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Association between serum 25-hydroxyvitamin D and prostate cancer in middle-aged and elderly Americans: a national population-based analysis of NHANES 2001–2018

Guohui Zhang[1*], Xiaoyan Guo[2,3], Cunle Zhu[1], Shihao Li[1], Zhijian Xu[1], Jing Liang[1] and Xiangwei Wang[1*]

Abstract

Background The impact of serum 25-hydroxyvitamin D [25(OH)D] on prostate cancer (PCa) development remains inconclusive. This investigation aimed to evaluate the association between 25(OH)D concentrations and PCa prevalence using data from a nationally representative cohort.

Methods A cross-sectional analysis was performed using data from individuals aged 40 years and older who participated in the National Health and Nutrition Examination Survey (NHANES) from 2001 to 2018. Comprehensive demographic and clinical information, including 25(OH)D levels and PCa status, was obtained. Multivariate logistic regression models were utilized to determine the association between serum 25(OH)D concentrations and PCa prevalence.

Results This study analyzed data from 17,989 individuals, with a mean age of 61.1 ± 12.8 years and an average serum 25(OH)D concentration of 68.3 ± 23.3 nmol/L. PCa was diagnosed in 3.3% (n = 848) of participants. After full adjustment for potential confounders, elevated serum 25(OH)D concentrations were positively associated with the prevalence of PCa (p for trend = 0.007). Each 10-unit increment in serum 25(OH)D was linked to a 7% increase in PCa prevalence. Curve fitting analysis demonstrated a linear, positive association between serum 25(OH)D levels and PCa frequency. This trend remained consistent across all sensitivity analyses, including restriction to participants aged ≥ 60 years, exclusion of outlier serum 25(OH)D values (> mean + 3SD), and complete-case analysis. Stratified analysis indicated that this association was notably stronger among individuals with cardiovascular disease (OR, 1.16 [95% CI, 1.08–1.24]; p for interaction = 0.025).

*Correspondence:
Guohui Zhang
ghzhang_gdmu@163.com
Xiangwei Wang
winn0324@gdmu.edu.cn

Full list of author information is available at the end of the article

Conclusion In adults over 40 in the U.S., higher serum 25(OH)D concentrations were positively correlated with PCa prevalence, with cardiovascular disease potentially modifying this relationship. Regulating serum 25(OH)D levels may contribute to mitigating PCa prevalence.

Keywords 25-hydroxyvitamin D, Prostate cancer, Cross-sectional study, Biomarkers, NHANES

Introduce

Prostate cancer (PCa) remains the most commonly diagnosed malignancy and the second leading cause of cancer-related death among men in the United States, exerting substantial social and economic impacts. Between 2014 and 2019, its incidence increased annually by 3%, with nearly half of the patients presenting with advanced-stage disease at initial diagnosis [1]. According to the American Cancer Society, 288,830 new PCa cases and 33,330 associated deaths were recorded in the U.S. in 2023. Addressing PCa prevention and treatment continues to pose global challenges. Although recent research has yielded significant progress, the underlying causes of PCa remain unclear. Its development and progression reflect a complex, multi-phase trajectory influenced by age, hereditary predisposition, environmental exposures, lifestyle patterns, physical activity levels, genetic risk factors, and the composition of the microbiota [2–4].

Vitamin D, a fat-soluble micronutrient, is primarily synthesized in the skin through a multistep photochemical process triggered by ultraviolet radiation and can also be obtained via dietary intake and supplementation [5]. In circulation, it predominantly exists as 25(OH)D, which plays a fundamental role in mediating intestinal calcium absorption, maintaining skeletal integrity, and regulating various physiological processes [5, 6]. Epidemiological studies examining the relationship between 25(OH)D levels and PCa incidence have yielded different outcomes. Initial investigations conducted before 2005 suggested a potential inverse relationship between serum 25(OH)D concentrations and PCa prevalence [7]. In contrast, studies published between 2005 and 2015 largely failed to demonstrate any statistically significant correlation [8, 9]. More recent analyses (2015–2025), particularly those focusing on subgroups such as individuals with cardiovascular disease (CVD), have identified a positive association [10–12]. This variability in outcomes may reflect the influence of diverse factors, including differences in population demographics, ethnicity, geographical region, sample size, study design, and advancements in assay precision for 25(OH)D quantification. Although the causal relationship remains unknown, contemporary evidence of higher methodological quality increasingly supports a positive link between elevated 25(OH)D levels and PCa development.

Understanding the relationship between serum 25(OH)D concentrations and PCa prevalence informs public health guidance. This study aimed to investigate the association between 25(OH)D levels and PCa among middle-aged and older adults in the United States, utilizing cross-sectional data from NHANES spanning 2001 to 2018.

Materials and methods

Study population

NHANES, a nationally representative survey, systematically evaluates the health and nutritional status of the non-institutionalized U.S. population by employing an extensive array of methodologies, including questionnaires, clinical examinations, laboratory testing, dietary assessments, and physical activity tracking. All participants provided written informed consent after being briefed on the study's objectives and procedures. The survey is administered by the National Center for Health Statistics (NCHS), within the Centers for Disease Control and Prevention (CDC). Its study protocol, including all data collection procedures, received approval from the NCHS Research Ethics Review Committee.

The NHANES database spanning 2001 to 2018 was queried for records pertaining to serum 25(OH)D concentrations and cases of PCa. From an initial cohort of 103,977 individuals, exclusions were applied to women ($n = 22{,}538$) and those under 40 years of age ($n = 61{,}425$). Records lacking serum 25(OH)D measurements ($n = 2{,}009$) or PCa information ($n = 16$) were also omitted. The final analytical dataset for this study was 17,989 (Fig. 1).

Assessment of serum 25(OH)D levels and PCa

The serum 25(OH)D concentration—including both 25(OH)D2 and 25(OH)D3—serves as the benchmark biomarker for evaluating vitamin D status [13]. In NHANES, serum 25(OH)D levels were measured from blood specimens collected irrespective of participants' fasting status, adhering to standardized protocols outlined in the NHANES Laboratory Procedures Manual. From 2001 to 2006, measurements employed the DiaSorin radioimmunoassay (RIA) kit (Stillwater, MN, USA). Beginning with the 2007 cycle and continuing through 2018, quantification was conducted using the more precise ultra-high performance liquid chromatography–tandem mass spectrometry (UHPLC-MS/MS). Supplementary Table 2 provided specific information on the limits of detection (LOD) for serum 25(OH)D. To enable comparison across survey cycles, the CDC implemented regression-based calibration, converting RIA-derived values into

