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ORIGINAL RESEARCH

Serum 25-hydroxyvitamin D level and risk of benign prostatic hyperplasia: a prospective cohort study of 195,074 males

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Abstract

Background: Benign prostatic hyperplasia (BPH) gives rise to benign prostatic enlargement owing to unregulated hyperplasia of the epithelial and fibromuscular components within the transition zone and periurethral area. Vitamin D is a pleiotropic steroid hormone with functions that encompass the modulation of calcium and phosphate metabolism and the preservation of skeletal health, but prospective evidence in BPH is unclear. **Methods**: We analyzed data from 195,074 participants in the UK Biobank (recruited 2006–2010) with valid vitamin D measurements and without prevalent BPH. Serum vitamin D was measured using the chemiluminescent immunoassay approach (units: nmol/L). Incident BPH cases were identified through linkage to hospital, primary care, and death registry records until 2022. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Vitamin D was modeled as both a continuous variable and in quartiles. Dose-response relationships were examined using restricted cubic splines, with thresholds determined by maximally selected rank statistics. Subgroup and sensitivity analyses assessed robustness. **Results**: Over a median follow-up of 13.3 years, 21,168 incident BPH cases were documented. Lower serum vitamin D was associated with an increased risk of BPH. Multivariable-adjusted HRs (95% CIs) were calculated for participants grouped by serum 25-hydroxyvitamin D (25(OH)D) quartiles, yielding values of 1.00 (reference), 0.95 (0.91, 0.99), 0.94 (0.90, 0.98), and 0.95 (0.91, 0.98) for the first to fourth quartiles, respectively. Each 1-standard deviation (SD = 20.9) increase corresponded to a 2% lower risk (HR = 0.98, 95% CI: 0.97–0.99). Restricted cubic spline analysis revealed a progressive decrease in risk with evidence of nonlinearity, which may exist due to saturation effect. **Conclusions**: Based on large-scale prospective cohort data from the UK Biobank, this study validates that serum 25(OH)D levels are inversely associated with BPH risk.

Keywords

Benign prostatic hyperplasia; Lower urinary tract symptoms; Vitamin D; 25-hydroxyvitamin D; UK Biobank

1. Introduction

Benign prostatic hyperplasia (BPH), a widespread urological condition in the world, gives rise to benign prostatic enlargement owing to unregulated hyperplasia of the epithelial and fibromuscular components within the transition zone (TZ) and periurethral area [1–3]. The prevalence of BPH varies from 50% to 75% in men aged 50 years and above, and reaches 80% in those aged 70 years and older [4]. Men suffering from BPH may manifest symptoms such as poor urinary flow, urinary frequency, hesitancy at the start of urination, post-void dribbling, and nocturia, which are categorized as voiding lower urinary tract symptoms (LUTS) [5]. While overall LUTS can arise from other pathological conditions, such as diabetes, neurological diseases or urinary tract infections (UTIs), prostatic enlargement in BPH is the most frequent cause of voiding LUTS [6]. The primary risks linked to LUTS in affected patients encompass UTIs and episodes of acute urinary retention (AUR). Alongside the age-related increase in BPH incidence, the prevalence of cardiovascular disease rises concomitantly with advancing age [7–9]. BPH-related LUTS symptoms and complications significantly impair patients' quality of life, and moderate-to-severe LUTS affects 79% of depressed patients versus 57% of non-depressed men [10, 11]. For patients, BPH imposes not only inconvenience of life, but also a severe economic burden. In 2006, £44 million was allocated to primary care, £69 million was spent on drug therapies, and £101 million was devoted to managing BPH-related complications, including AUR [12]. Extensive research should be focused on potentially modifiable risk factors, like metabolic, inflammatory, and lifestyle, to develop novel approaches to prevent or delay the progression of the disease [13–15].

