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The association between arthritis and the risk of lower urinary tract symptoms suggestive of benign prostate hyperplasia: evidence from the China Health and Retirement Longitudinal Study (CHARLS)

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Arthritis and Lower urinary tract symptoms suggestive of benign prostate hyperplasia (LUTS/BPH) are both common chronic conditions among middle-aged and elderly men in China. Currently, evidence regarding the association between these two conditions remains limited. This study utilized data from the 2011 China Health and Retirement Longitudinal Study (CHARLS), including 4,446 Chinese men aged 40 years and older, among whom 3,136 participants completed follow-up assessments in 2018. In the 2011 cross-sectional analysis, multivariable logistic regression prior to propensity score matching (PSM) indicated that individuals with arthritis had a higher risk of LUTS/BPH than those without arthritis (OR = 1.483, $P < 0.001$). Univariate logistic regression analysis after PSM further demonstrated that patients with arthritis had a significantly increased risk of developing LUTS/BPH compared to matched controls (OR = 1.530, $P = 0.002$). In the longitudinal cohort study, multivariable logistic regression before PSM showed that arthritis patients had a significantly increased risk of incident LUTS/BPH after seven years of follow-up (OR = 1.531, $P < 0.001$). Univariate logistic regression after PSM similarly showed an elevated risk of incident LUTS/BPH in arthritis patients compared to controls (OR = 1.634, $P < 0.001$). Arthritis significantly increases the risk of developing LUTS/BPH among middle-aged and elderly men in China. Prospective cohort studies and mechanistic investigations are urgently needed to further validate the association between the two.

Keywords Arthritis, Lower urinary tract symptoms, Benign prostate hyperplasia, CHARLS

Abbreviations

LUTS/BPH	Lower urinary tract symptoms suggestive of benign prostate hyperplasia
CHARLS	China Health and Retirement Longitudinal Study
PSM	Propensity score matching
OA	Osteoarthritis
RA	Rheumatoid arthritis

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BMI	Body mass index
HTN	Hypertension
DM	Diabetes mellitus

Benign prostatic hyperplasia (BPH) is a disease characterized by the excessive proliferation of stromal and epithelial cells in the transitional zone of the prostate[1]. Approximately 50% of men aged over 50 exhibit the pathological features of prostatic hyperplasia, and this prevalence further increases to over 80% in men aged 80 and above[2]. The disease causes urethral compression, resulting in obstructed urinary flow[1]. BPH is often accompanied by lower urinary tract symptoms (LUTS), which are mainly classified into irritative and obstructive types[3]. Irritative LUTS include frequency, urgency, nocturia, and urge urinary incontinence[3]. Obstructive LUTS are characterized by a slow, intermittent urinary stream and incomplete bladder emptying[3]. LUTS/BPH severely impact men's quality of life, daily activities, and overall health, causing significant distress[4]. Therefore, the urgent development of effective prevention and treatment strategies is required.

The term "arthritis" is derived from the Greek words meaning "disease of the joints[5]. " Arthritis is an acute or chronic inflammation of the joints, typically accompanied by pain and structural damage[5]. All types of arthritis exhibit clinical features such as mononuclear cell infiltration, inflammatory responses, synovial edema, synovial hyperplasia, joint stiffness, and articular cartilage degradation[6]. Currently, more than 100 types of arthritis have been identified, among which osteoarthritis is the most common[6].

Common risk factors, such as age, obesity, and metabolic syndrome, play significant roles in the occurrence and progression of both OA and BPH[1,7–9]. Research by Vickman et al. has demonstrated that patients with autoimmune diseases have an increased risk of developing BPH[10]. Recently, immune dysregulation and autoimmune responses have been recognized as key contributors to the pathogenesis of BPH[11]. Rheumatoid arthritis may share similar underlying inflammatory mechanisms with BPH. Previous studies have indicated that elevated uric acid levels in patients with gout may promote the development of prostatic hyperplasia by inducing oxidative stress responses[12,13].