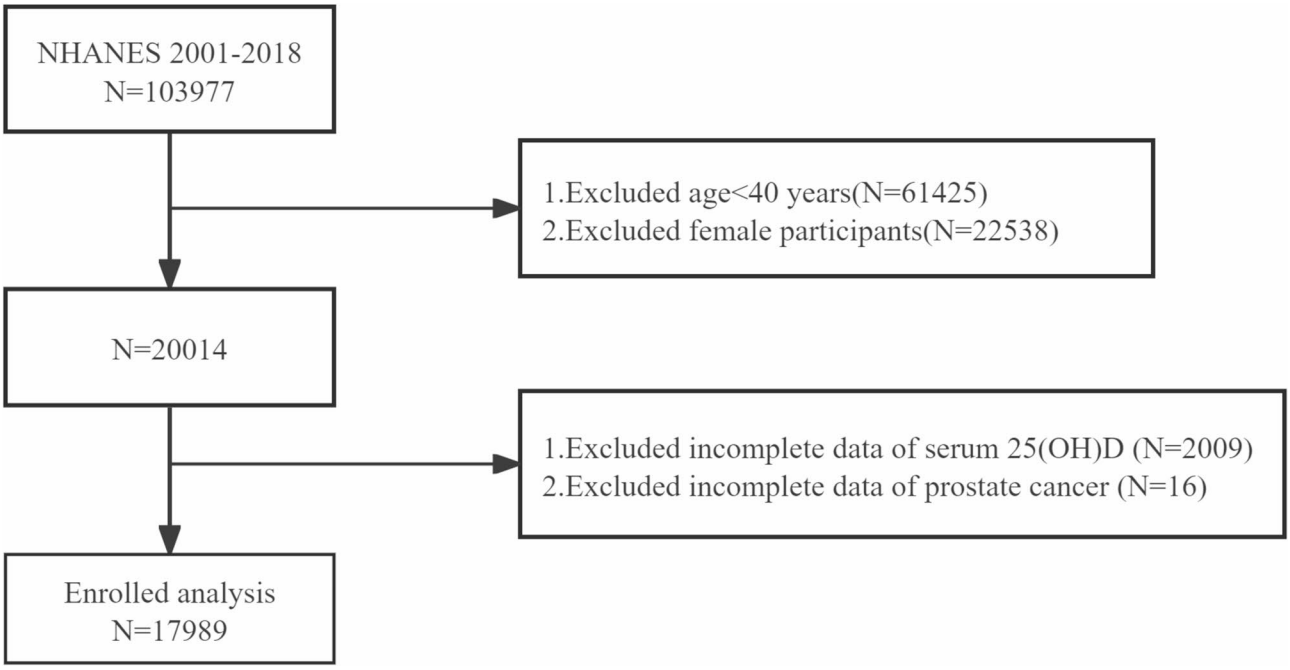

Fig. 1 Flow diagram of participant selection: Inclusion and exclusion criteria for the NHANES 2001–2018 analysis

UHPLC-MS/MS equivalents [14]. Comprehensive documentation regarding this standardization process is accessible via the official CDC platform.

PCa status was designated as the dependent variable and was ascertained through a validated questionnaire. Responses to the items "Have you ever been told that you have cancer?" (MCQ220) and "What kind of cancer was it?" (MCQ230) were utilized to identify participants with a self-reported diagnosis of PCa.

Covariates

A comprehensive set of covariates was incorporated to mitigate confounding effects. These included demographic variables (age, race, poverty-to-income ratio [PIR], educational attainment, and marital status), lifestyle factors (smoking status, alcohol intake, and physical activity), anthropometric indicators (body mass index [BMI] and waist circumference[WC]), clinical conditions (diabetes, hypertension, and CVD), and biochemical markers (albumin, cholesterol, creatinine, total bilirubin, total protein, and triglycerides).

Age was stratified into two categories: 40–60 years and ≥ 60 years. Race/ethnicity was categorized as Mexican American, non-Hispanic white, non-Hispanic black, other Hispanic, or other unspecified groups. Educational attainment was divided into three levels: less than high school, high school graduate, and more than high school. Marital status was grouped into married/living with a partner, widowed/divorced/separated, and never married. PIR was classified into low (≤ 1.3), moderate (1.3–3.5), and high (> 3.5) categories. BMI was grouped as ≥ 30 kg/m², 25–30 kg/m², and < 25 kg/m². Individuals with hypertension met inclusion criteria if they had a clinical diagnosis, were prescribed antihypertensive medication, or presented with an average blood pressure ≥ 140/90 mmHg [15]. Inclusion criteria for diabetes included a clinical diagnosis, antidiabetic medication use, fasting glucose ≥ 7.0 mmol/L, or HbA1c ≥ 6.5 mmol/L [16]. CVD was defined based on self-reported conditions such as congestive heart failure, coronary heart disease, angina, myocardial infarction, and stroke, consistent with definitions used in prior cohort studies [17]. Physical activity status was defined based on engagement in moderate-to-vigorous leisure-time physical activity reported within the previous 30 days (NHANES 2001–2006) or over a typical week (NHANES 2007–2018). Participants reporting such activity were categorized as active; others were labeled inactive. Smoking status was categorized as non-smoker (fewer than 100 cigarettes in lifetime), current smoker, or former smoker (cessation after smoking more than 100 cigarettes). Alcohol consumption was defined as non-drinker (≤ 12 drinks annually) or drinker (> 12 drinks annually).

Statistical analysis

Sampling weights provided by NHANES were applied to account for the complex multistage probability sampling design, thereby ensuring national representativeness of the non-institutionalized U.S. civilian population. Due to the limited number of participants diagnosed with PCa, multiple imputation was implemented to address missing covariate data, with the extent of missingness detailed in

Table 1 Characteristics of the population categorized by serum 25(OH)D (weighted)

Characteristic	25(OH)D, nmol/L					
	Overall	< 50 nmol/L	50–75 nmol/L	75–100 nmol/L	≥ 100 nmol/L	*p*-Value
NO.	17,989	5110	7613	4108	1158	
Age, Mean ± SD	61.1 ± 12.8	59.4 ± 12.4	60.9 ± 12.9	62.4 ± 12.9	65.3 ± 12.2	< 0.001
Age, n (%)						< 0.001
40–59 years	8255 (61.1)	2593 (65.7)	3546 (62.5)	1747 (59.4)	369 (47.6)	
≥ 60 years	9734 (38.9)	2517 (34.3)	4067 (37.5)	2361 (40.6)	789 (52.4)	
Race, n (%)						< 0.001
Mexican American	2474 (5.4)	938 (9.2)	1117 (5.8)	356 (2.9)	63 (1.5)	
Other Hispanic	1154 (3.8)	314 (5.1)	580 (4.5)	207 (2.1)	53 (2.36)	
Non-Hispanic White	9675 (77.0)	1608 (55.3)	4341 (78.4)	2919 (88.1)	807 (88.3)	
Non-Hispanic Black	3301 (8.1)	1826 (22.1)	1001 (5.6)	340 (2.8)	134 (3.3)	
Other Race	1385 (5.8)	424 (8.3)	574 (5.7)	286 (4.2)	101 (4.5)	
Education, n (%)						< 0.001
< High school	4757 (15.7)	1625 (20.9)	1990 (15.7)	928 (12.9)	214 (11.5)	
High school	4076 (23.2)	1184 (24.3)	1654 (22.0)	946 (23.9)	292 (23.7)	
> High school	9136 (61.2)	2293 (54.8)	3962 (62.3)	2232 (63.2)	649 (64.8)	
Matrimony, n (%)						< 0.001
Married/living with partner	13,091 (76.9)	3404 (69.0)	5757 (79.3)	3104 (79.5)	826 (75.2)	
Widowed/divorced/separated	3650 (16.6)	1198 (21.1)	1430 (15.3)	761 (14.7)	261 (18.9)	
Never married	1236 (6.5)	504 (9.9)	420 (5.4)	241 (5.8)	71 (5.9)	
PIR, Mean ± SD	3.4 ± 1.6	3.0 ± 1.6	3.4 ± 1.5	3.0 ± 1.5	3.7 ± 1.4	< 0.001
PIR, n (%)						< 0.001
Low (< 1)	2379 (8.4)	864 (13.6)	960 (7.7)	451 (6.5)	104 (4.9)	
Medium (1–3)	6749 (30.9)	2097 (38.2)	2826 (30.5)	1442 (27.3)	384 (26.3)	
High (> 3)	7527 (60.7)	1747 (48.2)	3284 (61.8)	1925 (66.1)	571 (68.8)	
Drinking status, n (%)						0.005
No	3228 (16.6)	961 (20.7)	1327 (16.3)	726 (14.7)	214 (14.4)	
Yes	13,616 (83.4)	3741 (79.3)	5836 (83.7)	3173 (85.3)	866 (85.6)	
Smoking status, n (%)						< 0.001
Never smoker	6992 (41.9)	1949 (41.1)	3040 (42.3)	1568 (40.4)	435 (43.0)	
Former smoker	7449 (39.5)	1761 (32.3)	3278 (40.2)	1886 (43.9)	524 (39.6)	
Current smoker	3535 (18.6)	1392 (26.7)	1291 (16.8)	654 (15.7)	198 (17.4)	
Hypertension, n (%)						0.002
No	8083 (51.0)	2146 (46.4)	3540 (51.8)	1918 (54.0)	479 (48.2)	
Yes	9899 (49.0)	2964 (53.6)	4068 (48.2)	2188 (46.0)	679 (51.9)	
Diabetes, n (%)						< 0.001
No	13,782 (81.7)	3635 (75.1)	5992 (83.1)	3287 (84.3)	868 (82.2)	< 0.001
Yes	4207 (18.3)	1475 (24.9)	1621 (17.0)	821 (15.7)	290 (17.8)	
CVD, n (%)						
No	14,437 (84.8)	4115 (83.8)	6154 (85.5)	3288 (85.3)	880 (82.1)	0.222
Yes	3550 (15.2)	995 (16.2)	1457 (14.5)	820 (14.7)	278 (17.9)	
Physical activity, n (%)						< 0.001
No	8625 (40.4)	2863 (51.3)	3510 (39.3)	1717 (34.5)	535 (38.8)	
Yes	9364 (59.6)	2247 (48.8)	4103 (60.8)	2391 (65.5)	623 (61.2)	
BMI (kg/m2), Mean ± SD	29.0 ± 5.5	30.0 ± 6.6	29.2 ± 5.3	28.2 ± 4.8	27.7 ± 4.7	< 0.001
BMI, n (%)						< 0.001
< 25	4255 (21.4)	1130 (19.8)	1683 (19.5)	1086 (23.7)	356 (28.4)	
25–30	7384 (43.1)	1853 (37.2)	3167 (42.5)	1851 (47.3)	513 (47.5)	
≥ 30	5922 (35.4)	1956 (43.0)	2605 (38.0)	1094 (29.0)	267 (24.1)	
25(OH)D(nmol/L), Mean ± SD	68.3 ± 23.3	38.9 ± 8.5	62.7 ± 6.9	84.9 ± 6.9	118.0 ± 19.8	< 0.001
WC, Mean ± SD	104.2 ± 14.0	106.2 ± 16.2	104.9 ± 13.6	102.6 ± 13.1	101.4 ± 12.6	< 0.001
TG, (mmol/L), Mean ± SD	2.0 ± 2.1	2.1 ± 3.4	2.0 ± 1.5	1.9 ± 1.7	1.6 ± 1.2	< 0.001
Cholesterol (mmol/L), Mean ± SD	5.1 ± 1.2	5.1 ± 1.3	5.2 ± 1.1	5.1 ± 1.1	5.0 ± 1.1	0.154

