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Uncovering the subtle relationship between vitamin D and kidney stones: a cross-sectional NHANES-based study

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Abstract

Objective This study investigated the potential correlation between serum vitamin D levels and the risk of kidney stones. To this end, the National Health and Nutrition Examination Survey (NHANES) database resources from 2007 to 2018 were utilized. The influence of other demographic characteristics, lifestyle habits, and chronic diseases on this relationship was also assessed.

Methods This study included 59,842 participants from the NHANES survey, and after exclusions, 24,323 individuals with complete data were analyzed. Logistic regression modeling assessed odds ratios (OR) and 95% confidence intervals (CI) between vitamin D levels and kidney stone risk, and multivariable adjustment models were constructed to control for potential confounders. To investigate the dose–response relationship between vitamin D and kidney stones, restricted cubic spline (RCS) modeling was employed. Subgroup and interaction analyses were also conducted.

Results The preliminary analyses indicated a statistically significant positive correlation between vitamin D levels and kidney stone risk before adjustment for potential confounding variables (OR = 1.01, $P < 0.001$). However, after gradual adjustment for age, gender, race, and multiple lifestyle and chronic diseases, this association became non-significant (OR = 1.00, $P = 0.186$). Furthermore, RCS analyses demonstrated that the non-linear relationship between vitamin D levels and kidney stone risk was no longer statistically significant after adjustment for confounders. In the subgroup analyses, only slight statistical associations were observed in the subgroups of vigorous exercise and those with diabetes, with no significant differences in the remaining subgroups.

Conclusion The present study indicates that serum vitamin D level is not an independent predictor of kidney stone risk. Rather, its effect may be co-regulated by multiple confounding factors. Further research is required to elucidate the precise mechanisms through which vitamin D contributes to kidney stone formation and to consider the combined effects of genetic polymorphisms, dose effects, and other factors.

Keywords Serum vitamin D, Kidney stones, Cross-sectional study, Confounding factors, Dose–response relationship

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Introduction

Kidney stones are composed of crystalline deposits of various substances in the urine, including calcium, oxalate, phosphate, and uric acid [1, 2]. They are formed through a complex process involving the supersaturation of urine constituents, the formation of crystalline nuclei, and a deficiency of substances that inhibit crystallization [3, 4]. The precise etiology of kidney stones remains unclear; however, numerous risk factors have been identified, including genetic predisposition, environmental influences, dietary habits, and metabolic abnormalities [5–7].

Vitamin D is a fat-soluble vitamin essential for maintaining optimal bone health. It exerts influence over bone mineralization by promoting the intestinal absorption of calcium and phosphorus and regulating the levels of calcium and phosphorus in the blood [8, 9]. Moreover, vitamin D plays a role in regulating kidney function, including calcium reabsorption and phosphate excretion [10, 11]. Consequently, vitamin D may indirectly influence kidney stone formation by modulating calcium and phosphate concentrations in the urine.

However, the literature on the relationship between vitamin D levels and kidney stone risk is inconclusive [12]. Some studies have indicated that elevated vitamin D levels may be associated with an increased risk of kidney stones [13–16], while others have not observed a significant association [17, 18]. This inconsistency may be attributed to various factors, including study design, sample selection, and data analysis methods. Accordingly, further rigorous, large-scale studies are required to elucidate this issue.

In light of the background above, this study employed the resources of the National Health and Nutrition Examination Survey (NHANES) database from 2007 to 2018 to investigate the potential correlation between serum vitamin D levels and the risk of kidney stones. Furthermore, the objective was to ascertain whether other demographic characteristics, lifestyle habits, and chronic diseases influence this relationship. This study intends to provide clinicians with more accurate preventive and therapeutic strategies to reduce the incidence of kidney stones.