Several observational studies have demonstrated a significant association between RA, gouty arthritis, and BPH[12,14,15]. Additionally, some questionnaire-based studies have indicated a positive correlation between the severity of OA and RA and LUTS[16–18]. However, existing evidence is largely derived from cross-sectional studies, and the causality as well as its direction remain unclear.

This study aims to investigate the association between arthritis and the risk of developing LUTS/BPH using data from the China Health and Retirement Longitudinal Study (CHARLS).

Materials and methods

Data sources and included population

The data for this study are derived from the China Health and Retirement Longitudinal Study (CHARLS), a nationwide prospective cohort study that was initiated in 2011. CHARLS employs a multi-stage probability proportional sampling method and recruited 17,705 participants from 150 counties and 400 villages across the country in the baseline survey. The participants were followed up in 2013, 2015 and 2018. Data was collected through questionnaires and physical examinations, covering demographic, socioeconomic, and health information. Detailed information is available at the following link: http://charls.pku.edu.cn/en/. The ethics committee at Peking University approved the CHARLS study (IRB00001052-11015), and written informed consent was provided by each participant. All methods were conducted in compliance with applicable guidelines and regulations. To investigate the potential association between arthritis and LUTS/BPH, we first conducted a cross-sectional study using baseline data from 2011, excluding participants who: lacked gender information, were female, were younger than 40 years, lacked diagnostic information on arthritis or LUTS/BPH, or had missing covariate data. Ultimately, the 2011 cross-sectional study included 4,446 eligible participants. However, the cross-sectional study can only identify associations between exposure and outcome, without establishing temporal sequences or causal relationships. Therefore, we designed a longitudinal cohort study combining data from 2011 to 2018. Based on the population included in the 2011 cross-sectional study, we further excluded participants who: had been diagnosed with LUTS/BPH in 2011 or lacked LUTS/BPH diagnostic information in 2018. Ultimately, the study included 3,136 participants (Fig. 1).

Diagnosis of arthritis and LUTS/BPH in CHARLS

In this study, arthritis was considered as the exposure variable and LUTS/BPH as the outcome variable. Participants with arthritis were identified through a questionnaire, which asked: "Has a doctor ever diagnosed you with arthritis or rheumatism?" Based on the responses to this question, we identified a broad definition of arthritis rather than specific types of arthritis[19]. LUTS/BPH diagnosis was based on the following question: "Have you ever been diagnosed with a prostate condition, such as benign prostatic hyperplasia (BPH), but not prostate cancer?" BPH is a term that defines the typical histological characteristics of the disease, and not all individuals with benign prostatic tissue hyperplasia seek medical care and treatment. When BPH-related LUTS occur, patients typically seek medical care and are diagnosed with LUTS/BPH. Therefore, asymptomatic individuals with benign prostatic tissue hyperplasia cannot be assessed through the questionnaire. If participants answered "yes," they were diagnosed with LUTS/BPH, using the same method as in previous studies[20,21].

Assessment of covariates in CHARLS

The study included the following covariates: age, Hukou (a kind of household registration in China), marital status, education level, smoking, alcohol consumption, body mass index (BMI), sleep duration, depression, hypertension(HTN), diabetes mellitus(DM), dyslipidemia, and heart disease. Age was divided into two groups: 40 to 60 years and over 60 years. Hukou is typically used to reflect participants' residential status, where an

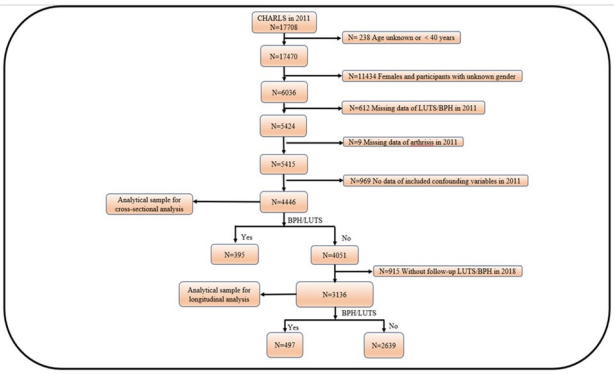

Fig. 1. Overall study design. Note: LUTS/BPH, lower urinary tract symptoms suggestive of benign prostatic hyperplasia.