Table 1 (continued)

Characteristic	25(OH)D, nmol/L					
	Overall	< 50 nmol/L	50–75 nmol/L	75–100 nmol/L	≥ 100 nmol/L	*p*-Value
TP (g/L), Mean ± SD	71.1 ± 4.6	71.6 ± 4.9	71.2 ± 4.4	70.9 ± 4.5	70.6 ± 4.5	< 0.001
CR (umol/L), Mean ± SD	92.2 ± 39.2	92.8 ± 58.7	90.6 ± 28.2	92.7 ± 33.1	97.5 ± 46.7	< 0.001
TB (umol/L), Mean ± SD	13.4 ± 5.7	12.9 ± 6.2	13.7 ± 5.2	13.6 ± 6.2	12.7 ± 5.0	< 0.001
Albumin (g/L), Mean ± SD	42.9 ± 3.1	42.1 ± 3.5	43.1 ± 3.0	43.2 ± 2.9	43.2 ± 3.4	< 0.001
Prostate cancer, n (%)						< 0.001
No	17,141 (96.7)	4911 (97.4)	7302 (97.3)	3866 (95.9)	1062 (94.3)	
Yes	848 (3.3)	199 (2.6)	311 (2.7)	242 (4.1)	96 (5.7)	

Abbreviation: SD, standard deviation; BMI, body mass index; PIR, poverty income ratio; WC, waist circumference; TG, triglycerides; TP, total protein; CVD, cardiovascular disease; CR, creatinine; TB, total bilirubin

Supplementary Table 1. All statistical analyses adhered to a two-sided significance threshold of $p \leq 0.05$. Data processing and analyses were conducted using R (version 4.2.0) and freestatistics (version 1.9.2).

Baseline characteristics were compared across serum 25(OH)D concentration categories (< 50 nmol/L, 50–75 nmol/L, 75–100 nmol/L, ≥ 100 nmol/L), reflecting conventional clinical reference thresholds. Continuous variables were summarized as means with standard deviations (SD), while categorical variables were expressed as percentages. Weighted univariate and multivariate logistic regression models were employed to examine the independent association between serum 25(OH) D levels and PCa prevalence. Model 1 was unadjusted. Model 2 incorporated adjustments for demographic variables, including age, race, marital status, educational attainment, WC, BMI, and PIR. Model 3 extended the adjustments to include behavioral and health-related factors—physical activity, alcohol intake, smoking status, hypertension, diabetes, and CVD. Model 4 additionally controlled for laboratory parameters—cholesterol, albumin, creatinine, total bilirubin, total protein, and triglycerides.

After adjusting for covariates in model 4, the association between serum 25(OH)D levels and PCa was examined using restricted cubic spline (RCS) regression to model the linear trend. Effect modification was subsequently assessed across various subgroups, including age, race, education level, marital status, hypertension, diabetes, CVD, smoking, and alcohol consumption status.

To assess the robustness of the results, several sensitivity analyses were conducted. First, given the elevated incidence of PCa in older populations, the analysis was repeated in participants aged 60 years and above. Second, participants with serum 25(OH)D concentrations exceeding the mean by more than three SDs were excluded to minimize the influence of outliers. Third, a complete-case analysis was performed by removing individuals with missing covariate data to account for potential bias due to incomplete information. Lastly, considering the use of two distinct analytical techniques for measuring serum 25(OH)D, logistic regression models were independently applied to each measurement method to validate the consistency of associations across assay types.

Results

This study analyzed 17,989 male participants, with a mean age of 61.1 ± 12.8 years. Serum 25(OH)D concentrations ranged from 8.32 to 422 nmol/L, averaging 68.3 ± 23.3 nmol/L. Compared with those with lower 25 (OH) D levels, participants with higher 25 (OH) D levels tended to be older (median age: 65.3 vs. 59.4 years), exhibited higher levels of physical activity (61.2% vs. 48.8%), were more frequently married or cohabitating (75.2% vs. 69.0%), attained higher educational levels (64.8% vs. 54.8%), reported greater household income (68.8% vs. 48.2%), had lower alcohol consumption (17.4% vs. 26.7%), and demonstrated a reduced prevalence of diabetes (17.8% vs. 24.9%) (all $p < 0.001$). PCa was diagnosed in 3.3% ($n = 848$) of the total cohort. An incremental increase in PCa prevalence was observed across ascending 25(OH)D categories (< 50 nmol/L: 2.6%, 50–75 nmol/L: 2.7%, 75–100 nmol/L: 4.1%, ≥ 100 nmol/L: 5.7%; $p < 0.001$).

Univariate logistic regression (Table 2) revealed positive associations between PCa prevalence and the following variables: age ≥ 60 years (OR 22.0, 95% CI: 13.25–36.57), waist circumference (OR 1.01, 95% CI: 1.00–1.02), diabetes (OR 1.56, 95% CI: 1.16–2.10), hypertension (OR 2.30, 95% CI: 1.73–3.06), middle-income status (OR 1.70, 95% CI: 1.09–2.66), and former smoking (OR 1.46, 95% CI: 1.11–1.91). In contrast, being unmarried (OR 0.25, 95% CI: 0.15–0.41), current smoking (OR 0.39, 95% CI: 0.24–0.61), elevated triglyceride levels (OR 0.82, 95% CI: 0.74–0.91), higher albumin (OR 0.92, 95% CI: 0.89–0.96), and total protein concentrations (OR 0.96, 95% CI: 0.93–0.99) were inversely associated with PCa prevalence (all $p < 0.05$).