As a pleiotropic steroid hormone, vitamin D owns vital functions that encompass the modulation of calcium and phosphate metabolism and the preservation of skeletal health [16–18]. In clinical practice, vitamin D levels above 75 nmol/L are considered sufficient, while levels below 50 nmol/L are deficient [19]. In recent years, the potential role of vitamin D in male urological and reproductive health has triggered the attention of scientists gradually [20–22]. Fundamental research has confirmed that prostate tissue expresses both the vitamin D receptor (VDR) and enzymes associated with vitamin D metabolism, and the expression is tissue-specific and differentiation state-dependent, which suggests that the prostate serving as a target for vitamin D [23, 24]. *In vitro* studies, the biologically active form of vitamin D inhibited the proliferation of prostatic epithelial and stromal cells, enhanced cellular differentiation, and exerted anti-inflammatory properties and immunomodulatory actions [25], which are directly related to the pathogenesis of BPH characterized by aberrant proliferation of both glandular and stromal elements. Based on these findings, sufficient vitamin D status might act as a protective role in preventing the development of BPH.

Nevertheless, epidemiological evidence still needs exploration. Clinical investigation has demonstrated that the reduction of serum 25-hydroxyvitamin D (25(OH)D), a form of vitamin D in the human body, correlates with increased prostate volume or more severe LUTS [26]; however, some studies reached the opposite conclusion [27, 28]. Inconsistent findings are likely to stem from limited sample sizes, population heterogeneity, inadequate confounding factor adjustment, and study design methods. Thus, an urgent need exists for a large-scale cohort study to appraise the longitudinal association between serum vitamin D and the risk of BPH.

Collecting baseline biospecimens and long-term health outcome information from hundreds of thousands of individuals, the United Kingdom Biobank (UKB), thereby, provides a unique platform for investigating the relationship between nutrients and chronic conditions [29]. Utilizing UKB database, the present study aims to systematically examine three key objectives: (1) correlation of baseline serum 25(OH)D with the incidence risk of BPH; (2) a dose–response pattern of the correlation; and (3) stability of the correlation across subgroups stratified by factors, embodying education, ethnicity and body mass index (BMI).

2. Methods

2.1 Research population

Throughout 2006–2010 across the United Kingdom, UKB enrolled roughly 500,000 participants aged 40–69 years for research. During the baseline evaluation, all participants were administered standardized questionnaires, underwent physical assessments, and provided biological samples (including blood and urine). Throughout longitudinal follow-up, data linkage is carried out with various health-related datasets, such as Hospital Episode Statistics (HES) for inpatient care, primary care records, death registration data, and self-reported health status information.

2.2 Outcome ascertainment

The primary definition of incident BPH in the UKB relied on inpatient hospital records, with consulting International Classification of Diseases, 10th Revision (ICD-10) coding categories N40.0 to N40.3. Follow-up duration was restricted to the period from the information of baseline evaluation to the initial onset of the following events: BPH diagnosis, participant withdrawal, death or the cessation of data linkage. Exclusion criteria included missing data of serum 25(OH)D (n = 54,773), baseline diagnosis of BPH (n = 12,707), and female individuals (n = 239,597). After adoption of exclusion criteria, 195,074 participants were considered for the final analysis. By March 2022, 21,168 incident events of BPH were ascertained via data linkage to hospital admission records, primary care records, and national death registry data (Fig. 1).

2.3 Appraisal of exposure

Venous blood samples from participants were stored in the biorepository of UKB at −80 °C or liquid nitrogen. After rigorous quality control screening, concentrations of circulating biomarkers were quantified in eligible samples, with the results released through the biomarker project of UKB (https://biobank.ndph.ox.ac.uk/ukb/refer.cgi?id=1227). Within the UK Biobank, about 500,000 individuals initially were included for the quantification and analysis of 34 serum biomarkers. Standardized biochemical assay protocols and sample selection criteria were employed in subsequent analyses. Employing the DiaSorin Liaison XL analyzer (LIAISON® XL, DiaSorin S.p.A., Saluggia, Italy), serum 25(OH)D was assayed by direct competitive chemiluminescent immunoassay (CLIA), and results were expressed in nanomoles per liter (nmol/L). Vitamin D was analyzed thereafter as both a continuous variable, with hazard ratios (HRs) presented for each 1-standard deviation (SD = 20.9) increment, and quartiles stratified by its distribution in the cohort.

2.4 Covariates

Predefined covariates encompassed BMI, ethnicity, household income, educational attainment, smoking status, alcohol consumption status, serum low-density lipoprotein (LDL) levels and the use of lipid-lowering medication, antihypertensive medication, and insulin therapy.