agricultural hukou indicates residence in rural areas, while a non-agricultural hukou indicates residence in urban areas. Marital status was categorized into two groups: Group 1, consisting of married individuals, including those living with their spouse and those temporarily separated due to work; and Group 2, including those separated, divorced, widowed, or never married. Education level was classified into two groups: below primary school and middle school or above. Smoking status was categorized into three groups: never smokers, former smokers, and current smokers. Alcohol consumption was categorized into three groups: never drinkers, those who drink less than once a month, and those who drink more than once a month. BMI was classified into three categories: < 18.5 kg/m^2, 18.5 to < 24.0 kg/m^2, and ≥ 24.0 kg/m^2. In CHARLS, depression levels were assessed using the CESD-10 scale, with a total score of 10 or higher indicating depression, and a score below 10 indicating normal levels[21]. HTN was self-reported or identified through physical examinations where diastolic pressure ≥ 90 mmHg or systolic pressure ≥ 140 mmHg, with any one of these criteria indicating HTN. DM was self-reported or diagnosed based on blood tests showing fasting glucose ≥ 126 mg/dL or glycated hemoglobin ≥ 6.5%, with either condition indicating DM. Data on dyslipidemia and heart disease were derived from the same question: "Have you ever been diagnosed with [disease]?" with responses of "yes" or "no." In the CHARLS questionnaire, dyslipidemia is diagnosed if patients report elevated levels of low-density lipoprotein, triglycerides, or total cholesterol, or decreased levels of high-density lipoprotein. Heart disease is diagnosed if patients report myocardial infarction, coronary heart disease, angina, congestive heart failure, or other cardiac conditions.

Statistical analysis in CHARLS

Categorical data are presented as frequencies and percentages (n [%]), and inter-group differences were compared using the chi-square test. To assess the association between arthritis and LUTS/BPH, we performed univariate and multivariate logistic regression analyses, calculating the odds ratios (OR) and their 95% confidence intervals (95% CI). Model 1 was the crude model (without adjusting for covariates), and Model 2 was the multivariate model adjusted for all covariates. Additionally, we assessed the variance inflation factor (VIF) for each covariate, and the results showed that all VIF values were below 5, indicating no significant multicollinearity among the covariates[22]. We conducted a subgroup analysis to evaluate the association between arthritis and LUTS/BPH in different subgroups, and used the likelihood ratio test to identify potential interactions. Subsequently, propensity score matching (PSM) was used to balance the covariates between the arthritis and non-arthritis groups, with nearest neighbor matching using a caliper of 0.02 and 1:1 no-replacement matching[20]. Finally, univariate logistic regression analysis (Model 3) was performed on the matched data. All analyses were performed using R version 4.4.2. Two-sided significance was calculated, with a significance level set at 0.05.

Results

Baseline characteristics of participants in observational study

A total of 4,446 participants were included in this study, and their basic characteristics are described in Table 1. In 2011, 395 participants were diagnosed with LUTS/BPH, while 4,051 were not. Participants with LUTS/BPH were older, predominantly had non-agricultural Hukou, had higher education levels, shorter sleep durations. Additionally, the prevalence of heart disease, dyslipidemia, DM, depression, and arthritis was significantly higher in participants with LUTS/BPH.

