BMJ Open

Cross-sectional study on the association between serum uric acid levels and the risk of benign prostatic hyperplasia

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To cite: Hua T, Zheng S, Ding J, *et al*. Cross-sectional study on the association between serum uric acid levels and the risk of benign prostatic hyperplasia. *BMJ Open* 2025;**15**:e092844. doi:10.1136/bmjopen-2024-092844

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-092844).

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Received 24 August 2024
Accepted 05 March 2025

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ABSTRACT

Objective Serum uric acid (SUA), a non-protein antioxidant, exerts anti-inflammatory and antioxidative stress effects. This study aimed to investigate the association between SUA levels and the risk of benign prostatic hyperplasia (BPH).

Methods This cross-sectional study included 48 653 adult men who underwent health checkups at the Health Examination Center of the Affiliated Hospital of Yangzhou University in 2022. Data on demographics, clinical history and laboratory parameters were collected. Multivariable logistic regression models were used to analyse the relationship between SUA levels and BPH risk, with further exploration in different subgroups.

Results Logistic regression analysis revealed a significantly decreased risk of BPH among participants in the highest SUA quartile (Q4) compared with those in the lowest quartile (Q1) (fully adjusted OR=0.83, 95% CI: 0.78 to 0.90, p<0.0001). Subgroup analyses demonstrated that this inverse association was more pronounced in subgroups of age>60 years (Q4: OR=0.77, 95% CI: 0.68 to 0.87, p<0.0001), non-obesity (Q4: OR=0.81, 95% CI: 0.75 to 0.87, p<0.0001), without non-alcoholic fatty liver disease (NAFLD) (Q4: OR=0.81, 95% CI: 0.73 to 0.89, p<0.0001), hypertension (Q4: OR=0.81, 95% CI: 0.74 to 0.89, p<0.0001) and without diabetes (Q4: OR=0.84, 95% CI: 0.78 to 0.90, p<0.0001). Curve fitting revealed that higher SUA levels were associated with a lower risk of BPH even in the presence of increased BPH risk factors such as diabetes and hypertension.

Conclusions This study demonstrates a significant inverse association between SUA levels and BPH risk, particularly in subgroups of older age, non-obesity, absence of NAFLD, hypertension and absence of diabetes. This suggests a potential protective role of SUA in BPH development, highlighting the potential value of maintaining SUA levels within a reasonable range for BPH prevention.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Large sample size (n=48 653) provides robust statistical power for analysis.
⇒ Comprehensive adjustment for multiple confounding factors through two distinct models.
⇒ Subgroup analyses explore effect modifications by key variables (age, obesity, etc).
⇒ Cross-sectional design cannot establish causality between serum uric acid levels and benign prostatic hyperplasia.
⇒ Study population limited to health examination centre visitors may introduce selection bias.

INTRODUCTION

Benign prostatic hyperplasia (BPH), an age-associated disease, is experiencing a rising prevalence among elderly men due to the escalating global ageing population. BPH typically manifests as prostate enlargement and accompanying lower urinary tract symptoms (LUTS), including difficulty urinating, frequent night-time urination and interrupted urine flow, severely impacting patients' quality of life and psychological well-being. While the pathogenesis of BPH remains incompletely understood, earlier research has identified several potential risk factors, including age, genetic predisposition, hormonal imbalances, chronic inflammation, lifestyle, oxidative stress, and metabolic disorders.[1 2]

Serum uric acid (SUA), the primary non-protein antioxidant in human blood,[3] has attracted significant research interest due to its fluctuating levels. Previous studies have extensively explored the strong association between elevated SUA levels and various metabolic diseases such as cardiovascular diseases, diabetes, hypertension, obesity and non-alcoholic fatty liver disease (NAFLD).[4 5] Furthermore, recent studies have indicated a close association between changes in SUA levels and urological diseases. In patients with BPH, SUA levels are positively correlated with the International Prostate Symptom Score and prostate-specific antigen (PSA), and negatively correlated with the free/total PSA ratio. This suggests that SUA levels may influence the severity of LUTS and prostate-specific biomarkers.[6] In recent years, hyperuricaemia has been recognised as an independent cardiovascular risk factor

and a significant marker of inflammation and oxidative stress.[7 8] Notably, inflammation and oxidative stress are widely recognised as key pathophysiological mechanisms driving BPH progression, sharing comorbidities with various metabolic diseases.[9 10]

Although existing studies have investigated the association between SUA levels and BPH risk, the current evidence remains insufficient to establish a definitive interaction between them. Some studies have yielded conflicting results, hindering the formation of a consensus.[11–13] To further explore the potential link between SUA levels and BPH risk, this study uses a large population-based sample to uncover the association between SUA and BPH, providing more comprehensive evidence supporting the protective role of SUA levels in BPH pathogenesis. Furthermore, by delving into the role of SUA in BPH development, we aim to explore novel preventive and therapeutic strategies targeting SUA regulation, thereby advancing the clinical management of BPH and improving patients' quality of life.