2.5 Statistical analysis

With regard to the study cohort, baseline characteristics were expressed as means with SD, and for continuous outcomes as medians with interquartile ranges (IQR), while categorical variables were described as counts and percentages. Opportune statistical tests, including *t*-tests, Wilcoxon rank-sum tests, and χ^2 tests, were utilized to compare group differences. To assess the relationship between serum 25(OH)D and the risk of BPH, Cox Proportional Hazards Models were conducted to generate HRs with 95% confidence intervals (CIs).

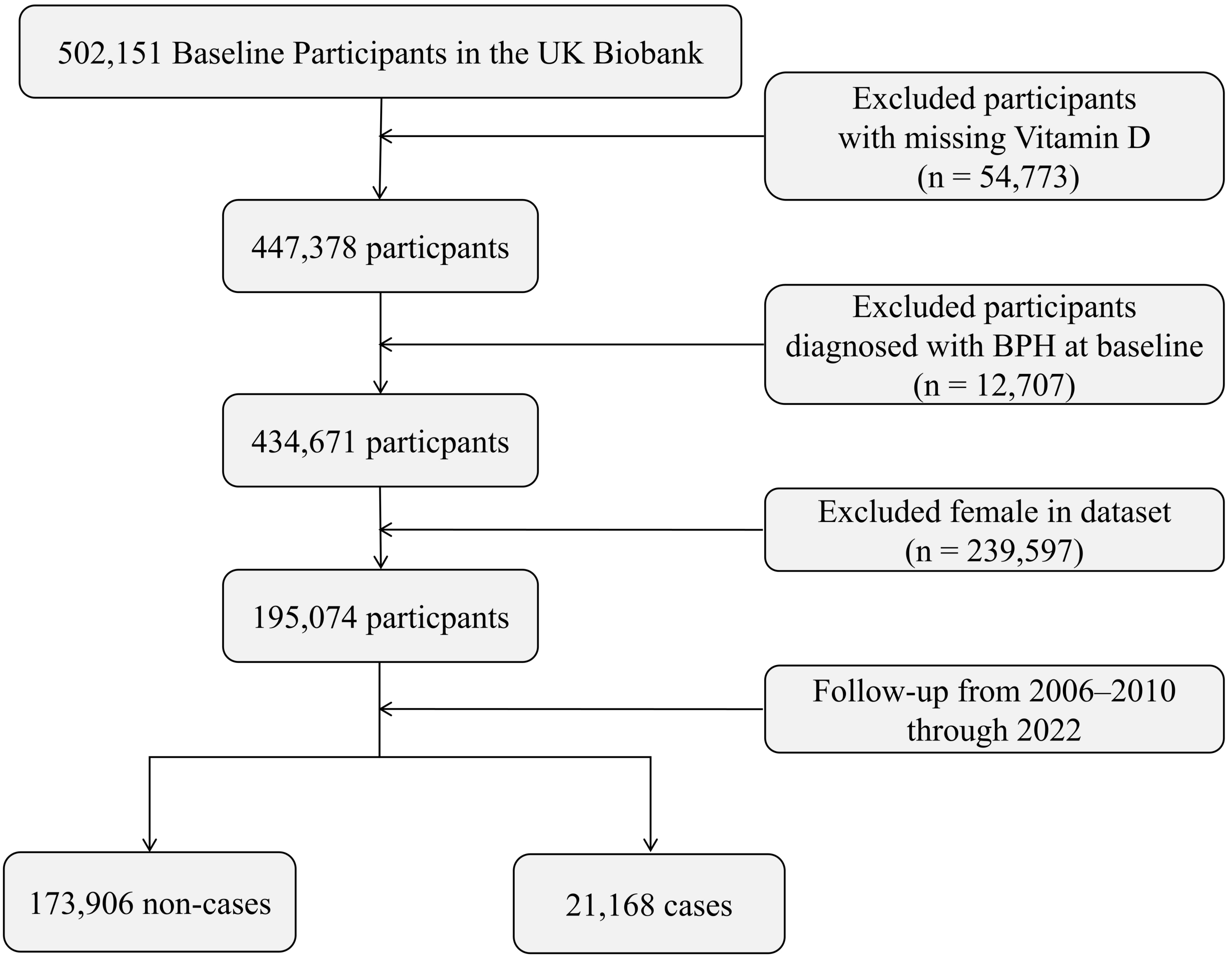

FIGURE 1. Flow chart of participant selection from the UK Biobank. BPH: Benign prostatic hyperplasia.