Association of arthritis with LUTS/BPH in cross-sectional studies

The 2011 cross-sectional study indicated that, in the unadjusted model, the prevalence of LUTS/BPH was higher in patients with arthritis compared to those without arthritis (model 1: OR: 1.597; 95% CI: 1.285–1.979; P < 0.001). After adjusting for covariates, this association remained significant (model 2: OR: 1.483; 95% CI: 1.178–1.863; P < 0.001). Following PSM, model 3 was developed using univariate logistic regression, and the results continued to show significance (model 3: OR: 1.530; 95% CI: 1.163–2.020; P = 0.002). Detailed information is provided in Table 2; Fig. 2. The results of PSM are presented in Supplementary Fig. 1 and Supplementary Fig. 2.

Characteristics		Overall cases	Non-LUTS/BPH	LUTS/BPH	*p*
Total		4,446	4,051	395	
Age (year), n (%)	<= 60	2,800 (63.0)	2,622 (64.7)	178 (45.1)	< 0.001
	> 60	1,646 (37.0)	1,429 (35.3)	217 (54.9)	
Hukou, n (%)	Nonagricultural	847 (19.1)	726 (17.9)	121 (30.6)	< 0.001
	Agricultural	3,599 (80.9)	3,325 (82.1)	274 (69.4)	
Marital status, n (%)	Married	4,107 (92.4)	3,744 (92.4)	363 (91.9)	0.784
	Others	339 (7.6)	307 (7.6)	32 (8.1)	
Educational levels, n (%)	Elementary school or below	2,505 (56.3)	2,308 (57.0)	197 (49.9)	0.008
	Middle school or above	1,941 (43.7)	1,743 (43.0)	198 (50.1)	
Smoking, n (%)	Yes	2,652 (59.6)	2,455 (60.6)	197 (49.9)	< 0.001
	No	1,140 (25.6)	1,031 (25.5)	109 (27.6)	
	Quitted	654 (14.7)	565 (13.9)	89 (22.5)	
Alcohol consumption, n (%)	Never	1,882 (42.3)	1,674 (41.3)	208 (52.7)	< 0.001
	Less than once a month	520 (11.7)	479 (11.8)	41 (10.4)	
	More than once a month	2,044 (46.0)	1,898 (46.9)	146 (37.0)	
BMI (kg/m2), n (%)	< 18.5	244 (5.5)	227 (5.6)	17 (4.3)	0.185
	>= 18.5 AND < 24	2,670 (60.1)	2,443 (60.3)	227 (57.5)	
	>= 24	1,532 (34.5)	1,381 (34.1)	151 (38.2)	
Sleeping time (h), n (%)	< 6	1,135 (25.5)	1,016 (25.1)	119 (30.1)	0.042
	>=6 AND <=8	2,960 (66.6)	2,707 (66.8)	253 (64.1)	
	> 8	351 (7.9)	328 (8.1)	23 (5.8)	
Depression, n (%)	Yes	1,284 (28.9)	1,131 (27.9)	153 (38.7)	< 0.001
	No	3,162 (71.1)	2,920 (72.1)	242 (61.3)	
HTN, n (%)	Yes	1,958 (44.0)	1,774 (43.8)	184 (46.6)	0.311
	No	2,488 (56.0)	2,277 (56.2)	211 (53.4)	
DM, n (%)	Yes	491 (11.0)	431 (10.6)	60 (15.2)	0.008
	No	3,955 (89.0)	3,620 (89.4)	335 (84.8)	
Dyslipidemia, n (%)	Yes	367 (8.3)	303 (7.5)	64 (16.2)	< 0.001
	No	4,079 (91.7)	3,748 (92.5)	331 (83.8)	
Heart disease, n (%)	Yes	376 (8.5)	304 (7.5)	72 (18.2)	< 0.001
	No	4,070 (91.5)	3,747 (92.5)	323 (81.8)	
Arthritis, n (%)	Yes	1,234 (27.8)	1,088 (26.9)	146 (37.0)	< 0.001
	No	3,212 (72.2)	2,963 (73.1)	249 (63.0)	

Table 1. Baseline characteristics of participants ($n = 4,446$). Note: BMI: body mass index; LUTS/BPH, lower urinary tract symptoms suggestive of benign prostatic hyperplasia; HTN, hypertension; DM, diabetes mellitus.