METHODS

Study population

This cross-sectional study investigated the association between SUA level and BPH. The study was conducted at the Health Examination Center of the Affiliated Hospital of Yangzhou University between January 2022 and December 2022. The study population consisted of all adult males (n=49 087) who participated in a health examination during the study period. All participants underwent a comprehensive health checkup, including prostate health assessments and blood biochemical examinations. As this was a retrospective study, informed consent was not required. Exclusion criteria included lack of liver and kidney ultrasound imaging (n=46), history of prostatectomy and transurethral resection of the prostate (n=222), patients with liver surgery (n=53), individuals under 18 years old (n=28) and missing SUA data (n=85). Finally, 48 653 eligible adult men were included in the study, as shown in figure 1.

Diagnostic criteria

Ultrasound was used to diagnose BPH, NAFLD and urolithiasis in this study (using an abdominal convex array probe, frequency: 3.5–5 MHz, LOGIQ E9, GE, USA). All ultrasound examinations and diagnoses were conducted by experienced ultrasonographers with over 5 years of experience, combined with medical history, chief complaints and other comprehensive judgements. The results were reviewed by another ultrasonographer. Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

The definition of BPH has changed significantly over the past 20 years, and it varies among researchers such as clinicians, pathologists and pharmaceutical companies. For pathologists, BPH is a microscopic diagnosis, specifically described as proliferation of prostatic stroma and epithelial cells; while for radiologists or clinicians, it can be diagnosed as benign prostatic enlargement (BPE) by ultrasound or three-dimensional imaging; and for urodynamics, elevated urinary pressure and low urinary flow rate are described as bladder outlet obstruction.[14] Since the subjects in this study were from a health examination population, they did not have the conditions for microscopic diagnosis. Therefore, this study used ultrasound to obtain clear images of the prostate in both transverse

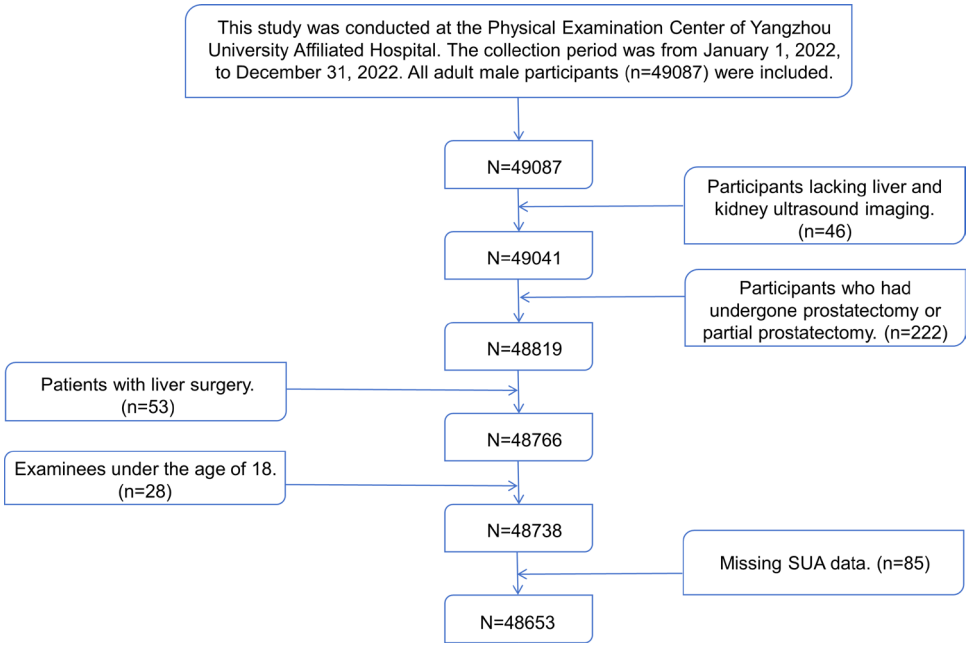

Figure 1 Flow chart of the participant screening process. The flow chart visually depicts the screening process for participants in the study. SUA, serum uric acid.

and sagittal planes, and measured and recorded its length, width and anteroposterior diameter. The volume was calculated using the ellipsoid volume formula (length×width×anteroposterior diameter×0.52). There is no consensus on how much prostate volume can be defined as BPE. Generally, a prostate volume of less than 20 cm^3 is considered normal; a volume of more than 30 cm^3 may be related to LUTS and the risk of BPH progression, suggesting possible prostatic hyperplasia.[14] Furthermore, a curve-fitting analysis (online supplemental figure 1) demonstrated a general trend of decreasing prostate volume with increasing SUA levels.

Urolithiasis was diagnosed by the presence of echogenic solid points and clusters in the kidney, ureter or bladder. The ultrasound diagnostic criteria for NAFLD were enhanced ultrasound echo signals in the near field of the liver, decreased structural clarity of the intrahepatic duct and echo attenuation in the far field of the liver.[15 16]

Participants were considered hypertensive if their blood pressure was ≥140/90 mm Hg or if they were receiving antihypertensive treatment. A history of diabetes mellitus included those taking antidiabetic medications or having a fasting blood glucose level of >7 mmol/L. Obesity was diagnosed with a body mass index (BMI) ≥28 kg/m^2.