Methods

Study population

All data for this study were obtained from the NHANES database, which contains the results of cross-sectional surveys conducted biennially by the Centers for Disease Control and Prevention (CDC) in the USA. The study protocol for the NHANES database was approved by the Ethics Review Board of the National Center for Health Statistics (NCHS), and all participants signed an informed consent form. According to NIH policy, data in the NHANES database were not obtained through direct contact with participants. They could be used directly for data analysis without further review by the institutional ethics committee. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

This study initially enrolled 59,842 participants, with information drawn from six consecutive cycles of the NHANES survey. This study excluded participants with missing data regarding kidney stones and those who were pregnant, lacked information regarding vitamin D, had incomplete demographic data, had chronic disease data missing, or lacked other biochemical indicators. In conclusion, 24,323 participants were included in the analysis (Fig. 1).

Evaluation of kidney stones

A history of kidney stones was ascertained by inquiring whether the subject had ever experienced such a condition. This was determined by asking, "Have you or the sample person (SP) ever had a kidney stone?" Those who responded in the affirmative were classified as having kidney stones, whereas those who responded negatively were classified as not having kidney stones.

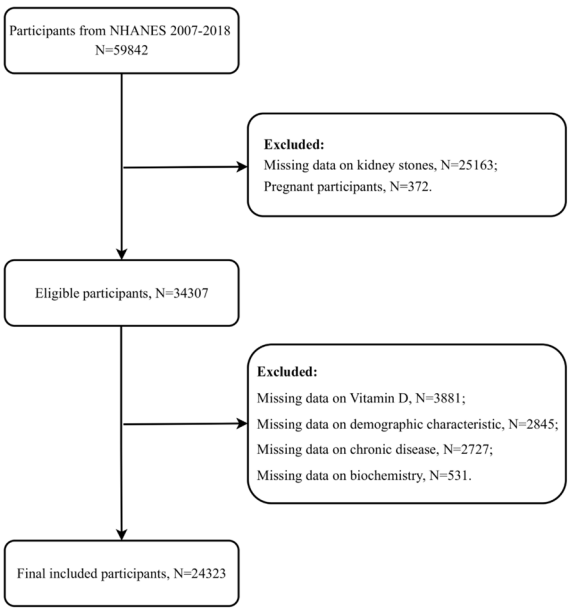

Fig. 1 Participant screening flowchart

Vitamin D assessment

Vitamin D was quantified in human serum using high-performance liquid chromatography-tandem mass spectrometry (HPLC–MS/MS) for 25-hydroxyvitamin D3 (25OHD3), 3-epi-25-hydroxyvitamin D3 (epi-25OHD3), and 25-hydroxyvitamin D2 (25OHD2). The total 25-hydroxyvitamin D (25OHD) is the sum of 25OHD2 and 25OHD3, but excludes epi-25OHD3 [19]. In this study, the total 25-hydroxyvitamin D was used as the variable to assess the vitamin D status of the participants.

Assessment of covariates

Multivariable-adjusted models were developed to ascertain the influence of confounding variables on the relationship between vitamin D and kidney stones. The following variables were considered as potential confounding factors: gender (male/female), age (years), race, education, marital status, family Poverty Income Ratio (PIR), drinking habits (yes/no), smoking status (yes/no), physical activity (vigorous/moderate/inactive), and a history of chronic diseases including diabetes mellitus, hypertension, coronary heart disease, stroke, and cancer.

The race category was divided into four groups. The categories were as follows: Mexican American, Non-Hispanic White, Non-Hispanic Black, and Other Race. Regarding educational attainment, participants were classified according to whether they had completed less than 9th grade, 9th to 12th grade, or more than 12th grade. Marital status was classified as either cohabitation or solitude. The PIR categorized Family income as defined in U.S. government reports. Family income categories were defined as follows: low (PIR $\leq$ 1.3), moderate (PIR > 1.3 to $\leq$ 3.5), and high (PIR > 3.5). Smoking status was determined based on the participant's responses to two questions: whether they had smoked at least 100 cigarettes in their lifetime and whether they were currently a smoker. Alcohol consumption was defined as the number of drinks of any type of alcoholic beverage consumed by the participant in any given year, with a minimum of 12 drinks. The variable "physical activity" was defined as whether the participant had engaged in any vigorous exercise that resulted in a significant increase in respiration or heart rate and whether the participant had been involved in any moderate-intensity exercise that resulted in a slight increase in respiration or heart rate. Variables about chronic medical history included diabetes (defined as a medical professional has diagnosed participant, or has a fasting plasma glucose level of 126 mg/dL or greater, or has a glycosylated hemoglobin level of 6.5% or greater, or is using diabetes medication), hypertension (defined as a self-report of high blood pressure or current use of prescription medication for high blood pressure), coronary heart disease (defined as a self-report of coronary heart disease, angina, or a heart attack), stroke (defined as a self-report of a stroke), and cancer (defined as a self-report of cancer).