Arthritis	Model 1 OR (95%CI) *P*- value	Model 2 OR (95%CI) *P*- value	Model 3 OR (95%CI) *P*- value
No	Reference	Reference	Reference
Yes	1.597 (1.285, 1.979), < 0.001	1.483 (1.178, 1.863), < 0.001	1.530 (1.163, 2.020), 0.002

Table 2. Association of arthritis with LUTS/BPH in cross-sectional studies. Note: Model 1: Unadjusted model; Model 2: Adjusted Age, Hukou, Marital status, Educational levels, Smoking, Alcohol consumption, BMI, Sleeping time, Depression, HTN, DM, Dyslipidemia, Heart disease; model3: univariate logistic regression after PSM; OR, odds ratio; CI, confidence interval.

Association of arthritis with LUTS/BPH in the longitudinal cohort study

The longitudinal cohort study included 3,136 eligible participants, of whom 848 were diagnosed with arthritis, and 2,288 were not. In comparison, participants with arthritis were older, predominantly had rural Hukou, had lower education levels, and shorter sleep durations. The prevalence of heart disease and depression was

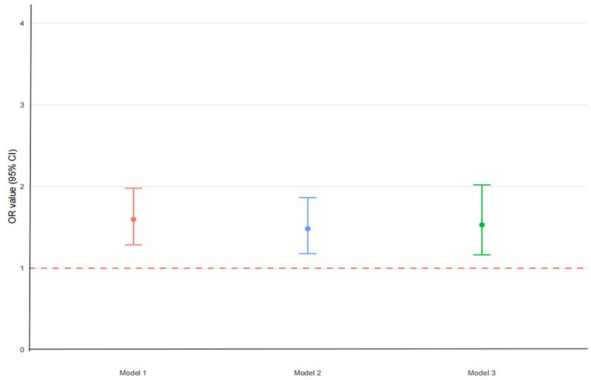

Fig. 2. ORs in three different models. Note: Model 1: Unadjusted model; Model 2: Adjusted Age, Hukou, Marital status, Educational levels, Smoking, Alcohol consumption, BMI, Sleeping time, Depression, HTN, DM, Dyslipidemia, Heart disease; model3: univariate logistic regression after PSM; OR, odds ratio; CI, confidence interval.

Arthritis	Model 1 OR (95%CI) *P*- value	Model 2 OR (95%CI) *P*- value	Model 3 OR (95%CI) *P*- value
No	Reference	Reference	Reference
Yes	1.537 (1.251, 1.883), < 0.001	1.531 (1.229, 1.902), < 0.001	1.634 (1.250, 2.146), < 0.001

Table 3. Association of arthritis with LUTS/BPH in the longitudinal cohort study. Note: Model 1: Unadjusted model; Model 2: Adjusted Age, Hukou, Marital status, Educational levels, Smoking, Alcohol consumption, BMI, Sleeping time, Depression, HTN, DM, Dyslipidemia, Heart disease; model3: univariate logistic regression after PSM; OR, odds ratio; CI, confidence interval.

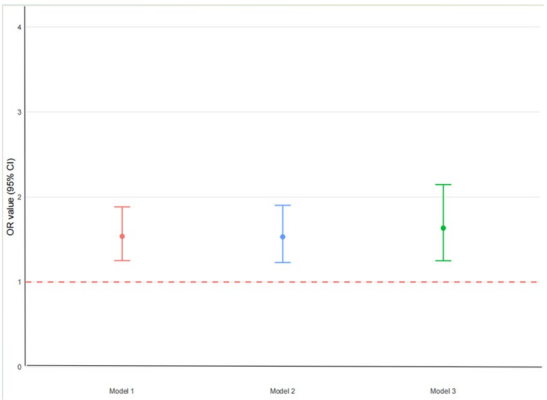

Fig. 3. ORs in three different models. Note: Model 1: Unadjusted model; Model 2: Adjusted Age, Hukou, Marital status, Educational levels, Smoking, Alcohol consumption, BMI, Sleeping time, Depression, HTN, DM, Dyslipidemia, Heart disease; model3: univariate logistic regression after PSM; OR, odds ratio; CI, confidence interval.