Laboratory tests

Blood samples were collected from all participants in the morning after at least 12 hours of overnight fasting. Collected venous blood samples were used for comprehensive biochemical analyses, including liver function indices: aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), renal function indicators such as creatinine (SCR), estimated glomerular filtration rate (eGFR), lipid indicators including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), etc. SUA, blood glucose (GLU), total protein (TP), platelet count (PLT), globulin (GLO), etc, were also measured. eGFR was estimated from SCR levels, sex and age using the CKD-EPI equation.

$eGFR = 141 \times \min(Scr/k,1)^{\alpha} \times \max(Scr/k,1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female], k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males.

The determination of laboratory data used a fully automatic biochemical analyser (C16000, Abbott Laboratories, USA), ensuring that all experimental operations were carried out in accordance with the manufacturer's specifications and that the equipment was calibrated before the experiment to ensure accuracy.

Prior to blood sample analysis, all samples were stored at 4°C to ensure the stability of biochemical indicators. Before biochemical testing, the samples were preheated at a constant temperature (37°C) for 20 min to eliminate the possible impact of sample refrigeration on the measurement results. The results of laboratory tests were subjected to quality control according to international standards and operating procedures to ensure standardisation and comparability of the experimental results.

Statistical analysis

Statistical analysis was performed using EmpowerStats (V.4.1, www.empowerstats.com) and R software (V.4.0.2). Baseline characteristics of the study population are presented as mean±SD and frequency (percentage) to accommodate different types of data. To ensure the reliability and accuracy of the results of this study, we used a multivariate logistic regression model to analyse the relationship between SUA levels and the risk of BPH. Previous studies have suggested that liver function may play an important role in uric acid metabolism. To control for potential confounding factors, this study included relevant examination indicators for analysis.[17] Renal function is related to the effect of the kidneys on the handling of chemicals in the body. Therefore, this study simultaneously considered age, BMI, hypertension, diabetes and related GLU levels, ultrasound and assessment indicators related to liver function health (ALT, AST, GGT, PLT, etc), renal function indicators (SCR, eGFR, etc), lipid levels reflecting metabolism (TC, TG, HDL, LDL, etc) and body nutrition and immune status indicators (TP, GLO, etc) as possible confounding factors. SUA levels were divided into quartiles, with the lowest quartile (Q1) as the reference group for comparison analysis, to calculate the ORs and their 95% CIs for BPH in the other groups.

To ensure the accuracy of the analysis, the study began with a screening of covariates, including descriptive statistical analysis to determine the distribution of each variable. Covariates were selected based on the following criteria: to examine all potential covariates, we examined the effect of each variable on the model one by one. Specifically, we removed one variable from the full model or added one variable to the basic model at a time, and assessed the change in the coefficient of the exposure variable. If the coefficient of the exposure variable deviated by more than 10% after removing or adding a certain variable, we considered that the variable might be a confounding factor and had a greater impact on the results, and thus was retained in the final model, as detailed in online supplemental table 1. Using the above method, combined with the analysis of preliminary data and professional knowledge, while excluding multicollinearity variables, two models of confounding factors that need to be adjusted were established. Model I: age, obesity, diabetes, NAFLD and hypertension; Model II: SCR, eGFR, PLT, AST/ALT, as well as age, obesity, diabetes, NAFLD and hypertension. At the same time, considering the different characteristics of the population, subgroup analysis, interaction tests and curve fitting were performed on variables such as age, obesity, diabetes, hypertension and NAFLD to further explore the possible effects of these factors on the relationship between the risk of BPH and SUA levels. Multiple imputation (MI) was performed on the population with missing data, and the main text presents the analysis results of the original data.

The data after MI processing were subjected to sensitivity analysis, as detailed in online supplemental table 2. All statistical tests were two-sided, and a p value<0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the study population

The baseline characteristics of the study population stratified by SUA quartiles are presented in table 1. With increasing SUA quartiles, we observed a statistically significant decreasing trend in HDL and eGFR (p<0.001), while the prevalence of metabolic diseases (urolithiasis, NAFLD, obesity, diabetes and hypertension) increased (p<0.001). Notably, the prevalence of BPH decreased significantly with increasing SUA levels, from 34.41% in Q1 to 21.82% in Q4 (p<0.001).

Table 2 presents the comparison between participants with and without BPH. The BPH group was characterised by higher mean age and systolic blood pressure, along with significantly lower mean SUA levels compared with the non-BPH group (372.28±81.41 vs 392.24±82.51 µmol/L, p<0.001).[18] Additionally, the BPH group showed higher prevalence of diabetes and urolithiasis, consistent with previous studies linking BPH with metabolic disorders.[19 20]

Association between SUA and BPH

Table 3 shows the association between SUA and BPH risk across SUA quartiles. In the unadjusted model, higher SUA levels were associated with progressively lower odds of BPH, with the strongest negative association observed in Q4 (OR=0.53, 95% CI: 0.50 to 0.56, p<0.0001). After adjusting for confounders in Model II, this inverse association persisted, with Q4 showing the most significant reduction in BPH risk (OR=0.83, 95% CI: 0.78 to 0.90, p<0.0001). These results suggest that elevated SUA levels are associated with reduced BPH risk, even after accounting for important confounding factors.