A positive association between serum 25(OH)D levels and PCa prevalence was observed in the unadjusted Model 1 (OR, 1.11; 95% CI: 1.06–1.16; $p < 0.001$). This

Table 2 Univariate logistic regression analysis of association between serum 25(OH)D and PCa prevalence (weighted)

Variable	Prostate cancer	
	OR (95%CI)	*P*-value
Age, n (%)		
40–59 years	1 (Reference)	
≥ 60 years	22.0 (13.25 ~ 36.57)	< 0.001
Race, n (%)		
Mexican American	1 (Reference)	
Other Hispanic	2.94 (1.37 ~ 6.27)	0.006
Non-Hispanic White	3.71 (2.63 ~ 5.23)	< 0.001
Non-Hispanic Black	5.08 (3.56 ~ 7.24)	< 0.001
Other Race	2.17 (1.14 ~ 4.12)	0.019
Educationl, n (%)		
< High school	1 (Reference)	
High school	0.78 (0.55 ~ 1.10)	0.157
> High school	0.84 (0.54 ~ 1.30)	0.423
Matrimony, n (%)		
Married/living with partner	1 (Reference)	
Widowed/divorced/separated	1.45 (1.00 ~ 2.09)	0.051
Never married	0.25 (0.15 ~ 0.41)	< 0.001
PIR, n (%)		
Low (< 1)	1 (Reference)	
Medium (1–3)	1.70 (1.09 ~ 2.66)	0.019
High (> 3)	1.55 (0.99 ~ 2.43)	0.056
Drinking status, n (%)		
No	1 (Reference)	
Yes	0.67 (0.42 ~ 1.07)	0.091
Smoking status, n (%)		
Never smoker	1 (Reference)	
Former smoker	1.46 (1.11 ~ 1.91)	0.007
Current smoker	0.39 (0.24 ~ 0.61)	< 0.001
Hypertension, n (%)		
No	1 (Reference)	
Yes	2.30 (1.73 ~ 3.06)	< 0.001
Diabetes, n (%)		
No	1 (Reference)	
Yes	1.56 (1.16 ~ 2.10)	0.003
WC (cm)	1.01 (1.00 ~ 1.02)	0.025
BMI (kg/m^2)	0.99 (0.97 ~ 1.01)	0.398
Physical activity, n (%)		
No	1 (Reference)	
Yes	1.03 (0.75 ~ 1.41)	0.846
Triglycerides (mmol/L)	0.82 (0.74 ~ 0.91)	< 0.001
Cholesterol (mmol/L)	0.91 (0.78 ~ 1.07)	0.237
Total protein (g/L)	0.96 (0.93 ~ 0.99)	0.015
Creatinine (umol/L)	1.00 (1.00 ~ 1.00)	< 0.001
Total bilirubin (umol/L)	1.00 (0.98 ~ 1.03)	0.695
Albumin (g/L)	0.92 (0.89 ~ 0.96)	< 0.001

Abbreviation: BMI, body mass index; PIR, poverty income ratio; WC, waist circumference; OR, odds ratio; 95% CI, 95% confidence interval;

association persisted in Models 2, 3, and 4 after sequential adjustments for demographic, clinical, and laboratory confounders, with adjusted ORs of 1.07 (95% CI: 1.02–1.12; $p = 0.003$), 1.07 (95% CI: 1.02–1.12; $p = 0.009$), and 1.07 (95% CI: 1.02–1.12; $p = 0.007$), respectively (Table 3). These estimates suggest a 7% increase in PCa prevalence for every 10-unit increment in 25(OH)D concentration. Elevated PCa prevalence was more frequently observed among individuals with serum 25(OH)D levels of 75–100 nmol/L and ≥ 100 nmol/L, compared to those with levels below 50 nmol/L. In Model 4, the ORs for the 75–100 nmol/L and ≥ 100 nmol/L groups were 1.52 (95% CI, 1.04–2.22; $p = 0.031$) and 1.67 (95% CI, 1.06–2.63; $p = 0.029$), respectively. Importantly, the p-trend analysis across clinical cutpoints (< 50, 50–75, 75–100, ≥ 100 nmol/L) was statistically significant (p for trend = 0.007), indicating a dose-response relationship between ascending serum 25(OH)D categories and increased PCa prevalence. This linear association was further corroborated by restricted cubic spline analysis (Fig. 2), which showed a progressive rise in PCa probability with higher 25(OH)D levels (nonlinear $P = 0.621$).

Subgroup analysis was conducted to evaluate the association between serum 25(OH)D levels and PCa susceptibility across diverse demographic and clinical categories. After adjusting for potential confounders, no statistically significant variation was identified among subgroups stratified by age, race, education level, marital status, hypertension, diabetes, alcohol intake, or smoking status (Fig. 3). In contrast, a significant interaction emerged when stratified by CVD status (p for interaction = 0.03), with individuals in the CVD group demonstrating a more pronounced association between serum 25(OH)D levels and PCa prevalence (OR, 1.16; 95% CI, 1.08–1.24) compared to those without CVD.

A consistent positive association between serum 25(OH)D concentrations and PCa prevalence was observed across sensitivity analyses. Among participants aged ≥ 60 years (unweighted $n = 9{,}734$), this relationship persisted whether age was modeled as a continuous variable (OR, 1.06; 95% CI, 1.03–1.09; $p < 0.001$) or categorized by serum 25(OH)D levels (75–100 nmol/L: OR, 1.30; 95% CI, 1.05–1.62; ≥100 nmol/L: OR, 1.49; 95% CI, 1.13–1.97) (p for trend < 0.001) (Table 4). In the full cohort (all age groups), after excluding individuals with extreme 25(OH)D values (unweighted $n = 17{,}820$), the strength and direction of the association remained consistent. The adjusted ORs for the 75–100 nmol/L and ≥ 100 nmol/L categories were 1.35 (95% CI, 1.10–1.67; $p < 0.01$) and 1.62 (95% CI, 1.22–2.15; $p < 0.01$), respectively (Table 4). Similarly, in the complete-case analysis of the full cohort (unweighted $n = 14{,}904$), a persistent positive association was observed between serum 25(OH)D concentrations and PCa prevalence for the ≥ 100 nmol/L group (OR, 1.54; 95% CI: 1.14–2.09; $p < 0.01$) (Table 4).

Stratified multivariable logistic regression, based on assay methodology (RIA: 2001–2006; UHPLC-MS/MS: 2007–2018), further supported a consistent positive

Table 3 Logistic regression analysis of the association between serum 25(OH)D and prostate cancer (weighted; unweighted *n* = 17,9894)

Variable	Model 1		Model 2		Model 3		Model 4	
	OR(95% CI)	*P*	OR(95% CI)	*P*	OR(95% CI)	*P*	OR(95% CI)	*P*
Per 10 nmol/L increase	1.11(1.06,1.16)	< 0.001	1.07(1.02,1.12)	0.003	1.07(1.02,1.12)	0.009	1.07(1.02,1.12)	0.007
Clinical cut-offs								
< 50 nmol/L	1		1		1		1	
50–75 nmol/L	1.07(0.76,1.49)	0.711	1.07(0.75,1.54)	0.694	1.03(0.72,1.49)	0.855	1.04(0.71,1.50)	0.853
75–100 nmol/L	1.61(1.14,2.27)	0.007	1.57(1.07,2.29)	0.021	1.49(1.02,2.19)	0.041	1.52(1.04,2.22)	0.031
≥ 100 nmol/L	2.30(1.53,3.46)	< 0.001	1.75(1.10,2.79)	0.018	1.67(1.05,2.65)	0.031	1.67(1.06,2.63)	0.029
p for trend		< 0.001		0.006		0.012		0.007

Model 1: adjusted for no covariates

Model 2: adjusted for age, race, matrimony, education qualification, waist circumference, BMI, and PIR

Model 3: further adjusted (from model 2) for physical activity, drinking status, smoking status, hypertension, diabetes, and CVD

Model 4: further adjusted (from model 3) for cholesterol, albumin, creatinine, total bilirubin, total protein, triglycerides

Abbreviation: OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index; PIR, poverty income ratio; CVD, cardiovascular disease

association between serum 25(OH)D levels and PCa prevalence in the UHPLC-MS/MS subsample. Compared with the < 50 nmol/L reference group, the ≥ 100 nmol/L group exhibited higher effect estimates across models: model 1 (OR = 2.68; 95% CI, 1.78–4.04), model 2 (OR = 1.73; 95% CI, 1.09–2.76), model 3 (OR = 1.62; 95% CI, 1.01–2.60), and model 4 (OR = 1.63; 95% CI, 1.00–2.65), all with significant trend tests (p for trend < 0.05) (Table S3). In contrast, no statistically significant relationship was identified in the 2001–2006 dataset based on RIA measurements (Table S3). This discrepancy may reflect greater variability associated with RIA, limited sample size, or distinct exposure profiles in earlier populations. Nevertheless, despite methodological differences, the direction of the effect estimates (OR > 1) aligns with results from the full cohort analysis.