Statistical analysis

The distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. The results are expressed as mean ± standard deviation or median (25th and 75th percentile). A one-way ANOVA or Kruskal–Wallis test was employed to compare these variables. Categorical variables are expressed as frequencies and percentages, and the chi-square test was employed to ascertain any significant differences between the groups. Logistic regression models were used to determine the odds ratios (ORs) and 95% confidence intervals (CIs) between vitamin D, vitamin D quartiles, and the risk of kidney stones. Three multivariable-adjusted models were constructed to address potential confounding variables. Model 1 was unadjusted. Model 2 incorporated age, gender, and race as covariates. Model 3 extends the adjustments made in Model 2 by additionally accounting for educational attainment, marital status, family PIR, smoking, alcohol consumption, physical activity, diabetes, hypertension, coronary heart disease, stroke, and cancer. Restricted cubic spline (RCS) modeling was employed to ascertain the potential existence of a dose–response relationship between vitamin D and kidney stones. To investigate the relationship between vitamin D and kidney stone risk in different subgroups, we conducted a subgroup analysis, dividing the cohort by gender, race, education, marital status, family PIR, smoking, alcohol consumption, diabetes, hypertension, coronary heart disease, stroke, and cancer, and performed interaction analyses. In two-sided tests, a p-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using R 4.4.0 (http://www.R-project.org, The R Foundation) and SPSS version 23.0 (SPSS, IBM, Corp., Armonk, NY, USA). The figures were plotted using GraphPad Prism version 9.0 (GraphPad Software, Inc., USA).

Results

Baseline characteristics of participants with and without kidney stones

A total of 24,323 participants were included in this study, of whom 2,390 had a history of kidney stones, and the remaining 21,933 did not. A more significant proportion of participants with kidney stones were male (56.74% vs. 49.25%), and the mean age was significantly higher than that of the group without kidney stones (57.00 vs. 49.00 years). The racial distribution revealed a higher proportion of non-Hispanic white individuals among

participants with kidney stones (56.65%) and a relatively lower proportion of Mexican American and non-Hispanic black individuals. No significant differences were observed between the two groups regarding educational level and family PIR. However, the proportion of cohabitating individuals was higher among those with kidney stones (63.72%). The prevalence of smoking was higher in the kidney stones group (52.22%), while alcohol consumption was more common among participants without kidney stones (69.21%). Furthermore, participants with kidney stones exhibited lower levels of physical activity. Regarding the presence of additional medical conditions, participants with kidney stones demonstrated a higher prevalence of diabetes (30.54%), hypertension (50.88%), coronary heart disease (8.16%), stroke (5.69%), and cancer (15.44%). Furthermore, individuals with kidney stones exhibited higher body mass index (BMI 29.50 kg/m^2), fasting plasma glucose (FPG 97.00 mg/dL), glycosylated hemoglobin (HbA1c 5.70%), triglycerides (TG 136.00 mg/dL), creatinine (0.91 mg/dL), blood urea nitrogen (BUN 14.00 mg/dL), and uric acid (5.60 mg/dL) were significantly higher ($P<0.01$) in participants with kidney stones compared to those without. Conversely, the mean level of high-density lipoprotein cholesterol (HDL-c 47.00 mg/dL) was significantly lower ($P<0.01$) in participants with kidney stones. It is noteworthy that vitamin D levels were also higher in participants with kidney stones (65.85 nmol/L vs. 61.95 nmol/L, $P<0.001$) (Table 1).