Subgroup analysis

To investigate potential effect modifications, we performed subgroup analyses by age, obesity, diabetes, hypertension and NAFLD (table 4). The inverse association between SUA and BPH risk was more pronounced in individuals older than 60 years (Q4: OR=0.77, 95% CI: 0.68 to 0.87, p<0.0001), non-obese individuals (Q4: OR=0.81, 95% CI: 0.75 to 0.87, p<0.0001), those with hypertension (Q4: OR=0.81, 95% CI: 0.74 to 0.89, p<0.0001) and those without NAFLD (Q4: OR=0.81, 95% CI: 0.73 to 0.89, p<0.0001).

Interestingly, while the non-diabetic group showed a consistent reduction in BPH risk with increasing SUA levels, the diabetic group exhibited a different pattern with a trend towards increased risk in Q3, though curve-fitting analysis (figure 2) confirmed an overall negative association between SUA and BPH risk even in diabetic individuals.

The curve-fitting analyses (figure 2) visually confirmed the negative association between SUA levels and BPH risk across all subgroups. Notably, in individuals younger than 40 years (figure 2), where BPH prevalence was low, the association appeared weaker.

DISCUSSION

This large-scale population-based study tested the hypothesis that SUA levels are associated with BPH risk. Our primary finding revealed a significant inverse correlation between SUA levels and BPH prevalence, with higher SUA levels associated with lower BPH risk. Specifically, compared with the lowest SUA quartile, the highest quartile exhibited a 17% reduced risk of BPH (OR=0.83, 95% CI: 0.78 to 0.90) after adjusting for confounders. This inverse correlation was more pronounced in individuals older than 60 years, non-obese individuals, those with hypertension and those without NAFLD or diabetes, suggesting potential effect modification by these factors.

One of the most prevalent manifestations of BPH in ageing males is LUTS. A recent large-scale Korean study indicated that elevated SUA levels are associated with a reduced risk of LUTS, suggesting a potential suppressive effect of SUA on LUTS development.[13] The precise pathogenesis of BPH remains elusive, but factors like age, hormonal fluctuations, chronic inflammation, oxidative stress and metabolic disturbances are implicated in its pathology.[4] Studies have shown an inverse correlation between SUA and androgen levels, hinting at a possible role of SUA in the onset and progression of BPH.[21] SUA, the end product of purine metabolism, is linked to various metabolic disorders, including metabolic syndrome and diabetes.[22] While it can contribute to cardiovascular diseases by stimulating the renin-angiotensin system,[23] its potent antioxidant properties have also been recognised for potentially mitigating oxidative stress-related diseases.[24]

The role of SUA in the prostate, particularly in the context of prostate cancer, has been a subject of ongoing debate. A Mendelian randomisation study suggested a potential causal link between high SUA levels and increased prostate cancer risk.[25] Conversely, Lee *et al* demonstrated a 'J-shaped' relationship between SUA and prostate cancer mortality during androgen deprivation therapy.[26] A meta-analysis of 24 articles further indicated that high SUA levels might be positively correlated with the risk of male cancers.[27] However, a US population-based study reported a negative association between SUA and BPH risk, highlighting SUA as a potential protective factor.[12] This protective effect is further supported by research highlighting the antioxidant properties of SUA as a possible basis for its anticancer activity.[28]

Evidently, the findings regarding SUA's role in prostate disease are complex and often contradictory. From being considered a risk factor for prostate cancer to a potential protective agent against BPH, the role of SUA seems to vary across populations. While initial research