Discussion

This large cross-sectional analysis involving 17,989 middle-aged and older adults in the U.S. identified a positive linear association between serum 25(OH)D concentrations and PCa prevalence, with higher 25(OH)D levels correlating with increased odds of PCa (OR: 1.07; 95% CI: 1.02–1.12; $p = 0.007$). Consistency across nonlinear modeling, subgroup stratification, and sensitivity assessments reinforced the applicability of 25(OH)D as a potential indicator for PCa prevalence burden. Moreover, the presence of CVD appeared to modify the association between serum 25(OH)D and PCa prevalence, indicating a potential interaction effect.

Previous nested case-control investigations examining the association between serum 25(OH)D concentrations and PCa prevalence have produced inconsistent results. A study conducted in Finland reported an inversely linear association, where individuals in the lowest quartile (median 27.8 nmol/L) exhibited a significantly higher PCa prevalence compared to those in the highest quartile (median 70.3 nmol/L) (nonadjusted OR 3.1 and adjusted OR 3.5) [7]. In contrast, data from a cohort of 2,073 Nordic men, including 622 PCa cases, demonstrated a non-linear, U-shaped association, indicating increased prevalence among participants with both low (≤ 19 nmol/L) and high (≥ 80 nmol/L) serum 25(OH)D levels [18]. Notably, both studies involved populations with relatively low mean 25(OH)D concentrations, such as an average of 51 ± 19.4 nmol/L reported among Nordic men [18]. These lower values may reflect regional disparities in sun exposure and dietary vitamin D intake [19], which could partially account for divergent prevalence trends when compared to cohorts with higher baseline 25(OH)D status. Moreover, a meta-analysis including 11 randomized clinical trials found no statistically significant association between serum 25(OH)D levels and PCa prevalence, with a pooled odds ratio (OR) of 1.03 (95% CI: 0.96–1.10; $p = 0.41$) comparing individuals in the highest versus lowest vitamin D quantiles [20]. Variability in study outcomes may largely stem from methodological differences, including heterogeneity in participant selection and sample size, inconsistent 25(OH)D thresholds, variations in follow-up duration, and insufficient adjustment for confounding variables.

This study identified a positive association between elevated serum 25(OH)D concentrations and increased prevalence of PCa among individuals aged 40 years and older. A nested case–control study conducted in Norway, which followed 4,212 participants over a period exceeding 10 years, reported a significant correlation between higher 25(OH)D levels and PCa incidence, with the association more pronounced during summer and autumn—likely reflecting seasonal variations in sunlight exposure [21]. A meta-analysis including 21 controlled clinical studies, involving 11,941 PCa cases and 13,870 controls from Europe and North America, further demonstrated that higher circulating 25(OH)D levels were linked to a greater likelihood of PCa [22]. Similar patterns were corroborated in other meta-analyses comprising diverse

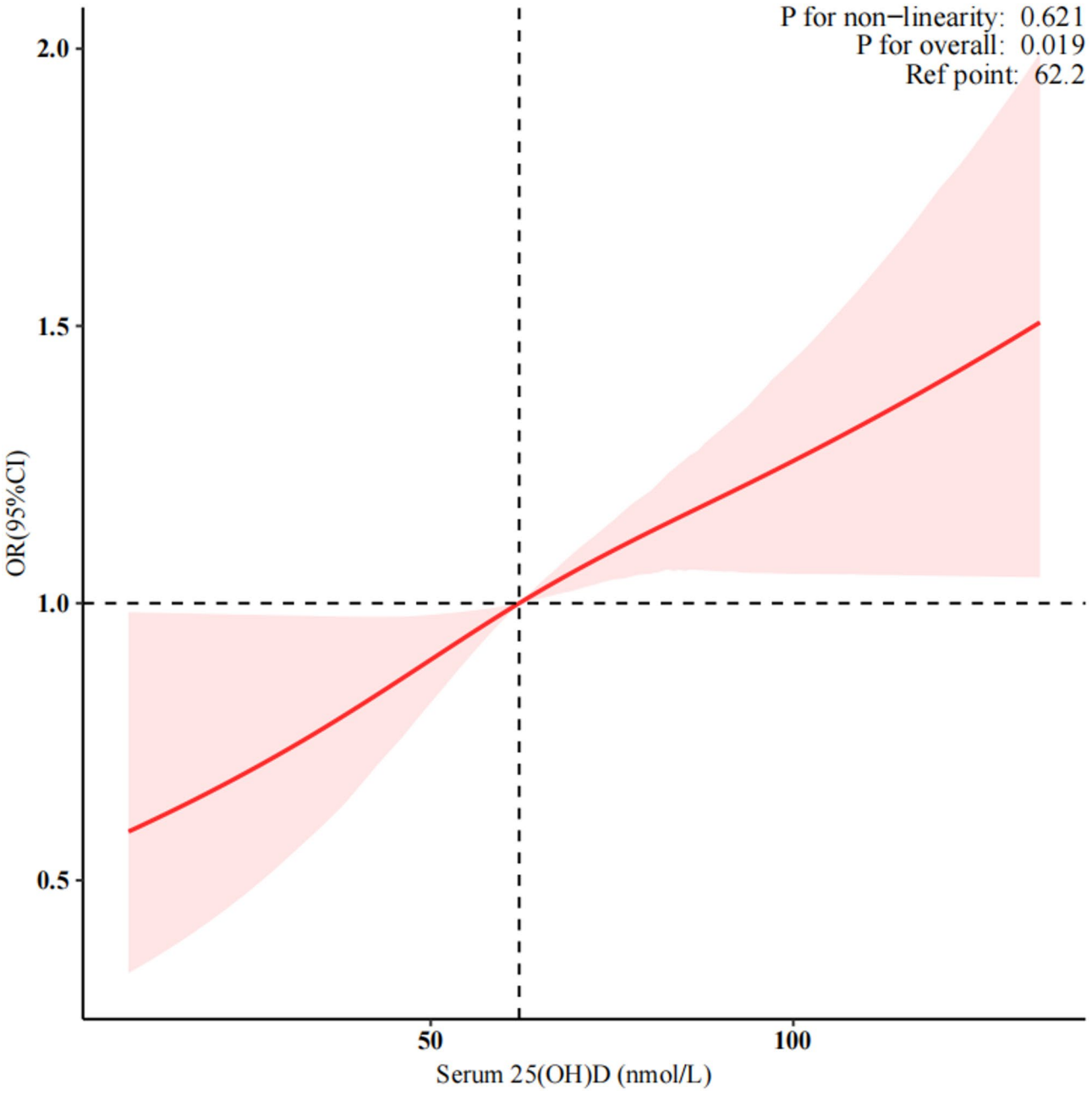

Fig. 2 Restricted cubic spline regression analysis of the dose-response relationship between serum 25(OH)D levels and PCa prevalence. Note: The lower limit of detection (LOD) of the 25(OH)D assay was 3.75 nmol/L for 2001–2006 and 2.03 nmol/L for 2007–2018

study cohorts [10]. In the present analysis, the mean serum 25(OH)D concentration was 68.3 nmol/L, surpassing the ≥ 50 nmol/L threshold recommended by the National Academy of Medicine (US) [23]. These findings suggest that maintaining serum 25(OH)D levels within the range of 50–75 nmol/L may represent an optimal target. A notable increase in PCa prevalence was observed when serum 25(OH)D concentrations exceeded 75 nmol/L (75–100 nmol/L group: OR 1.52, 95% CI 1.04–2.22, $p = 0.031$; ≥100 nmol/L group: OR 1.67, 95% CI 1.06–2.63, $p = 0.029$). In contrast, no elevated prevalence was detected within the 50–75 nmol/L range (OR 1.04, 95% CI 0.71–1.50, $p = 0.853$). Routine clinical monitoring of serum 25(OH)D is advisable to prevent sustained levels exceeding 75 nmol/L. Consistent with previous protocols, two distinct assay techniques were utilized to quantify serum 25(OH)D levels [24]. Sensitivity analyses revealed that the LC-MS/MS method more effectively identified associations between 25(OH)D and PCa compared to the traditional RIA assay, emphasizing the