The models were fitted using the Cox Proportional Hazards (CoxPH) function from the survival package (version 3.5-7) in R. The proportional hazards assumption was assessed both globally and for each covariate using Schoenfeld residuals (via the cox.zph function), and no material violations were found. Moreover, linear trends were tested using quartile medians as a continuous variable. Restricted cubic spline (RCS) models with 3 knots placed at the 10th, 50th, and 90th percentiles of the 25(OH)D distribution were fitted using the rms package (version 6.7-0) to flexibly model potential nonlinear associations; the nonlinearity was tested by a likelihood ratio test comparing the spline model to a linear one. In addition, three sensitivity analyses were performed considering further adjustment for diet score, exclusion of early events within the first 3 years, and excluding participants with missing covariates. All tests ran two-tailed analysis, and statistical significance was ruled as a p-value < 0.05. Entire statistical analyses were implemented in the R statistical computing environment (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1 Baseline characteristics

195,074 participants comprised the analytic cohort, with 21,168 incident BPH cases documented over a median 13.3-year follow-up. The baseline serum 25(OH)D concentration was recorded as a mean ± SD of 48.27 ± 20.92 nmol/L. The majority of participants were of White ethnicity (94.35%) and had attained college-level education (45.49%), with 60.81% reporting a high household income ($\geq$£31,000). The incidents of overweight ($25 \leq \text{BMI} \leq 30$) and obesity ($\text{BMI} > 30$) among the cohort was 49.65% and 25.13%, respectively; 12.52% of participants were current smokers, and 93.85% reported current alcohol intake. In terms of combined medication, 24.33% of participants existed taking anti-hypertensive medication, 22.65% for lipid-lowering medication, and 1.47% for insulin therapy. On this basis, the blood lipid levels of participants were 3.43 ± 0.80 mmol/L. Detailed baseline characteristics are presented in Table 1.

Prospective follow-up data revealed that decreased serum vitamin D levels correlated with a higher risk of incident BPH, with corresponding results presented in Table 2. Multivariable-adjusted HRs (95% CIs) were calculated for participants grouped by serum 25(OH)D quartiles, yielding values of 1.00 (reference), 0.95 (0.91, 0.99), 0.94 (0.90, 0.98), and 0.95 (0.91, 0.98) for the first to fourth quartiles, respectively; the corresponding p-value for linear trend was $<$ 0.05. Hence, relative to the lowest quartile group, participants in each of the other three 25(OH)D quartiles exhibited a 5–6% reduction in the likelihood of incident BPH development. When serum 25(OH)D was treated as a continuous variable, each 1-standard deviation (SD = 20.9) increment was linked to

TABLE 1. Baseline characteristics.

Variable	Overall, mean (SD) or n (%) (195,074)
Vitamin D (nmol/L)	48.27 (20.92)
Household income (£)	
<31,000	76,451 (39.19)
≥31,000	118,623 (60.81)
Body mass index (kg/m^2)	
<25	49,181 (25.21)
25–30	96,862 (49.65)
>30	49,031 (25.13)
Ethnicity	
White	184,052 (94.35)
Non-white	11,022 (5.65)
Education	
College or above	88,748 (45.49)
High school or equivalent	73,400 (37.63)
Less than high school	32,926 (16.88)
Smoking status	
Never	96,693 (49.57)
Previous	73,952 (37.91)
Current	24,429 (12.52)
Alcohol intake	
Never	5202 (2.67)
Previous	6793 (3.48)
Current	183,079 (93.85)
Lipid-lowering medication	
No	150,897 (77.35)
Yes	44,177 (22.65)
Anti-hypertensive medication	
No	147,612 (75.67)
Yes	47,462 (24.33)
Insulin therapy	
No	192,215 (98.53)
Yes	2859 (1.47)
LDL (mmol/L)	3.43 (0.80)

SD: standard deviation; LDL: low-density lipoprotein.

a 2% attenuation in the risk of incident BPH (HR = 0.98, 95% CI: 0.97–0.99; $p = 0.004$). RCS analysis showed progressive incident BPH risk elevation with decreasing serum 25(OH)D, significant nonlinearity (p-nonlinearity = 0.006) (Fig. 2).

