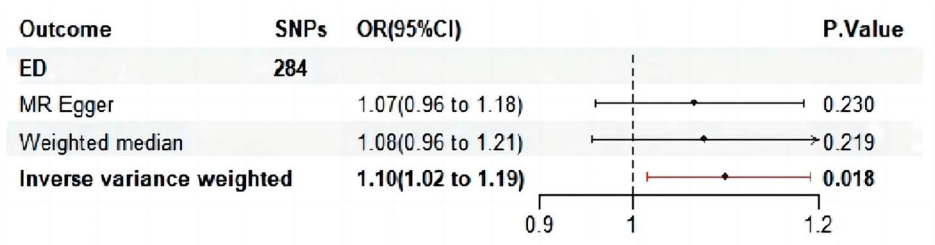

Figure 3. Causal relationship between serum uric acid level and erectile dysfunction.

Table 1. Genetic prediction of the causal relationship between serum uric acid levels and male sexual hormones as well as ED by multivariate mendelian randomization analysis.

Outcome	SNPs	β (95% CI)	*P* value
SHBG	217	–0.094 (–0.141, –0.047)	9.67×10^{-5}
Testosterone	217	–0.051 (–0.087, –0.015)	5.72×10^{-3}
Estradiol	217	–0.031 (–0.079, 0.017)	.206
FSH	218	0.046 (–0.058, 0.150)	.391
LH	218	0.074 (–0.033, 0.181)	.174
ED	218	0.976 (0.904, 1.053)[a]	.523

Abbreviation: ED, erectile dysfunction; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone–binding globulin; SNP, single-nucleotide polymorphism. [a]Odds ratio (95% CI) for ED.

The increase in SHBG ($\beta = -0.06$; 95% CI, –0.09 to –0.02; $P = 4.82 \times 10^{-4}$) and E2 levels ($\beta = -0.04$; 95% CI, –0.07 to –0.00; $P = .037$) could significantly reduce SUA levels. In addition, the weighted median method showed consistent results. The simple mode method demonstrated a significant causal relationship between testosterone and SUA levels ($\beta = -0.08$; 95% CI, –0.15 to –0.00; $P = .044$). However, no significant effects of FSH, LH levels, and ED on SUA were observed (Table S11).

MVMR analysis

MVMR analysis was conducted to adjust for confounding factors (type 2 diabetes, hypertension, hyperlipidemia, obesity, smoking), and the results are shown in Table 1. After adjusting for potential risk factors, causal relationships between SUA and SHBG as well as testosterone levels were weakened but still significant (SHBG, $\beta = -0.094$, $P = 9.67 \times 10^{-5}$; testosterone, $\beta = -0.051$, $P = 5.72 \times 10^{-3}$). However, the significant causal relationship between SUA and ED disappeared. In addition, no significant causal relationships were found between SUA and E2, FSH, and LH levels (Table S12).

Mediation analysis

We further explored the potential mediating role of SHBG in the association between SUA and testosterone levels, since SHBG could bind to testosterone and it affects testosterone levels (Table 2). SUA has negative causal relationships with testosterone and SHBG levels. Moreover, we conducted an MR analysis between SHBG and testosterone levels (Table S13). Given these results, we calculated the mediation effect of SHBG on the causal relationship between SUA and testosterone levels as –0.104 (95% CI, –0.135 to –0.073), with a proportion of 98.1%. This suggested that the effect of SUA on testosterone levels might be mainly mediated by changes in SHBG levels.

Discussion

In this study, we investigated the causal relationship between SUA and male sexual hormones as well as ED using genetic data for the first time. The results showed a causal relationship between increased SUA and decreased SHBG, which mediated the decrease of the testosterone level. Yet, the increase in SHBG and E2 could significantly reduce SUA levels. No significant causal effect of SUA on E2, FSH, and LH levels was observed. Moreover, there may be a causal relationship between SUA and ED, but further research is needed.

We first found a bidirectional causal relationship between SUA and SHBG levels by UVMR analysis. A large cross-sectional study reported that SHBG in adolescents is negatively correlated with uric acid, which was also observed in diabetic men.[15,28] The mechanism might be that intracellular uric acid reduces SHBG production by inactivating adenosine monophosphate–activated protein kinase or reducing endothelial nitric oxide synthase activity and leading to hyperinsulinemia.[29] In addition, clinical studies suggested that SUA might trigger oxidative stress and tissue damage, which cause the release of inflammatory cytokines tumor necrosis factor α and interleukin 1β, decreasing the production of SHBG.[30] However, studies have demonstrated that a low level of SHBG is related to alterations in several features of metabolic syndrome.[31] As part of the metabolic syndrome, hyperuricemia is likely to be affected by SHBG. Moreover, SHBG is the main transport protein for testosterone and E2, modulating their biological activity; thus, it is considered to exert an indirect effect on SUA by regulating the levels of sexual hormones such as E2.[32]