significantly higher in participants with arthritis. After eight years of follow-up, the prevalence of LUTS/BPH in the arthritis group was 20.3%, significantly higher than the 14.2% in the non-arthritis group ($P < 0.001$) (Supplementary Table 1). The results presented in Table 3 show a significant association between arthritis and the risk of incident LUTS/BPH in the longitudinal cohort study. After adjusting for covariates, the risk of incident LUTS/BPH was significantly higher in participants with arthritis (Model 2: OR: 1.531; 95% CI: 1.229–1.902; $P < 0.001$). This association remained significant after propensity score matching (PSM) (Model 3: OR: 1.634; 95% CI: 1.250–2.146; $P < 0.001$). Detailed information is provided in Table 3; Fig. 3. The results of propensity score matching are presented in Supplementary Fig. 3 and Supplementary Fig. 4.

Moreover, Fig. 4 shows the results of the subgroup and interaction analyses. In all subgroups, the OR was greater than 1, and it remained significant in most subgroups. For participants with non-agricultural Hukou

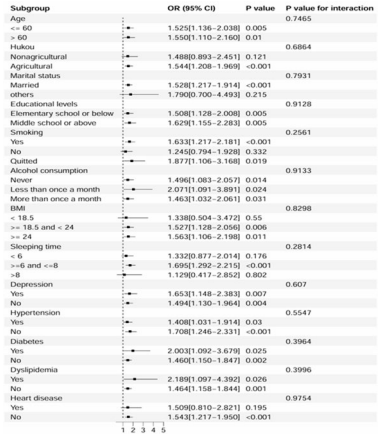

Fig. 4. Association between arthritis and LUTS/BPH in subgroup and interactive analyses. Note: In the multivariable logistic regression models, covariates were adjusted as model2 in previous analyses except for subgroup variables.

(OR: 1.488; 95% CI: 0.893–2.451; $P = 0.121$), unmarried participants (OR: 1.790; 95% CI: 0.700-4.493; $P = 0.215$), never-smokers (OR: 1.245; 95% CI: 0.794–1.928; $P = 0.332$), those with BMI < 18.5 (OR: 1.338; 95% CI: 0.504–3.472; $P = 0.55$), those with sleep durations of less than 6 h (OR: 1.332; 95% CI: 0.877–2.014; $P = 0.176$), those with sleep durations greater than 8 h (OR: 1.129; 95% CI: 0.417–2.852; $P = 0.802$), and heart disease patients (OR: 1.509; 95% CI: 0.810–2.821; $P = 0.195$). The increased odds ratios (ORs) with marginal significance may be attributed to the smaller sample sizes in those subgroups. Notably, no significant interaction effects of covariates were detected (all P for interaction > 0.05).

Discussion

To explore the association between arthritis and LUTS/BPH, this study conducted both cross-sectional and longitudinal analyses using nationally representative data from middle-aged and elderly Chinese populations. The 2011 cross-sectional analysis revealed a significant association between arthritis and the prevalence of LUTS/BPH. Furthermore, the seven-year longitudinal follow-up study indicated that patients with arthritis had a significantly increased risk of developing incident LUTS/BPH.

The 2011 cross-sectional study found that individuals diagnosed with LUTS/BPH exhibited significantly higher prevalence rates of depression, DM, dyslipidemia, and heart disease. Medical and surgical treatments for BPH may further impair patients' quality of life, thereby exacerbating depressive symptoms[23]. Another retrospective study based on CHARLS data revealed that patients with depression had a significantly increased risk of new-onset LUTS/BPH[20], suggesting a possible bidirectional association between the two conditions. Components of metabolic syndrome, such as DM and dyslipidemia, may synergistically promote the development of LUTS/BPH through multiple pathways, including alterations in sex hormone levels and chronic low-grade inflammation[24]. A previous observational study found that patients with a history of BPH had significantly higher risks of heart failure and atrial fibrillation compared to those without such history[25]. Studies have suggested that the pathophysiological mechanisms of BPH and cardiovascular diseases may partially overlap[25,26]. Given the primary focus of this study on the association between arthritis and LUTS/BPH, other comorbidities were considered potential confounding variables. Future studies are warranted to further explore the directional relationships and underlying mechanisms between LUTS/BPH and these diseases.