3.2 Subgroup analyses

Potential effect modification by education, ethnicity, and BMI was further examined (Table 3). Stratified by educational level, a consistent inverse relationship between serum 25(OH)D and incident BPH was identified under the college-educated subgroup (HR per 1-SD increase = 0.97, 95% CI: 0.95–0.99; $p = 0.001$). Conversely, the association was weaker and failed to reach statistical significance in participants with lower educational attainment—specifically, high school or equivalent (HR = 0.99, 95% CI: 0.97–1.01; $p = 0.355$) and less than high school (HR = 1.00, 95% CI: 0.98–1.03; $p = 0.909$)—with an interaction p-value of 0.057. Stratified by ethnicity, the negative correlation between serum 25(OH)D and incident BPH remained statistically robust among White participants (HR per 1-SD increment = 0.98, 95% CI: 0.97–0.99; $p = 0.012$), whereas a statistically significant relation among non-White participants was non-existent (HR = 0.97, 95% CI: 0.91–1.04; $p = 0.411$). Notably, the interaction effect by ethnicity failed reaching statistical significance (p-value for interaction = 0.423). By BMI category, a 1-SD elevation in serum 25(OH)D corresponded to an HR of 0.99 (95% CI: 0.96–1.01; $p = 0.315$) in normal-weight examinees (BMI <25), 0.98 (95% CI: 0.97–1.00; $p = 0.063$) within overweight group, and 0.98 (95% CI: 0.96–1.00; $p = 0.099$) in obese population, with none of significant evidence about the related interaction of BMI (p-interaction = 0.523).

3.3 Sensitivity analyses

Robustness of primary findings was further validated by several sensitivity analyses (Table 4). When additional diet score (0–1, 2–3, 4–5, and 6–7) were included in the model, the results were consistent with the above findings: the HR per SD increase was attenuated (HR = 0.98, 95% CI: 0.97–1.00; $p = 0.011$). When events within the first 3 years of follow-up were precluded, the sensitivity analysis yielded findings almost indistinguishable from the main results (HR per 1-SD = 0.97, 95% CI: 0.96–0.99; $p < 0.001$), thus alleviating potential reverse causality biases. Besides, another analysis, following exclusion of participants without clear covariate data, also yielded results consistent with the primary analysis (HR per 1-SD increment = 0.98, 95% CI: 0.97–1.00; $p = 0.042$).

4. Discussion

Leveraging large-scale prospective cohort data from the UK Biobank, this study, to our knowledge, represents the first systematic evaluation of the longitudinal association between serum 25(OH)D concentrations and the risk of incident BPH in this population. The key findings of this study are summarized as follows: low level serum 25(OH)D was significantly associated with an elevated risk of BPH, whereas higher serum 25(OH)D exerted a consistent protective effect against BPH, with a clear dose–response relationship. In continuous variable analyses, each 1-SD increment in serum 25(OH)D was related to a 2% lower risk of BPH. RCS analysis further confirmed a nonlinear link between serum 25(OH)D and BPH risk ($p < 0.05$). Importantly, the findings held up consistently under extensive subgroup analyses (stratified by education, ethnicity, and BMI) and multiple sensitivity analyses, providing stable prospective epidemiological evidence supporting a potential protective effect of serum 25(OH)D against BPH development. Besides, in analyzing the covariates of our included population, it was found that the combined proportion of overweight and obesity reached as high as 74.78%, which cor-

TABLE 2. Associations between serum vitamin D and incident benign prostatic hyperplasia.

Plasma Vitamin D (nmol/L)	Cases/Person-years	HR (95% CI)	*p*-value	*p* for trend
Q1, lowest (10.0∼32.1)	4746/612,378	1.00 (reference)	NA	0.009
Q2 (32.2∼46.5)	5094/612,557	0.95 (0.91, 0.99)	0.007	
Q3 (46.6∼62.0)	5497/611,687	0.94 (0.90, 0.98)	0.001	
Q4, highest (62.1∼133.0)	5831/610,383	0.95 (0.91, 0.98)	0.006	
Per SD increases (20.9)	21,168/2,447,005	0.98 (0.97, 0.99)	0.004	NA

Model adjusted for household income, body mass index, ethnicity, education, smoking status, alcohol intake, lipid-lowering medication, antihypertensive medication, insulin therapy and low-density lipoprotein. SD: standard deviation; HR: hazard ratio; CI: confidence interval; NA: not applicable.