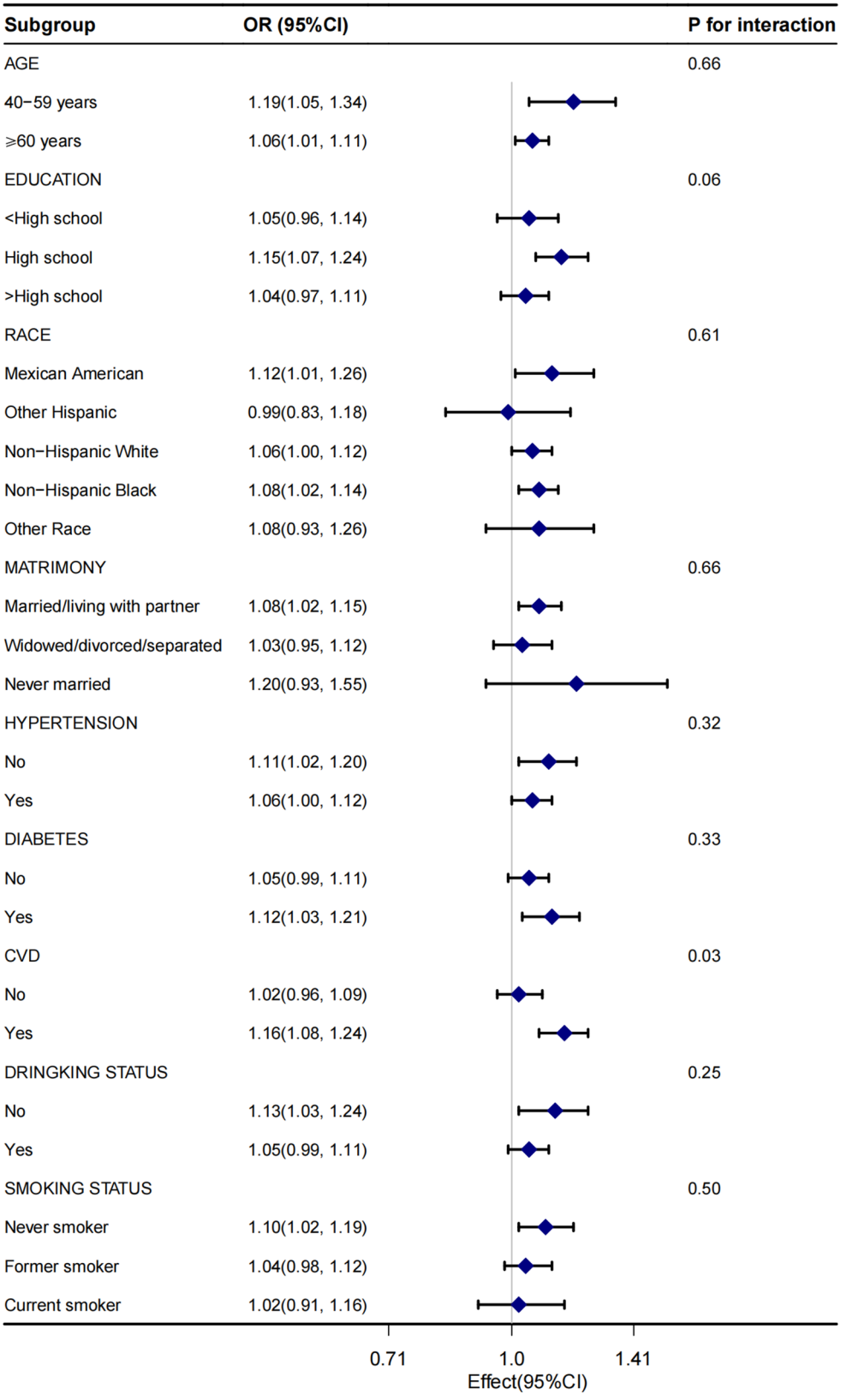

Fig. 3 Forest plot of association between serum 25(OH)D and PCa. Subgroup analysis was stratified by age, race, education qualification, matrimony, hypertension, and diabetes, smoking status, alcohol consumption and cardiovascular disease (CVD). Note: Hypertension: Confirmed diagnosis, antihypertensive medication use, or average blood pressure ≥ 140/90 mmHg; Diabetes: Clinical diagnosis, drug use, fasting blood glucose ≥ 7.0 mmol/L, or glycosylated hemoglobin ≥ 6.5 mmol/L; CVD: Classified as congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack, or stroke

Table 4 Logistic regression analysis of the association between serum 25(OH)D and PCa (unweighted)

Participants aged ≥ 60 years (*n* = 9,734)				
Variable	**Adjusted OR**	**95% CI**	***P***	***P* for trend**
Per 10 nmol/L increase	1.06	1.03,1.09	< 0.001	
Clinical cut-offs				
< 50 nmol/L	1			< 0.001
50–75 nmol/L	0.96	0.79,1.17	0.69	
75–100 nmol/L	1.30	1.05,1.62	0.02	
≥ 100 nmol/L	1.49	1.13,1.97	< 0.01	
Excluding participants with extreme serum 25(OH)D levels (*n* = 17,820)				
Per 10 nmol/L increase	1.08	1.04,1.11	< 0.001	
Clinical cut-offs				
< 50 nmol/L	1			< 0.001
50–75 nmol/L	0.97	0.80,1.18	0.80	
75–100 nmol/L	1.35	1.10,1.67	< 0.01	
≥ 100 nmol/L	1.62	1.22,2.15	< 0.01	
Excluding participants missing values for covariates (*n* = 14,904)				
Per 10 nmol/L increase	1.07	1.04,1.10	< 0.001	
Clinical cut-offs				
< 50 nmol/L	1			< 0.01
50–75 nmol/L	0.91	0.74,1.14	0.42	
75–100 nmol/L	1.25	0.98,1.58	0.07	
≥ 100 nmol/L	1.54	1.14,2.09	< 0.01	

Adjusted for age, race, matrimony, education, waist circumference, BMI, PIR, physical activity, drinking status, smoking status, hypertension, diabetes, CVD, cholesterol, albumin, creatinine, total bilirubin, total protein, and triglycerides

Abbreviation: OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index; PIR, poverty income ratio; CVD, cardiovascular disease

influence of measurement precision in nutritional epidemiological studies. Although statistical significance was not reached within the RIA subgroup, all point estimates (full cohort, RIA subgroup, MS subgroup) aligned in direction (OR > 1), suggesting a consistent trend across methodologies that is not entirely confounded by measurement error.

Although the mechanisms underlying the positive association between 25(OH)D levels and PCa prevalence remain unresolved, the observed relationship aligns with current biological evidence. First, Miller et al. reported that 1-α,25-(OH)2D3 promoted the proliferation of PCa cells in a dose-dependent manner through its interaction with specific biologically active receptors [25]. At physiological concentrations, it enhanced cellular proliferation, whereas supra-physiological levels induced differentiation [25]. Second, findings from molecular and epidemiological research suggest that the development of PCa is influenced by single nucleotide polymorphisms in multiple genes [26, 27]. The physiological actions of vitamin D are mediated primarily through the vitamin D receptor (VDR) and its downstream target genes [28]. Variants within the VDR gene have been linked to increased susceptibility to PCa [29–32]. One of the primary endocrine roles of 25(OH)D and VDR involves the regulation of metabolic pathways, particularly those governing energy homeostasis [33]. Given that activated innate and adaptive immune cells demand substantial energy resources [34], vitamin D and VDR are recognized as key modulators of immune function [35]. Because the signaling cascades that regulate cell proliferation, differentiation, and apoptosis are shared by both immune and malignant cells [36], it is plausible that vitamin D may play a role in the progression of PCa. Finally, disruptions in vitamin D signaling pathways have been observed in various malignancies, potentially contributing to PCa pathogenesis [37]. Nonetheless, the precise biological processes through which vitamin D operates in humans remain unclear, and additional prospective studies are needed to clarify its involvement in PCa progression.