In this study, MR analysis revealed that there was a negative causal relationship between SUA and testosterone levels, where SHBG was mediating the pathway. A survey of 7796 males in the United States found a significant negative correlation between SUA and total testosterone levels, which well supported our conclusion.[33] It is believed that the increase in SUA could lead to metabolic syndrome and insulin resistance, increasing the testosterone converted to E2 and decreasing testosterone production by Leydig cells.[34-37] In this study, we suggested that high SUA could decrease the level of SHBG, which binds to testosterone with high affinity, causing the decrease of the testosterone level.[38] Epidemiologic studies reported that total testosterone was negatively correlated

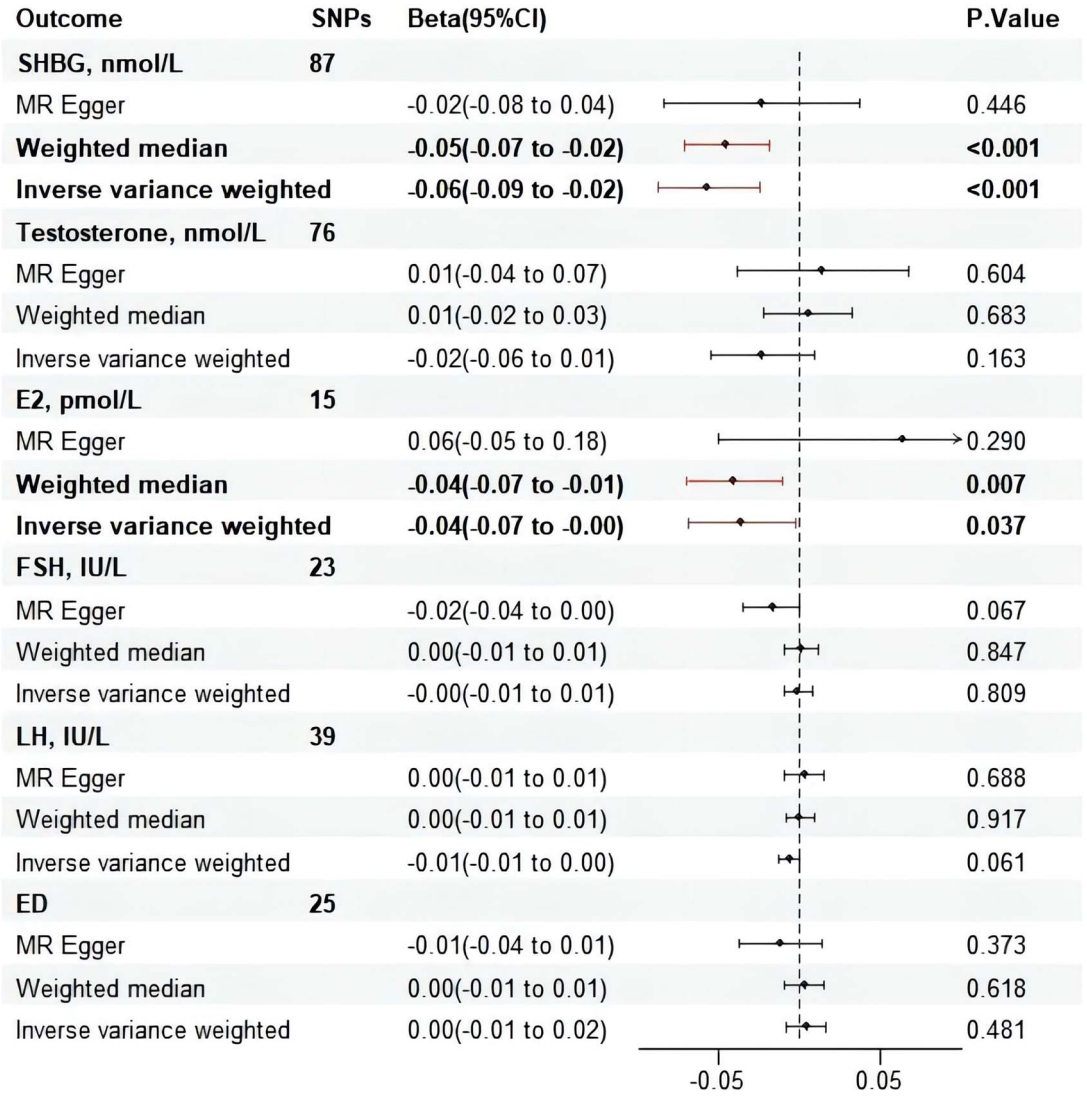

Figure 4. Reverse causal effect of sexual hormone levels and erectile dysfunction on serum uric acid levels. Odds ratio for erectile dysfunction is shown in the figure.