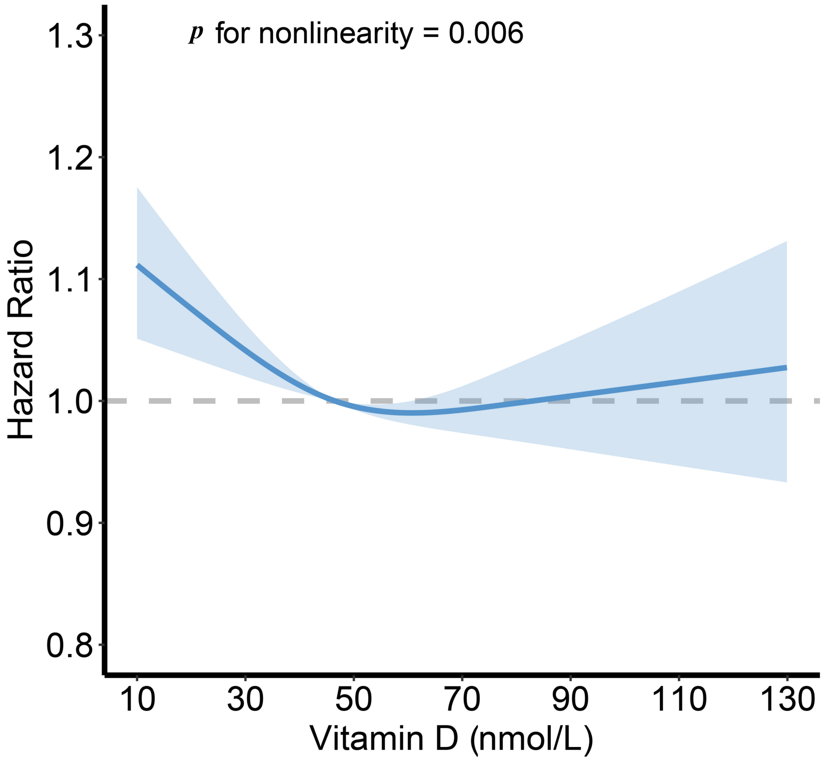

FIGURE 2. The dose-response association between vitamin D and incident benign prostatic hyperplasia. Model adjusted for household income, body mass index, ethnicity, education, smoking status, alcohol intake, lipid-lowering medication, antihypertensive medication, insulin therapy and low-density lipoprotein. Three knots were applied in the model.

TABLE 3. Associations between vitamin D and incident benign prostatic hyperplasia stratified by education, body mass index and ethnicity.

Subgroup	HR (95% CI)	*p* value	*p* for interaction
Education			
College or above	0.97 (0.95, 0.99)	0.001	0.057
High school or equivalent	0.99 (0.97, 1.01)	0.355	
Less than high school	1.00 (0.98, 1.03)	0.909	
Ethnicity			
White	0.98 (0.97, 0.99)	0.012	0.423
Non-white	0.97 (0.91, 1.04)	0.411	
Body mass index (kg/m^2)			
<25	0.99 (0.96, 1.01)	0.315	0.523
25–30	0.98 (0.97, 1.00)	0.063	
>30	0.98 (0.96, 1.00)	0.099	

HR indicates effects of increased plasma Vitamin D per SD on benign prostatic hyperplasia. Model was adjusted for household income, body mass index, ethnicity, education, smoking status, alcohol intake, lipid-lowering medication, antihypertensive medication, insulin therapy and low-density lipoprotein except for subgroup variable. HR: hazard ratio; CI: confidence interval.

TABLE 4. Sensitivity analysis.

Plasma Vitamin D (nmol/L)	HR (95% CI)	*p*-value	*p* for trend
Adjusted for diet score			
Q1	Reference		
Q2	0.95 (0.91, 0.99)	0.012	
Q3	0.94 (0.91, 0.98)	0.003	0.022
Q4	0.95 (0.91, 0.99)	0.014	
Per SD increase	0.98 (0.97, 1.00)	0.011	
Excluding events within 3 years			
Q1	Reference		
Q2	0.95 (0.91, 1.00)	0.035	
Q3	0.92 (0.88, 0.96)	<0.001	0.001
Q4	0.93 (0.89, 0.98)	0.002	
Per SD increase	0.97 (0.96, 0.99)	<0.001	
Excluding participants with missing values			
Q1	Reference		
Q2	0.94 (0.90, 0.98)	0.005	
Q3	0.93 (0.89, 0.97)	0.001	0.030
Q4	0.95 (0.91, 0.99)	0.018	
Per SD increase	0.98 (0.97, 1.00)	0.042	