Baseline characteristics of participants based on vitamin D quartiles

The participants were distributed according to vitamin D quartiles, with significant demographic and clinical characteristics differences. Participants' age increased stepwise with rising vitamin D levels, with the highest quartile exhibiting the oldest participants (60.00 years). The higher vitamin D quartiles were characterized by an overrepresentation of non-Hispanic white individuals, while the lower quartiles exhibited an overrepresentation of non-Hispanic black individuals. The proportion of participants with an education level of 12th grade or higher increased with increasing vitamin D levels. In the highest quartile, 59.99% of participants had a 12th grade education or higher. The proportion of cohabiting individuals increased in conjunction with rising vitamin D levels. The proportion of individuals in the high PIR category increased as vitamin D levels increased. As vitamin D levels increased, the proportion of individuals who engaged in smoking and alcohol consumption also increased. The highest quartile of vitamin D levels was associated with a higher prevalence of physical activity. The prevalence of hypertension, coronary heart disease, stroke, and cancer demonstrated a positive correlation with increasing vitamin D levels. Significant variations were observed in anthropometric and biochemical parameters, including BMI, FPG, HbA1c, total cholesterol (TC), TG, HDL-c, creatinine, BUN, uric acid, and total calcium, across vitamin D quartiles ($P<0.01$). It is noteworthy that the prevalence of kidney stones increased progressively with increasing vitamin D levels, from 7.86% in the lowest quartile to 10.86% in the highest quartile ($P<0.001$) (Table 2).

Relationship between vitamin D and kidney stones in different models

Of the three models exploring the relationship between vitamin D and kidney stones, model 1, before unadjustment, demonstrated a statistically significant positive correlation between vitamin D levels and the risk of kidney stones (OR = 1.01, 95% CI: 1.01–1.01, $P<0.001$). However, after adjusting for gender, age, and race in Model 2, the association became non-significant (OR = 1.00, 95% CI: 1.00–1.00, $P=0.066$). Furthermore, after adjusting for multiple potential confounding variables (including education level, marital status, family PIR, smoking, alcohol consumption, physical activity, diabetes, hypertension, coronary heart disease, stroke, and cancer) in Model 3, the association between vitamin D levels and kidney stone risk remained non-significant (OR = 1.00, 95%CI: 1.00–1.00, $P=0.186$). Upon examination of vitamin D quartiles, the highest quartile was significantly associated with kidney stones in the unadjusted model compared to the lowest quartile (quartile 4 OR 1.43, 95% CI 1.26–1.62, $P<0.001$). However, this association was no longer significant after total adjustment (quartile 4 OR 0.91, 95% CI 0.80–1.05, $P=0.198$). These results suggest that vitamin D levels may not independently predict kidney stone risk (Table 3).

RCS analysis

Figure 2A depicts the RCS analysis without adjustment for confounders, which reveals a significant non-linear positive correlation between vitamin D levels and the risk of kidney stone (P for overall <0.001, P for non-linear $=0.004$). These findings suggest that, before applying control variables, the risk of kidney stone incidence increased significantly with increasing vitamin D levels, particularly within the range of vitamin D levels from 0 to 100 nmol/L, with a stepwise increasing trend in the OR and its 95% CI. However, in Fig. 2B, we conducted a more comprehensive statistical analysis, adjusted for a multitude of potentially confounding variables, including gender, age, race, education level, marital status, family PIR, smoking habits, drinking habits, physical activity level, diabetes, hypertension, coronary heart disease, stroke,