Table 1 Study population characteristics according to SUA classification

Variables	Q1 (n=12 155)	Q2 (n=12 147)	Q3 (n=12 172)	Q4 (n=12 179)	P value
AGE (years)	53.22±14.87	49.87±14.82	47.94±14.63	46.42±15.29	<0.001
SBP (mm Hg)	131.08±18.64	129.98±17.68	130.58±17.43	131.90±17.37	<0.001
DBP (mm Hg)	81.19±11.27	81.54±11.22	82.53±11.18	83.76±11.72	<0.001
BMI (kg/m^2)	24.13±3.10	24.88±3.10	25.56±3.19	26.56±3.42	<0.001
WAIST (cm)	84.85±8.43	86.76±11.72	88.23±8.35	90.80±8.58	<0.001
ALT (U/L)	26.52±28.93	29.28±23.37	32.97±27.15	39.97±36.16	<0.001
AST (U/L)	22.76±16.55	23.30±11.09	24.43±12.72	27.01±19.95	<0.001
AST/ALT	1.05±0.51	0.98±0.59	0.92±0.41	0.87±0.49	<0.001
GGT (U/L)	33.33±38.68	36.94±37.87	41.87±40.17	50.22±48.41	<0.001
PLT (×10^9/L)	209.69±56.55	215.06±55.38	218.69±55.00	225.82±58.34	<0.001
GLO (g/L)	28.47±4.08	28.67±4.15	28.92±3.97	29.50±4.16	<0.001
GLU (mmol/L)	6.03±2.00	5.67±1.45	5.58±1.22	5.60±1.22	<0.001
TP (g/L)	72.92±4.41	73.46±4.51	73.95±4.31	74.85±4.49	<0.001
TC (mmol/L)	4.74±0.91	4.82±0.92	4.89±0.92	5.01±0.96	<0.001
TG (mmol/L)	1.70±1.64	1.92±1.72	2.11±1.78	2.54±2.07	<0.001
HDL (mmol/L)	1.27±0.31	1.21±0.27	1.17±0.26	1.12±0.24	<0.001
LDL (mmol/L)	2.71±0.73	2.77±0.74	2.82±0.74	2.86±0.77	<0.001
SCR (µmol/L)	72.31±20.84	74.66±19.85	76.48±21.36	80.43±23.05	<0.001
EGFR (mL/min/1.73 m^2)	91.07±16.15	90.64±16.58	90.04±17.16	87.37±19.40	<0.001
UROLITHIASIS					<0.001
No	11 148 (91.72%)	11 168 (91.94%)	10 983 (90.23%)	10 808 (88.74%)	
Yes	1007 (8.28%)	979 (8.06%)	1189 (9.77%)	1371 (11.26%)	
NAFLD					<0.001
No	8775 (72.19%)	7683 (63.25%)	6380 (52.42%)	4774 (39.20%)	
Yes	3380 (27.81%)	4464 (36.75%)	5792 (47.58%)	7405 (60.80%)	
OBESITY					<0.001
No	10 905 (89.72%)	10 380 (85.45%)	9717 (79.83%)	8486 (69.68%)	
Yes	1250 (10.28%)	1767 (14.55%)	2455 (20.17%)	3693 (30.32%)	
DIABETES					<0.001
No	11 266 (92.69%)	11 735 (96.61%)	11 876 (97.57%)	11 892 (97.64%)	
Yes	889 (7.31%)	412 (3.39%)	296 (2.43%)	287 (2.36%)	
HYPERTENSION					<0.001
No	6807 (56.00%)	7015 (57.75%)	6757 (55.51%)	6182 (50.76%)	
Yes	5348 (44.00%)	5132 (42.25%)	5415 (44.49%)	5997 (49.24%)	
BPH					<0.001
No	7973 (65.59%)	8733 (71.89%)	9112 (74.86%)	9522 (78.18%)	
Yes	4182 (34.41%)	3414 (28.11%)	3060 (25.14%)	2657 (21.82%)	

Q1–Q4: represent the four quartile groups of SUA from lowest to highest.
n: represents the number of participants in each quartile for each variable. The difference in n between variables may be due to missing data or specific exclusion criteria.
Mean±SD: data are reported as mean±SD.
P values<0.05 are considered to have statistical significance. If the variable is continuous, the Kruskal-Wallis rank-sum test was used; if the count variable has a theoretical number<10, Fisher's exact probability test was used.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BPH, benign prostatic hyperplasia; DBP, diastolic blood pressure; EGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; GLO, globulin; GLU, glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; PLT, platelet count; SBP, systolic blood pressure; SCR, creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides; TP, total protein; WAIST, waist circumference.

Table 2 Study population characteristics according to BPH classification

Variables	No BPH (n=35 340)	BPH (n=13 313)	P value
AGE (years)	44.68±13.31	61.78±12.37	<0.001
SBP (mm Hg)	128.72±16.80	136.63±19.07	<0.001
DBP (mm Hg)	81.85±11.42	83.35±11.24	<0.001
BMI (kg/m^2)	25.46±3.45	24.82±2.94	<0.001
WAIST (cm)	87.85±8.92	87.26±11.24	<0.001
ALT (U/L)	34.47±32.49	26.14±19.34	<0.001
AST (U/L)	24.76±17.16	23.36±10.08	<0.001
AST/ALT	0.91±0.51	1.07±0.46	<0.001
GGT (U/L)	41.98±42.19	36.92±41.20	<0.001
PLT (×10^9/L)	223.05±55.64	202.17±56.45	<0.001
GLO (g/L)	28.86±4.08	28.96±4.17	0.024
GLU (mmol/L)	5.61±1.43	6.01±1.68	<0.001
TP (g/L)	74.03±4.45	73.17±4.53	<0.001
TC (mmol/L)	4.88±0.93	4.82±0.94	<0.001
TG (mmol/L)	2.11±1.87	1.95±1.74	<0.001
HDL (mmol/L)	1.18±0.27	1.22±0.30	<0.001
LDL (mmol/L)	2.81±0.74	2.73±0.76	<0.001
SCR (µmol/L)	75.63±22.14	76.88±19.75	<0.001
EGFR (mL/min/1.73 m^2)	104.27±15.24	91.43±15.59	<0.001
SUA (µmol/L)	392.24±82.51	372.28±81.41	<0.001
UROLITHIASIS			<0.001
No	32 249 (91.25%)	11 858 (89.07%)	
Yes	3091 (8.75%)	1455 (10.93%)	
NAFLD			<0.001
No	19 384 (54.85%)	8228 (61.80%)	
Yes	15 956 (45.15%)	5085 (38.20%)	
OBESITY			<0.001
No	27 982 (79.18%)	11 506 (86.43%)	
Yes	7358 (20.82%)	1807 (13.57%)	
DIABETES			<0.001
No	34 386 (97.30%)	12 383 (93.01%)	
Yes	954 (2.70%)	930 (6.99%)	