Model adjusted for household income, body mass index, ethnicity, education, smoking status, alcohol intake, lipid-lowering medication, antihypertensive medication, insulin therapy and low-density lipoprotein. HR: hazard ratio; CI: confidence interval; SD: standard deviation.

roborates the epidemiological feature of a high co-occurrence between metabolic syndrome and BPH; regarding medication use, which reflects the comorbid burden, our data further validates that metabolic diseases (hypertension, hyperlipidemia, and diabetes) exhibit a clustering among BPH patients to some extent. Notably, the insulin therapy data captured in our study only reflects diabetes requiring insulin therapy, the overall prevalence of diabetes would be further increased while users of oral hypoglycemic agents were collected.

In addition to epidemiological evidence, the biological possibility of the negative correlation between serum 25(OH)D and BPH could be observed, which was supported by lots of preclinical research. As not only a classical target organ of vitamin D, but also possessing the capacity for local vitamin D metabolism, the prostate exhibits intrinsic specific enzymatic activity responsible for the activation and degradation of 25(OH)D [30]. Within prostatic stromal and epithelial cell populations, effective expression of the VDR and 1α-hydroxylase (CYP27B1) is detected, which enables the activation of circulating 25(OH)D to 1,25-Dihydroxyvitamin D_3 (1,25$(OH)_2D_3$) [31, 32]. After binding to the VDR, upregulated 1,25$(OH)_2D_3$ mediates prostatic cell antiproliferation via two key pathways: on one hand, 1,25$(OH)_2D_3$ enhances the expression of cyclin-dependent kinase inhibitors (CDKIs) p21 and p27 to arrest the cell cycle at the G_0/G_1 phase [33]; on the other hand, insulin-like growth factor 1 (IGF-1) pathway would be suppressed by 1,25$(OH)_2D_3$, which attenuates mitogenic signal transduction and abrogating proliferative drive [34, 35]. Apart from direct antiproliferative actions on prostatic cells, vitamin D exhibits significant anti-inflammatory properties, which aligns with histopathological evidence documenting chronic inflammatory infiltration as a prevalent pathological hallmark of BPH tissue [36]. For instance, the nuclear factor-kappa B (NF-κB) pathway was inhibited by vitamin D in prostatic tissue, which mediates the downregulation of pro-inflammatory cytokines, including interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [37], thereby mitigating local inflammatory responses associated with BPH progression. Moreover, vitamin D may regulate transforming growth factor-beta (TGF-β) signaling and inhibit the differentiation of prostatic fibroblasts into myofibroblasts, which thereby reduce stromal fibrosis [38, 39]. Furthermore, low vitamin D maybe one of the reasons of exacerbating prostatic tissue damage caused by mitochondrial dysfunction and oxidative stress [40–42]. Notably, vitamin D may regulate androgen-sensitive BPH via VDR-mediated modulation of sex hormone metabolism, specifically inhibiting 5α-reductase to reduce dihydrotestosterone (DHT) production—a key therapeutic target for BPH [43, 44].

The dose–response relationship identified in this study holds substantial clinical relevance, which is validated by more and more epidemiological investigations, bolstering further support for the robustness of this association. Based on an observational investigation conducted across the United States, serum 25(OH)D quantified before prostate biopsy exhibited an inverse relationship with prostate volume at diagnosis [45, 46]. Further demonstrated by meta-analyses, the association between polymorphisms of VDR gene and the susceptibility to BPH provided cumulative supportive evidence [47]. The findings above collectively suggest that vitamin D supplementation or activation of VDR may help dampen inflammatory responses and slow disease progression in individuals with BPH [48]. Of particular note, a nonlinear association was revealed via RCS analysis in present study, suggesting that the protective effect of vitamin D may exhibit a "saturation effect", *i.e.*, whereby further benefits plateau once exceeding certain concentration threshold, which corresponds to those documented for vitamin D in other chronic conditions [27]. Sensitivity analyses remained consistent after including participants with dietary quality scores, which confirmed the robustness of vitamin D for a protective role across diverse diets.