Table 1 Baseline characteristics of participants with and without kidney stones

Variables	Total (*n* = 24,323)	Without kidney stones (*n* = 21,933)	Kidney stones (*n* = 2390)	*P*
Gender, *n* (%)				< 0.001
Male	12,159 (49.99)	10,803 (49.25)	1356 (56.74)	
Female	12,164 (50.01)	11,130 (50.75)	1034 (43.26)	
Age (years)	50.00 (35.00, 64.00)	49.00 (34.00, 63.00)	57.00 (43.00, 68.00)	< 0.001
Race, *n* (%)				< 0.001
Mexican American	3551 (14.60)	3254 (14.84)	297 (12.43)	
Non-Hispanic White	10,731 (44.12)	9377 (42.75)	1354 (56.65)	
Non-Hispanic Black	4914 (20.20)	4607 (21.00)	307 (12.85)	
Other Race	5127 (21.08)	4695 (21.41)	432 (18.08)	
Education level, *n* (%)				0.777
Less than 9th grade	2238 (9.20)	2009 (9.16)	229 (9.58)	
9–12th grade	8865 (36.45)	7993 (36.44)	872 (36.49)	
More than 12th grade	13,220 (54.35)	11,931 (54.40)	1289 (53.93)	
Marital status, *n* (%)				< 0.001
Cohabitation	14,480 (59.53)	12,957 (59.08)	1523 (63.72)	
Solitude	9843 (40.47)	8976 (40.92)	867 (36.28)	
Family PIR, *n* (%)				0.364
Low (≤ 1.3)	7676 (31.56)	6939 (31.64)	737 (30.84)	
Medium (1.3–3.5)	9190 (37.78)	8255 (37.64)	935 (39.12)	
High (> 3.5)	7457 (30.66)	6739 (30.73)	718 (30.04)	
Smoke, *n* (%)				< 0.001
Yes	11,065 (45.49)	9817 (44.76)	1248 (52.22)	
No	13,258 (54.51)	12,116 (55.24)	1142 (47.78)	
Alcohol, *n* (%)				0.008
Yes	16,771 (68.95)	15,180 (69.21)	1591 (66.57)	
No	7552 (31.05)	6753 (30.79)	799 (33.43)	
Physical activity, *n* (%)				< 0.001
Inactive	6245 (25.68)	5503 (25.09)	742 (31.05)	
Moderate	9103 (37.43)	8230 (37.52)	873 (36.53)	
Vigorous	8975 (36.90)	8200 (37.39)	775 (32.43)	
Diabetes mellitus, *n* (%)				< 0.001
Yes	4749 (19.52)	4019 (18.32)	730 (30.54)	
No	19,574 (80.48)	17,914 (81.68)	1660 (69.46)	
Hypertension, *n* (%)				< 0.001
Yes	8959 (36.83)	7743 (35.30)	1216 (50.88)	
No	15,364 (63.17)	14,190 (64.70)	1174 (49.12)	
Coronary heart disease, *n* (%)				< 0.001
Yes	1035 (4.26)	840 (3.83)	195 (8.16)	
No	23,288 (95.74)	21,093 (96.17)	2195 (91.84)	
Stroke, *n* (%)				< 0.001
Yes	930 (3.82)	794 (3.62)	136 (5.69)	
No	23,393 (96.18)	21,139 (96.38)	2254 (94.31)	
Cancer, *n* (%)				< 0.001
Yes	2397 (9.85)	2028 (9.25)	369 (15.44)	
No	21,926 (90.15)	19,905 (90.75)	2021 (84.56)	
BMI (kg/m^2)	28.20 (24.50, 32.86)	28.03 (24.30, 32.70)	29.50 (25.80, 34.10)	< 0.001
FPG (mg/dL)	93.00 (86.00, 105.00)	93.00 (86.00, 104.00)	97.00 (88.00, 113.00)	< 0.001
HbA1c (%)	5.50 (5.30, 5.90)	5.50 (5.20, 5.90)	5.70 (5.40, 6.10)	< 0.001
TC (mg/dL)	189.00 (163.00, 218.00)	189.00 (164.00, 218.00)	188.00 (161.00, 215.00)	0.009

Table 1 (continued)