This study has some notable strengths. First, the analysis utilizes data derived from the nationally representative NHANES database, enabling broader applicability of the results to populations beyond the U.S. context. Additionally, the implementation of sampling weights and the adjustment for a wide range of potential confounders enhances the robustness and validity of the statistical inferences.

Despite these strengths, several limitations merit consideration. First, although multiple confounding variables are adjusted for, the possibility of residual confounding cannot be excluded. Serum 25(OH)D is assessed through a single time-point measurement, which may not accurately reflect long-term vitamin D status; moreover, seasonal fluctuations in vitamin D levels are not incorporated into the analysis, potentially introducing temporal bias. Second, reliance on self-reported PCa diagnosis, while generally valid for cancer identification, lacks precision regarding diagnostic timing and clinical staging [38]. Third, the asymptomatic nature of early-stage PCa may contribute to underdiagnosis, especially in populations with restricted access to routine health evaluations, resulting in incomplete case identification. The elevated PCa prevalence observed among individuals with CVD may, in part, reflect more intensive diagnostic surveillance within this group, as frequent clinical follow-ups increase the likelihood of cancer detection. Unexpectedly higher ORs in subgroups such as non-smokers, non-drinkers, and younger individuals may stem from disparities in screening frequency-those with healthier lifestyles tend to engage more consistently in preventive health practices, thereby raising the probability of early PCa detection. Consequently, the observed associations may partially reflect differential diagnostic exposure rather than underlying biological variation. Fourth, the categorization of physical activity and alcohol intake—derived from predefined NHANES questionnaire items—lacks precision and may overlook variability in individual behavior patterns. Fifth, although multiple imputation

was applied to address missing covariate data (Table S1), this method relies on the assumption that data are missing at random. If the absence of data correlates with unobserved factors, the imputation process could introduce systematic bias. Furthermore, due to limitations inherent to the NHANES database, information on clinical staging and treatment details of PCa cases is unavailable, impeding stratified analyses of how serum 25(OH)D levels may relate to PCa progression. Lastly, the cross-sectional design restricts the ability to infer causality between serum 25(OH)D concentrations and PCa prevalence, highlighting the need for longitudinal research to validate this association.

Conclusion

In summary, elevated serum 25(OH)D concentrations are found to be positively associated with PCa prevalence among middle-aged and older adults in the U.S. The observed association raises concerns about the potential adverse implications of excessive 25(OH)D levels for PCa prevalence, particularly among individuals with concomitant CVD. Validation through prospective cohort studies is necessary to confirm these findings and clarify the underlying mechanisms.

Abbreviations

25(OH)D	25-hydroxyvitamin D
PCa	Prostate cancer
NHANES	National Health and Nutrition Examination Survey
CVD	Cardiovascular disease
US	United States
NCHS	National Center for Health Statistics
CDC	Centers for Disease Control and Prevention
RIA	Rradioimmunoassay
MS	Mass Spectrometry
UHPLC-MS/MS	Ultra-high performance liquid chromatography-tandem mass spectrometry
PIR	Poverty-to-income ratio
BMI	Body mass index
OR	Odds ratio
CI	Confidence interval
VDR	Vitamin D receptor
LOD	Limit of detectio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14360-0.

Supplementary Material 1

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Author contributions

GHZ was the principal designer of the study's framework. XYG, SHL and CLZ are responsible for collecting the data set. GHZ and XZJ assisted in reviewing the literature. WXW and JL combined the data and performed the analysis. GHZ and XYG wrote the manuscript together. WXW and ZGH are both correspondents and are responsible for the research process and results. All authors participated in the revision process and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The NHANES was approved by the Ethics Committee of the National Center for Health Statistics (NCHS). And all participants signed written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Urology, Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong Province, China
[2]Department of Development and Planning, Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong Province, China
[3]Guangdong Provincial Key Laboratory of Autophagy and Major Chronic Non- communicable Diseases, Key Laboratory of Prevention and Management of Chronic Kidney Diseases of Zhanjiang City, Institute of Nephrology, Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong Province, China

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References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17–48. https://doi.org/10.3322/caac.21763.
2. Bergengren O, Pekala KR, Matsoukas K, Fainberg J, Mungovan SF, Bratt O, Bray F, Brawley O, Luckenbaugh AN, Mucci L, Morgan TM, Carlsson SV. 2022 Update on prostate Cancer epidemiology and risk Factors-A systematic review. Eur Urol. 2023;84(2):191–206. https://doi.org/10.1016/j.eururo.2023.04.021.
3. Wang G, Zhao D, Spring DJ, DePinho RA. Genetics and biology of prostate cancer. Genes Dev. 2018;32(17–18):1105–40. https://doi.org/10.1101/gad.315739.118.
4. Rizzo A, Santoni M, Mollica V, Fiorentino M, Brandi G, Massari F. Microbiota and prostate cancer. Semin Cancer Biol. 2022;86(Pt 3):1058–65. https://doi.org/10.1016/j.semcancer.2021.09.007.
5. Bikle D, Christakos S. New aspects of vitamin D metabolism and action - addressing the skin as source and target. Nat Rev Endocrinol. 2020;16(4):234–52. https://doi.org/10.1038/s41574-019-0312-5.
6. de la Guía-Galipienso F, Martínez-Ferran M, Vallecillo N, Lavie CJ, Sanchis-Gomar F, Pareja-Galeano H. Vitamin D and cardiovascular health. Clin Nutr. 2021;40(5):2946–57. https://doi.org/10.1016/j.clnu.2020.12.025.
7. Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). Cancer Causes Control. 2000;11(9):847–52. https://doi.org/10.1023/a:1008923802001.
8. Ahn J, Peters U, Albanes D, Purdue MP, Abnet CC, Chatterjee N, Horst RL, Hollis BW, Huang WY, Shikany JM, Hayes RB, Prostate. Lung, colorectal, and ovarian Cancer screening trial project team. Serum vitamin D concentration and prostate cancer risk: a nested case-control study. J Natl Cancer Inst. 2008;100(11):796–804. https://doi.org/10.1093/jnci/djn152.
9. Travis RC, Crowe FL, Allen NE, Appleby PN, Roddam AW, Tjønneland A, Olsen A, Linseisen J, Kaaks R, Boeing H, Kröger J, Trichopoulou A, Dilis V, Trichopoulos D, Vineis P, Palli D, Tumino R, Sieri S, Bueno-de-Mesquita HB,

van Duijnhoven FJ, Chirlaque MD, Barricarte A, Larrañaga N, González CA, Argüelles MV, Sánchez MJ, Stattin P, Hallmans G, Khaw KT, Bingham S, Rinaldi S, Slimani N, Jenab M, Riboli E, Key TJ. Serum vitamin D and risk of prostate cancer in a case-control analysis nested within the European prospective investigation into Cancer and nutrition (EPIC). Am J Epidemiol. 2009;169(10):1223–32. https://doi.org/10.1093/aje/kwp022.