n: indicates the total number of samples and the number of participants in each group. NO BPH group is the non-prostatic hyperplasia group, BPH group is the prostatic hyperplasia group.
Mean±SD: Data are reported as mean±SD.
Standardise diff.: standardised difference, used to show the size of the standardised difference between the two groups.
P values<0.05 are considered to have statistical significance. If the variable is continuous, the Kruskal-Wallis rank-sum test was used; if the count variable has a theoretical number<10, Fisher's exact probability test was used.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BPH, benign prostatic hyperplasia; DBP, diastolic blood pressure; EGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; GLO, globulin; GLU, glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; PLT, platelet count; SBP, systolic blood pressure; SCR, creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides; TP, total protein; WAIST, waist circumference.

provided preliminary understanding, the precise mechanisms underlying these relationships remain a focal point of scientific inquiry. Against this intricate backdrop, we employed subgroup analysis to gain a deeper understanding of the nuanced relationship between SUA levels and BPH risk. First, considering age as a pivotal factor in BPH development, our study showed a more prominent inverse correlation between elevated SUA levels and BPH risk in older subgroups. This could be attributed to the increased BPH risk, altered metabolism and elevated oxidative stress levels in middle-aged and elderly populations. As an antioxidant, SUA might exert stronger

Table 3 Association between SUA and BPH

	OR (95% CI), p value		
	Non-adjusted	Adjust I	Adjust II
Q1	1 (ref)	1 (ref)	1 (ref)
Q2	0.75 (0.71 to 0.79), <0.0001	0.93 (0.87 to 0.99), 0.0200	0.93 (0.88 to 0.99), 0.0336
Q3	0.64 (0.61 to 0.68), <0.0001	0.92 (0.86 to 0.98), 0.0099	0.93 (0.87 to 0.99), 0.0313
Q4	0.53 (0.50 to 0.56), <0.0001	0.81 (0.76 to 0.87), <0.0001	0.83 (0.78 to 0.90), <0.0001

Adjust I: age, obesity, hypertension, diabetes, NAFLD.
Adjust II: age, obesity, hypertension, diabetes, NAFLD, PLT, SCR, AST/ALT, eGFR.
Q1–Q4: represent the four quartile groups of SUA from lowest to highest, used to assess the relationship between uric acid levels and the risk of BPH.
P values<0.05 are considered to have statistical significance.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BPH, benign prostatic hyperplasia; eGFR, estimated glomerular filtration rate; NAFLD, non-alcoholic fatty liver disease; PLT, platelet count; SCR, creatinine; SUA, serum uric acid.

protective effects within this demographic.[29 30] Second, in non-obese and NAFLD-free subgroups, a stronger inverse correlation was observed. This suggests that SUA might effectively mitigate BPH risk through mechanisms like reducing oxidative stress and inflammation in individuals with less severe metabolic disturbances.[31] Notably, even in hypertensive and diabetic patients, where diabetes itself increases BPH risk,[21] higher SUA levels were associated with a reduced BPH risk. This implies that the potential benefits of SUA in combating inflammation and oxidative stress might outweigh the negative implications of hypertension and diabetes. Maintaining appropriate SUA levels could emerge as a potentially effective preventative and interventional strategy for BPH treatment in diabetic patients.

Therefore, the inverse correlation between SUA levels and BPH risk could be explained by several mechanisms. First, oxidative stress is closely linked to prostate tissue damage and exacerbated inflammatory responses. By scavenging free radicals and reducing oxidative stress, SUA