Variables	Total (*n* = 24,323)	Without kidney stones (*n* = 21,933)	Kidney stones (*n* = 2390)	*P*
TG (mg/dL)	121.00 (81.00, 187.00)	120.00 (80.00, 185.00)	136.00 (92.00, 204.00)	< 0.001
HDL-c (mg/dL)	50.00 (41.00, 61.00)	51.00 (42.00, 62.00)	47.00 (40.00, 58.00)	< 0.001
Creatinine (mg/dL)	0.85 (0.72, 1.01)	0.85 (0.72, 1.01)	0.91 (0.75, 1.06)	< 0.001
BUN (mg/dL)	13.00 (10.00, 16.00)	13.00 (10.00, 16.00)	14.00 (11.00, 18.00)	< 0.001
Uric acid (mg/dL)	5.40 (4.50, 6.40)	5.40 (4.40, 6.40)	5.60 (4.60, 6.60)	< 0.001
Total Calcium (mg/dL)	9.40 (9.20, 9.60)	9.40 (9.20, 9.60)	9.40 (9.10, 9.60)	0.003
Vitamin D (nmol/L)	62.35 (45.15, 80.85)	61.95 (44.75, 80.55)	65.85 (49.31, 83.06)	< 0.001

Data are shown as median (25th, 75th percentiles) or percentages, $p < 0.05$ considered statistically significant

PIR, Poverty-to-income ratio; BMI, Body mass index; FPG, Fasting plasma glucose; HbA1c, Hemoglobin A1c; TC, Total cholesterol; TG, Triglyceride; HDL-c, High-density lipoprotein cholesterol; BUN: Blood urea nitrogen

and cancer, before applying the RCS analysis once more. The results demonstrated that the correlation between vitamin D levels and the risk of kidney stones did not attain statistical significance (P for overall = 0.373, P for non-linear = 0.502). This finding suggests that the association between vitamin D levels and the risk of kidney stones became non-significant, and the trend in the risk ratio was no longer clear after accounting for the effects of the aforementioned confounding factors.

Subgroup analysis

Figure 3 presents the findings of a subgroup analysis of vitamin D levels and the risk of kidney stones. This analysis was conducted to explore the variability of this association across demographic characteristics, lifestyle, and health status. The analysis results demonstrated that after adjusting for several confounding variables, including demographic characteristics, lifestyle habits, and multiple chronic diseases, the OR and its 95% CI did not significantly deviate from 1.00 among the subgroups. The only exception was the slight statistical association observed in the subgroups of vigorous physical activity and those with diabetes ($P = 0.024$ and $P = 0.034$). Subgroup analysis revealed that none of the other subgroups reached statistical significance ($P > 0.05$), suggesting that within these specific subgroups, the direct effect of vitamin D levels on the risk of developing kidney stones was limited or absent. This finding lends further support to the multivariable nature of the risk of kidney stone development, suggesting that vitamin D levels may not be a significant determinant of kidney stone risk or that other, more potent risk factors may mask its effect.

Discussion

This study evaluated the potential relationship between serum vitamin D levels and kidney stone risk. The data used in this study were obtained from the NHANES database and were collected between 2007 and 2018. The findings indicated a statistically significant positive correlation between vitamin D levels and kidney stone risk in a preliminary model that did not account for potential confounding variables. This finding is consistent with some previous findings, suggesting that vitamin D may contribute to kidney stone formation to some extent. However, as we introduced an increasing number of confounding variables (e.g., gender, age, race, socioeconomic status, lifestyle habits, and history of multiple chronic diseases) into the model, the positive association between vitamin D levels and kidney stone risk diminished and eventually became non-significant. Furthermore, we investigated the dose–response relationship between vitamin D levels and the risk of kidney stone incidence using RCS modeling. A significant non-linear positive relationship was identified in the absence of adjustment for confounders, particularly at lower vitamin D levels. However, this non-linear relationship became non-significant after adjustment for multiple confounders. These findings suggest that the effect of vitamin D levels on the risk of kidney stones may not exist independently but is moderated by a combination of factors.