Table 2. Mediation effect of SHBG in the causal relationship between SUA and testosterone levels.

Effect[a]	*β*	SE	*P* value
Total[b]	–0.106	0.035	.002
Direct *α*[c]	–0.159	0.025	<.001
Direct *β*[d]	0.654	0.016	<.001
	Effect size	**95% CI**	**Proportion (%)**
Mediation[e]	–0.104	–0.135, –0.073	98.1

Abbreviation: MR, mendelian randomization; SHBG, sex hormone–binding globulin; SUA, serum uric acid. [a]Exposure: SUA. Mediator: SHBG. Outcome: testosterone. [b]The causal effect of SUA on testosterone in MR analysis. Beta of inverse variance weighted method was used for mediation analysis. [c]The causal effect of SUA on SHBG in MR analysis. [d]The causal effect of SHBG on testosterone in MR analysis. [e]The effect of SUA on testosterone mediated through SHBG.

with SUA and positively correlated with SHBG in overweight men, which is consistent with the findings in our study.[39] A clinical study also revealed the positive correlation between SHBG and total testosterone levels in male patients with hypogonadism.[40] The mechanism might be related to the hypothalamic-pituitary feedback or the prolongation of the circulating half-life of the ligand.[41]

We found that SUA did not have a significant causal effect on E2, while reverse MR analysis showed that E2 had a negative causal relationship with SUA levels. At present, the relationship between SUA and E2 is controversial. Clinical studies revealed that high E2 levels might be a protective factor for hyperuricemia, which is consistent with our results.[42] E2 could increase the sensitivity to insulin, thereby promoting the resecretion of uric acid in the renal tubular epithelial, increasing the urinary excretion and lowering the SUA level.[43] However, some observational studies failed to find a significant correlation between SUA and E2 levels.[44] The reason might be that high SUA feedback regulates hormone secretion in the hypothalamus, thus reducing the production of testosterone

and estrogen.[45] In a word, we should focus on the decrease of E2 level in men, which could increase their SUA level, thereby reducing SHBG and testosterone levels and triggering ED disease.

We found no significant causal relationship between SUA and FSH and LH levels, which could assist in testosterone synthesis. Patients with gout had lower levels of FSH and LH.[46] However, FSH is negatively correlated with the SUA level in male patients with diabetes, while LH is positively correlated with SUA in female patients who are postmenopausal.[44] The controversial results might be due to potential factors associated with different populations.

In this study, we found that SUA could increase the risk of ED by UVMR, while the significance disappeared when conducting MVMR. Interestingly, there exists a controversy regarding their relationship in observational studies. Salem et al reported that SUA significantly increased in patients with ED, as also observed in a meta-analysis.[47,48] However, hyperuricemia was not considered an independent predictor of ED in a cross-sectional study.[49] Actually, the conclusions of observational studies might be biased when not corrected for essential confounders. A number of potential risk factors have recently been proposed for ED and could be confounders for the causal relationship estimate, which should be considered in future observational studies.[25] In addition, given the causal effect of SUA on testosterone, we speculated that there should exist a causal relationship between SUA and ED. As reported by Onyeji and Clavijo, ED occurred when testosterone decreased and reached a certain threshold.[50] Therefore, we believed that the relationship between SUA and ED might be nonlinear; thus, the current MR analysis did not find the direct causal effect.[51] In addition, given the causal relationship that exists between SUA and sexual hormones such as testosterone and E2, we speculated that it was particularly important to pay more attention to SUA and E2 levels when considering the therapy for men who were hypogonadal, especially patients with ED.[52]

Admittedly, there are some limitations of our study. Data were all from European populations, which somewhat limits the generalization of the findings to other populations. Moreover, there might be some crossover among samples that detected SUA, sexual hormone levels, and ED, which might cause the models to be overfitted and reduce the strength of causal inference.[53] Nevertheless, the *F* statistics of SNPs used for MR analysis were >10; thus, the bias was not very noticeable.

Conclusions

This study provided genetic evidence for the causal relationship between SUA and male sexual hormones (SHBG, testosterone, and E2). Given the causal effect of SUA on the testosterone level, we must focus on the SUA and E2 levels in men, especially in patients with hypogonadism and ED. Moreover, accurate raw data from individuals were needed for a better understanding of the relationship between SUA and ED.

Acknowledgments

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Author contributions

B.W., H.C., W.-D.F., and Z.-X.G. conceived and designed the analysis. H.C., W.-D.F., J.-L.F., and C.Z. performed the analysis. H.C. and W.-D.F. wrote the manuscript. J.-L.F. and B.W. reviewed the manuscript.

Supplementary material

Supplementary material is available at *Sexual Medicine* online.

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Conflicts of interest

None declared.

Data availability

The data for this study were sourced from publicly available archives and former investigative studies.

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