Table 4 Subgroup analysis

		Q1	Q2	Q3	Q4	
Subgroup	n	Ref	OR (95% CI), p value	OR (95% CI), p value	OR (95% CI), p value	P interaction
AGE						0.2628
≤40 years	15 933	1 (ref)	1.13 (0.87 to 1.46), 0.3711	0.88 (0.67 to 1.15), 0.3469	0.95 (0.72 to 1.25), 0.6894	
>40, ≤60 years	22 052	1 (ref)	0.91 (0.84 to 0.99), 0.0327	0.94 (0.86 to 1.03), 0.1709	0.86 (0.78 to 0.94), 0.0016	
>60 years	10 668	1 (ref)	0.92 (0.83 to 1.02), 0.1176	0.90 (0.81 to 1.01), 0.0688	0.77 (0.68 to 0.87), <0.0001	
OBESITY						0.0685
No	39 488	1 (ref)	0.94 (0.88 to 1.01), 0.0829	0.92 (0.86 to 0.99), 0.0308	0.81 (0.75 to 0.87), <0.0001	
Yes	9165	1 (ref)	0.88 (0.72 to 1.07), 0.1919	0.98 (0.82 to 1.18), 0.8569	0.97 (0.81 to 1.16), 0.7348	
DIABETES						0.0748
No	46 769	1 (ref)	0.94 (0.88 to 1.00), 0.0552	0.92 (0.86 to 0.99), 0.0171	0.84 (0.78 to 0.90), <0.0001	
Yes	1884	1 (ref)	0.86 (0.67 to 1.11), 0.2406	1.26 (0.94 to 1.69), 0.1152	0.78 (0.57 to 1.06), 0.1108	
HYPERTENSION						0.3631
No	26 761	1 (ref)	0.95 (0.86 to 1.04), 0.2443	0.93 (0.84 to 1.02), 0.1305	0.90 (0.80 to 1.01), 0.0632	
Yes	21 892	1 (ref)	0.93 (0.85 to 1.02), 0.1186	0.95 (0.86 to 1.03), 0.2116	0.81 (0.74 to 0.89), <0.0001	
NAFLD						0.4546
No	27 612	1 (ref)	0.91 (0.85 to 0.99), 0.0248	0.91 (0.84 to 1.00), 0.0385	0.81 (0.73 to 0.89), <0.0001	
Yes	21 041	1 (ref)	0.99 (0.88 to 1.11), 0.8534	0.99 (0.88 to 1.10), 0.8175	0.90 (0.81 to 1.01), 0.0680	

Q1–Q4: represent the four quartile groups of serum uric acid from lowest to highest.
n: indicates the number of participants in each quartile group (Q1–Q4) under each category of age (AGE), obesity (OBESITY), diabetes (DIABETES), hypertension (HYPERTENSION) and non-alcoholic fatty liver disease (NAFLD).
OR (95% CI): represents the OR and its 95% CI relative to the reference group (ref).
P values<0.05 are considered to have statistical significance.
The P interaction value represents the statistical significance of interaction among two or more variables. P interaction<0.05: indicates the presence of a significant interaction.
Subgroup analysis and interaction tests were adjusted in the full model.