Based on the present study and existing evidence, future research endeavors could be expanded and spread. First, leveraging validated genetic variants as instrumental variables, Mendelian randomization (MR) could be carried out to further interrogate the causal relationship between circulating vitamin D status and BPH susceptibility [49]. Second, adequate sample size randomized controlled trials (RCTs), which preferably are double-blind and placebo-controlled, should be performed to rigorously investigate the influence of vitamin D supplementation in avoiding BPH onset or attenuating disease progression. Third, the detailed and intricate molecular mechanisms underlying the link between vitamin D and BPH pathogenesis warrant further investigation, with particular emphasis on the reciprocal crosstalk with androgen signaling pathways. Fourth, vitamin D might be linked to various heterogeneous disease phenotypes of BPH, such as stromal-predominant versus epithelial-predominant hyperplasia, which could shed light on identifying potential subtype protective effects and therapeutic implications.

Notwithstanding the stringent study design, several limitations need to be elucidated. First of all, serum 25(OH)D was assessed solely at baseline, failing to capture long-term variability or trend in vitamin D. Nonetheless, 25(OH)D levels were regarded as exhibiting long-term stability in individuals, with an intraclass correlation coefficient (ICC) of approximately 0.7 [50]. Secondly, BPH diagnoses within UKB were primarily derived from routine electronic health records, which may have led to underdiagnosis of mild or asymptomatic cases, which tends to bias effect estimates toward the null value, rendering our findings conservative. Additionally, while extensive adjustments for potential confounders were performed, unmeasured factors like detailed cumulative sun exposure duration may still affect vitamin D levels, and residual confounding cannot be entirely excluded. Finally, given that the UK Biobank cohort is predominantly of European ancestry, the generalizability of these findings to non-European populations warrants further investigation.

5. Conclusions

Based on large-scale prospective cohort data from UKB, the inverse correlation between serum 25(OH)D levels and BPH was validated, where a nonlinear pattern is further identified by RCS analysis. Moreover, following rigorous multivariable adjustments for diverse potential confounders, the association of both remains robust, which highlights the clinical protective role of vitamin D for BPH, offering a viable avenue for prevention and management.

ABBREVIATIONS

BPH, benign prostatic hyperplasia; TZ, transition zone; LUTS, lower urinary tract symptoms; UTIs, urinary tract infections; AUR, acute urinary retention; 25(OH)D, 25-hydroxyvitamin D; UKB, United Kingdom Biobank; HES, Hospital Episode Statistics; ICD-10, International Classification of Diseases, 10th Revision; BMI, body mass index; CLIA, chemiluminescent immunoassay; HRs, hazard ratios; SD, standard deviation; LDL, low-density lipoprotein; IQR, interquartile ranges; CIs, confidence intervals; RCS, Restricted cubic spline; VDR, vitamin D receptor; CYP27B1, 1α-hydroxylase; IGF-1, insulin-like growth factor 1; NF-κB, nuclear factor-kappa B; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; TGF-β, transforming growth factor-beta; DHT, dihydrotestosterone; MR, mendelian randomization; RCTs, randomized controlled trials; ICC, intraclass correlation coefficient; CoxPH, Cox proportional hazards; CDKIs, cyclin-dependent kinase inhibitors; 1,25(OH)$_2$D$_3$, 1,25-Dihydroxyvitamin D$_3$.

AVAILABILITY OF DATA AND MATERIALS

The datasets utilized and/or analyzed in the present study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

YMY—methodology, writing-original draft. CC—writing-original draft. YX—formal analysis. FQ—revised the original draft. JHY—conceptualization. FXZ—project administration. XDW—conceptualization, funding acquisition.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The original data for this study were obtained from UK Biobank. The UK Biobank cohort study obtained ethical clearance from the North West Multi-Center Research Ethics Committee (Approved Research ID 105913) which is available online (https://www.ukbiobank.ac.uk/), and all participants provided written informed consent at the time of enrollment. The present data analysis was conducted in compliance with the Declaration of Helsinki and applicable regulatory guidelines and standards.

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Not applicable.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests. Jiuhong Yuan is serving as one of the Editorial Board members of this journal. We declare that Jiuhong Yuan had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to XZY.

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