Previous studies have provided preliminary evidence of a close association between arthritis and LUTS/BPH. For example, a cross-sectional survey involving 3,143 Finnish men showed that patients with arthritis had a significantly increased relative risk of developing LUTS[27]. Another observational study reported that the risk of developing BPH was increased by 77% in patients with arthritis[28]. This study, based on seven years of follow-up data, demonstrated that individuals diagnosed with arthritis in 2011 had a significantly higher risk of developing LUTS/BPH by 2018 compared to those without arthritis. This conclusion remained robust before and after propensity score matching.

Although this study clearly demonstrated an association between arthritis and LUTS/BPH, the underlying mechanisms remain unclear. A recent longitudinal study showed that men with musculoskeletal pain had a 37% higher progression rate of LUTS compared to men without pain[29]. Senders et al. suggested that central sensitization (CS) may exacerbate LUTS caused by BPH or other obstructive conditions[30]. Central sensitization (CS) is a sensory processing disorder characterized by an exaggerated response of the nervous system to harmful stimuli, with arthritis-related pain potentially acting as one such harmful stimulus[30,31]. Additionally, the pro-inflammatory state in patients with arthritis may represent another important mechanism underlying this association. Previous studies have demonstrated significantly elevated immune cell counts and increased levels of various cytokines, such as IL-6 and IL-8, in patients with osteoarthritis[32]. The complex network of cytokines and growth factors involved in prostatic inflammatory responses may contribute to tissue damage and chronic repair processes, potentially promoting BPH[33].

The results of this study indicate that patients with arthritis have a significantly increased risk of developing incident LUTS/BPH. In clinical practice, particular attention should be paid to this high-risk group, with timely urodynamic evaluation being especially crucial.

This study has several limitations. First, this study applied a broad definition of arthritis without distinguishing specific types, following the method used by Li et al.[19]. Second, a simplified definition of LUTS/BPH was employed based on the study by Yang et al.[20]. These definitions primarily relied on self-reports, lacking objective diagnostic tools such as laboratory tests and imaging. Although this may introduce bias, objective diagnostic methods are difficult to implement widely in large-scale population studies. Third, although PSM was applied to balance baseline covariates, potential unmeasured confounders in the CHARLS dataset may still affect the results. Additionally, since the study population primarily consisted of middle-aged and elderly Chinese individuals, caution should be exercised when generalizing the results to other populations. Finally, due to the observational design of this study, establishing causality between the two remains challenging. Therefore, further prospective cohort and mechanistic studies are required to validate these associations.

Conclusion

In conclusion, this study observed a significant association between arthritis and an increased risk of LUTS/BPH through both cross-sectional and longitudinal designs, which requires further validation through prospective cohort and mechanistic studies. The findings highlight the need for clinicians to pay close attention to urinary symptoms in arthritis patients and to promptly conduct relevant assessments, such as urodynamics. Future studies may focus on whether managing arthritis symptoms impacts the onset and progression of LUTS/BPH, and related clinical intervention studies need to be conducted.

Data availability

The sources of all original data are listed in the " Data sources and included population " section of the " Materials and methods " section. If the data cannot be accessed, please contact the corresponding author.

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Author contributions

S.L. and P.W. designed the study; C.L. and S.C. analyzed the data and drafted initial manuscript; Q.M., N.W. and B, L acquired the data and searched the literatures; S.L. and P.W. reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Competing interests

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Additional information

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