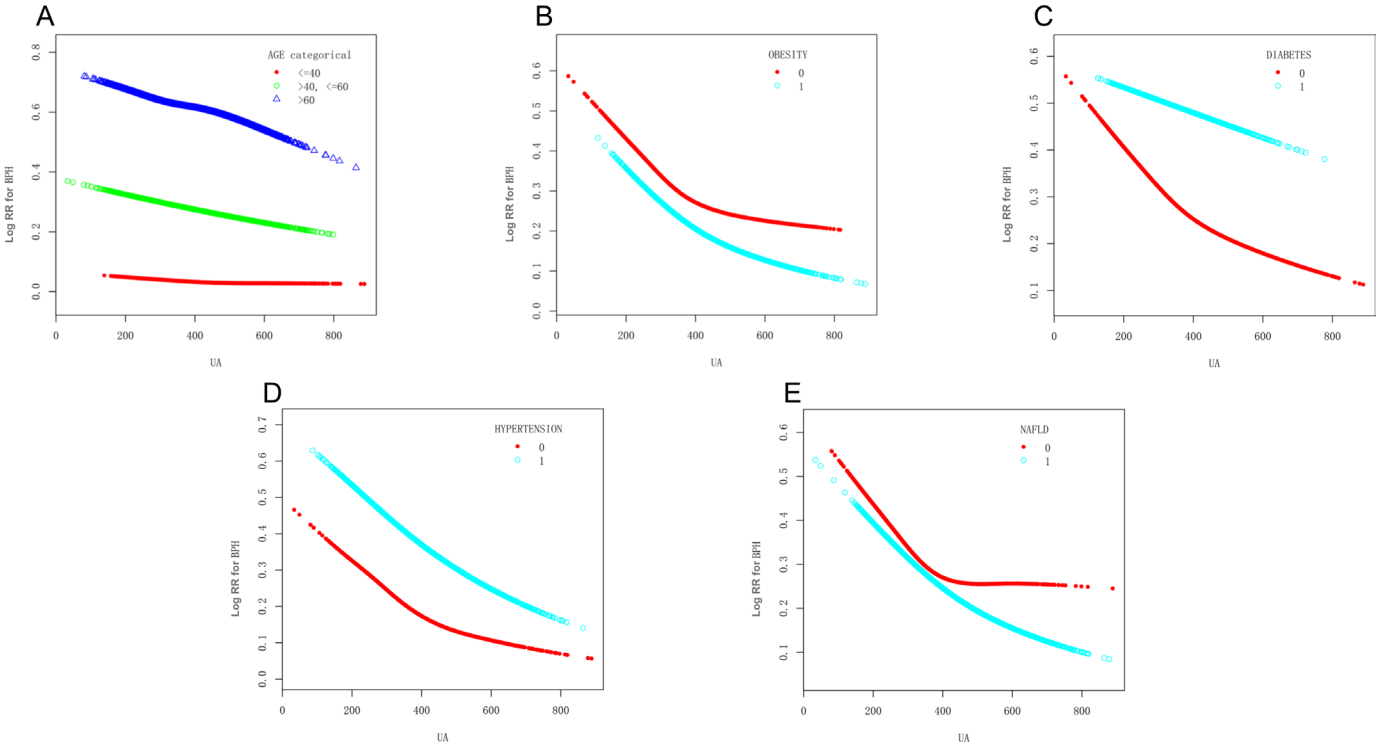

Figure 2 Curve-fitting analysis of the association between serum uric acid (SUA) levels and benign prostatic hyperplasia (BPH) risk across different groups. The association between SUA and the log relative risk (Log RR) of BPH is shown, stratified by (A) age (<40, >40 and ≤60, >60 years); (B) obesity (0=no, 1=yes); (C) diabetes (0=no, 1=yes); (D) hypertension (0=no, 1=yes) and (E) non-alcoholic fatty liver disease (NAFLD) (0=no, 1=yes). A downward slope indicates an inverse association (higher SUA, lower BPH risk).

might lower BPH risk.[31] This antioxidant capacity, already demonstrated in combating chronic inflammation and oxidative stress,[19] could be one mechanism underlying its potential protective effect on BPH. Second, the inverse correlation between SUA levels and hormone levels, especially androgens crucial for prostate growth,[23] suggests an indirect influence on prostate growth and hyperplasia. Moreover, appropriate SUA levels might regulate vasoconstriction and blood flow,[32] potentially contributing to prostate tissue health and mitigating tissue hypoxia, inflammation and damage caused by poor blood flow or congestion, thereby counteracting BPH development.

These findings suggest that SUA levels could serve as an ancillary indicator for BPH risk assessment in clinical practice. However, it is crucial to acknowledge that the implementation and effectiveness of this recommendation might differ across countries due to variations in lifestyles, socio-economic conditions and healthcare systems. In resource-limited settings, simple lifestyle modifications and dietary adjustments could effectively manage SUA levels.[33] In developed countries, a comprehensive approach might involve combining medication with regular SUA monitoring. Nevertheless, it is paramount to emphasise that the inverse correlation between elevated SUA and reduced BPH risk does not negate the health risks associated with hyperuricaemia itself. Despite its potential protective role against BPH, elevated SUA levels are linked to hypertension, cardiovascular diseases and various metabolic disorders.[4 24] Therefore, managing and maintaining SUA levels within a higher, yet reasonable, range holds potential value in the prevention of BPH.

Our study has limitations. While we found a significant inverse correlation between SUA levels and BPH risk, the inherent limitations of a cross-sectional design restrict our ability to infer causality. Furthermore, selection bias might be present due to the recruitment of participants from individuals undergoing health checkups, potentially representing a healthier population with favourable health behaviours and socio-economic status, which could impact the results. Although we attempted to control for confounders through multivariate adjustments, data limitations prevented us from excluding all potential confounding factors such as dietary habits, lifestyles and economic capabilities. However, a study on a US population that adjusted for potential confounders such as dietary habits, lifestyles, economic capabilities and education levels still demonstrated a significant inverse correlation between SUA and BPH risk,[34] increasing the credibility of our findings.

Future research should employ more comprehensive data from multicentre, prospective cohort studies, and experiments to further validate the association between SUA and BPH, elucidate their causal relationship and unravel the role of SUA in BPH pathogenesis, including its influence on oxidative stress and inflammatory responses in prostate tissue.

CONCLUSION

This large-scale population-based cross-sectional study identified an inverse association between SUA levels and BPH. This association was more pronounced in specific subgroups, including individuals aged>60 years, non-obese individuals and those without hypertension, NAFLD or diabetes. Notably, even in the presence of hypertension or diabetes, which are known risk factors for BPH, we observed a statistical association between higher SUA levels and lower BPH prevalence. These observations provide preliminary evidence for a potential biological association between SUA levels and BPH. Meanwhile, considering the established associations between hyperuricaemia and various metabolic diseases, any future clinical applications regarding SUA level modulation would need to balance potential benefits and risks.

Acknowledgements We express our sincere gratitude to Director Xiaoping Yu from the Health Examination Center of the Affiliated Hospital of Yangzhou University for his support of this research.

Contributors TH, SZ, JD, ZG and XW conducted the research and collected the data. TH, YL and XW designed the study. YL and XW provided study supervision and finalised the manuscript. YL and TQ acquired funding for the project. TH, SZ, JD and WZ performed data analysis. TH, SZ and JD prepared the manuscript. All authors have read and approved the final manuscript. XW is the guarantor of this work.

Funding This study was funded by the National Natural Science Foundation of China (grant no. 82002675), the Jiangsu Province Science and Technology Plan Youth Fund Project (grant no. BK2020938), the 2022 Yangzhou City Social Development Guiding Project (grant no. YZ2022104) and the Yangzhou City Key Medical Discipline Cultivation Project (grant no. YZYXZDXK-016).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. Ethical approval was obtained from the Ethics Committee of the Affiliated Hospital of Yangzhou University (approval number: 2023-YKL01-13), ensuring compliance with relevant ethical and legal standards. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are not publicly available due to privacy concerns. Data are however available from the corresponding author upon reasonable request.

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