10. Gao J, Wei W, Wang G, Zhou H, Fu Y, Liu N. Circulating vitamin D concentration and risk of prostate cancer: a dose-response meta-analysis of prospective studies. Ther Clin Risk Manag. 2018;14:95–104. https://doi.org/10.2147/TCRM.S149325. Published 2018 Jan 9.
11. Yang J, Dong Y, Naugler CT, de Koning L. Serum 25-hydroxyvitamin D and risk of cancer in a large community population under investigation for cardiovascular disease: a retrospective cohort study. BMJ Open. 2022;12(1):e056543. https://doi.org/10.1136/bmjopen-2021-056543. Published 2022 Jan 19.
12. Atoum MF, AlKateeb D, AlHaj Mahmoud SA. The Fok1 vitamin D receptor gene polymorphism and 25(OH) D serum levels and prostate cancer among Jordanian men. Asian Pac J Cancer Prev. 2015;16(6):2227–30. https://doi.org/10.7314/apjcp.2015.16.6.2227.
13. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Endocrine society. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society.clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30. https://doi.org/10.1210/jc.2011-0385.
14. Yetley EA, Pfeiffer CM, Schleicher RL, Phinney KW, Lacher DA, Christakos S, Eckfeldt JH, Fleet JC, Howard G, Hoofnagle AN, Hui SL, Lensmeyer GL, Massaro J, Peacock M, Rosner B, Wiebe D, Bailey RL, Coates PM, Looker AC, Sempos C, Johnson CL, Picciano MF. Vitamin D roundtable on the NHANES monitoring of serum 25(OH)D: assay challenges and options for resolving them. NHANES monitoring of serum 25-hydroxyvitamin D: a roundtable summary. J Nutr. 2010;140(11):S2030–45. https://doi.org/10.3945/jn.110.121483.
15. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Sr, Williamson JD, Wright JT Jr., ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA. Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary. Hypertension. 2018;71(6):e13-e115. https://doi.org/10.1161/HYP.0000000000000065
16. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Cusi K, Das SR, Gibbons CH, Giurini JM, Hilliard ME, Isaacs D, Johnson EL, Kahan S, Khunti K, Kosiborod M, Leon J, Lyons SK, Murdock L, Perry ML, Prahalad P, Pratley RE, Seley JJ, Stanton RC, Sun JK, Woodward CC, Young-Hyman D, Gabbay RA, on behalf of the American Diabetes Association. Summary of revisions: standards of care in Diabetes-2023. Diabetes Care. 2023;46(Suppl 1):S5–9. https://doi.org/10.2337/dc23-Srev.
17. Zhang Q, Xiao S, Jiao X, Shen Y. The triglyceride-glucose index is a predictor for cardiovascular and all-cause mortality in CVD patients with diabetes or pre-diabetes: evidence from NHANES 2001–2018. Cardiovasc Diabetol. 2023;22(1):279. https://doi.org/10.1186/s12933-023-02030-z. Published 2023 Oct 17.
18. Tuohimaa P, Tenkanen L, Ahonen M, Lumme S, Jellum E, Hallmans G, Stattin P, Harvei S, Hakulinen T, Luostarinen T, Dillner J, Lehtinen M, Hakama M. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the nordic countries. Int J Cancer. 2004;108(1):104–8. https://doi.org/10.1002/ijc.11375.
19. Lamberg-Allardt CJ, Outila TA, Kärkkainen MU, Rita HJ, Valsta LM. Vitamin D deficiency and bone health in healthy adults in Finland: could this be a concern in other parts of Europe? J Bone Min Res. 2001;16(11):2066–73. https://doi.org/10.1359/jbmr.2001.16.11.2066.
20. Gandini S, Boniol M, Haukka J, Byrnes G, Cox B, Sneyd MJ, Mullie P, Autier P. Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. Int J Cancer. 2011;128(6):1414–24. https://doi.org/10.1002/ijc.25439.
21. Meyer HE, Robsahm TE, Bjørge T, Brustad M, Blomhoff R, Vitamin D. season, and risk of prostate cancer: a nested case-control study within Norwegian health studies. Am J Clin Nutr. 2013;97(1):147–54. https://doi.org/10.3945/ajcn.112.039222.
22. Xu Y, Shao X, Yao Y, Xu L, Chang L, Jiang Z, Lin Z. Positive association between Circulating 25-hydroxyvitamin D levels and prostate cancer risk: new findings from an updated meta-analysis. J Cancer Res Clin Oncol. 2014;140(9):1465–77. https://doi.org/10.1007/s00432-014-1706-3.
23. Institute of Medicine (US). Committee to review dietary reference intakes for vitamin D and calcium. In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Dietary reference intakes for calcium and vitamin. Washington (DC): National Academies Press (US); 2011. https://doi.org/10.17226/13050.
24. Binkley N, Sempos CT, Vitamin D, Standardization Program (VDSP). Standardizing vitamin D assays: the way forward. J Bone Min Res. 2014;29(8):1709–14. https://doi.org/10.1002/jbmr.2252.
25. Miller GJ, Stapleton GE, Ferrara JA, Lucia MS, Pfister S, Hedlund TE, Upadhya P. The human prostatic carcinoma cell line LNCaP expresses biologically active, specific receptors for 1 alpha,25-dihydroxyvitamin D3. Cancer Res. 1992;52(3):515–20.
26. Smith JR, Freije D, Carpten JD, Grönberg H, Xu J, Isaacs SD, Brownstein MJ, Bova GS, Guo H, Bujnovszky P, Nusskern DR, Damber JE, Bergh A, Emanuelsson M, Kallioniemi OP, Walker-Daniels J, Bailey-Wilson JE, Beaty TH, Meyers DA, Walsh PC, Collins FS, Trent JM, Isaacs WB. Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. Science. 1996;274(5291):1371–4. https://doi.org/10.1126/science.274.5291.1371.
27. Rebbeck TR, Walker AH, Zeigler-Johnson C, Weisburg S, Martin AM, Nathanson KL, Wein AJ, Malkowicz SB. Association of HPC2/ELAC2 genotypes and prostate cancer. Am J Hum Genet. 2000;67(4):1014–9. https://doi.org/10.1086/303096.
28. Maestro MA, Molnár F, Carlberg C. Vitamin D and its synthetic analogs. J Med Chem. 2019;62(15):6854–75. https://doi.org/10.1021/acs.jmedchem.9b00208.
29. Ingles SA, Coetzee GA, Ross RK, Henderson BE, Kolonel LN, Crocitto L, Wang W, Haile RW. Association of prostate cancer with vitamin D receptor haplotypes in African-Americans. Cancer Res. 1998;58(8):1620–3.
30. Feldman D. Androgen and vitamin D receptor gene polymorphisms: the long and short of prostate cancer risk. J Natl Cancer Inst. 1997;89(2):109–11. https://doi.org/10.1093/jnci/89.2.109.
31. Tayeb MT, Clark C, Haites NE, Sharp L, Murray GI, McLeod HL. CYP3A4 and VDR gene polymorphisms and the risk of prostate cancer in men with benign prostate hyperplasia. Br J Cancer. 2003;88(6):928–32. https://doi.org/10.1038/sj.bjc.6600825.
32. Torkko KC, van Bokhoven A, Mai P, Beuten J, Balic I, Byers TE, Hokanson JE, Norris JM, Barón AE, Lucia MS, Thompson IM, Leach RJ. VDR and SRD5A2 polymorphisms combine to increase risk for prostate cancer in both non-Hispanic white and Hispanic white men. Clin Cancer Res. 2008;14(10):3223–9. https://doi.org/10.1158/1078-0432.CCR-07-4894.
33. Hanel A, Carlberg C. Vitamin D and evolution: Pharmacologic implications. Biochem Pharmacol. 2020;173:113595. https://doi.org/10.1016/j.bcp.2019.07.024.
34. Müller V, de Boer RJ, Bonhoeffer S, Szathmáry E. An evolutionary perspective on the systems of adaptive immunity. Biol Rev Camb Philos Soc. 2018;93(1):505–28. https://doi.org/10.1111/brv.12355.
35. Vanherwegen AS, Gysemans C, Mathieu C. Vitamin D endocrinology on the cross-road between immunity and metabolism. Mol Cell Endocrinol. 2017;453:52–67. https://doi.org/10.1016/j.mce.2017.04.018.
36. Cortes M, Chen MJ, Stachura DL, Liu SY, Kwan W, Wright F, Vo LT, Theodore LN, Esain V, Frost IM, Schlaeger TM, Goessling W, Daley GQ, North TE. Developmental vitamin D availability impacts hematopoietic stem cell production. Cell Rep. 2016;17(2):458–68. https://doi.org/10.1016/j.celrep.2016.09.012.
37. Jeon SM, Shin EA. Exploring vitamin D metabolism and function in cancer. Exp Mol Med. 2018;50(4):1–14. https://doi.org/10.1038/s12276-018-0038-9. Published 2018 Apr 16.
38. Shafrir AL, Wise LA, Palmer JR, Shuaib ZO, Katuska LM, Vinayak P, Kvaskoff M, Terry KL, Missmer SA. Validity of self-reported endometriosis: a comparison across four cohorts. Hum Reprod. 2021;36(5):1268–78. https://doi.org/10.1093/humrep/deab012.

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