In recent years, the relationship between serum vitamin D levels and kidney stone risk has emerged as a prominent area of investigation in nutrition and urology. As our understanding of vitamin D's physiological functions has deepened, academic attention has also focused on its potential role in kidney stone formation. However, the current body of research exhibits inconsistency. Some studies have indicated that elevated vitamin D levels may exacerbate the risk of kidney stones [13–16], while others have failed to observe a significant correlation [17, 18]. Several meta-analyses have shown an association between vitamin D and a significant increase in the risk of kidney stones [20, 21]. A prospective study demonstrated that total vitamin D intake was

Table 2 Baseline characteristics of participants based on vitamin D quartiles

Variables	Vitamin D				*P*
	Quartile 1 (*n* = 6066)	Quartile 2 (*n* = 6075)	Quartile 3 (*n* = 6098)	Quartile 4 (*n* = 6084)	
Gender, *n* (%)					< 0.001
Male	2936 (48.40)	3326 (54.75)	3279 (53.77)	2618 (43.03)	
Female	3130 (51.60)	2749 (45.25)	2819 (46.23)	3466 (56.97)	
Age (years)	44.00 (31.00,58.75)	46.00 (33.00,61.00)	50.00 (37.00,64.00)	60.00 (44.00,71.00)	< 0.001
Race, *n* (%)					< 0.001
Mexican American	1123 (18.51)	1232 (20.28)	808 (13.25)	388 (6.38)	
Non-Hispanic White	1188 (19.58)	2247 (36.99)	3219 (52.79)	4077 (67.01)	
Non-Hispanic Black	2440 (40.22)	1080 (17.78)	740 (12.14)	654 (10.75)	
Other Race	1315 (21.68)	1516 (24.95)	1331 (21.83)	965 (15.86)	
Education level, *n* (%)					< 0.001
Less than 9th grade	522 (8.61)	724 (11.92)	578 (9.48)	414 (6.80)	
9–12th grade	2480 (40.88)	2230 (36.71)	2135 (35.01)	2020 (33.20)	
More than 12th grade	3064 (50.51)	3121 (51.37)	3385 (55.51)	3650 (59.99)	
Marital status, *n* (%)					< 0.001
Cohabitation	3145 (51.85)	3661 (60.26)	3897 (63.91)	3777 (62.08)	
Solitude	2921 (48.15)	2414 (39.74)	2201 (36.09)	2307 (37.92)	
Family PIR, *n* (%)					< 0.001
Low (≤ 1.3)	2314 (38.15)	2090 (34.40)	1765 (28.94)	2365 (38.87)	
Medium (1.3–3.5)	2400 (39.56)	2362 (38.88)	2216 (36.34)	1507 (24.77)	
High (> 3.5)	1352 (22.29)	1623 (26.72)	2117 (34.72)	2212 (36.36)	
Smoke, *n* (%)					< 0.001
Yes	2651 (43.70)	2656 (43.72)	2866 (47.00)	2892 (47.53)	
No	3415 (56.30)	3419 (56.28)	3232 (53.00)	3192 (52.47)	
Alcohol, *n* (%)					< 0.001
Yes	4065 (67.01)	4150 (68.31)	4367 (71.61)	4189 (68.85)	
No	2001 (32.99)	1925 (31.69)	1731 (28.39)	1895 (31.15)	
Physical activity, *n* (%)					< 0.001
Inactive	1846 (30.43)	1496 (24.63)	1436 (23.55)	1467 (24.11)	
Moderate	2164 (35.67)	2258 (37.17)	2278 (37.36)	2403 (39.50)	
Vigorous	2056 (33.89)	2321 (38.21)	2384 (39.09)	2214 (36.39)	
Diabetes mellitus, *n* (%)					0.015
Yes	1253 (20.66)	1159 (19.08)	1127 (18.48)	1210 (19.89)	
No	4813 (79.34)	4916 (80.92)	4971 (81.52)	4874 (80.11)	
Hypertension, *n* (%)					< 0.001
Yes	2081 (34.31)	1958 (32.23)	2176 (35.68)	2744 (45.10)	
No	3985 (65.69)	4117 (67.77)	3922 (64.32)	3340 (54.90)	
Coronary heart disease, *n* (%)					< 0.001
Yes	195 (3.21)	234 (3.85)	257 (4.21)	349 (5.74)	
No	5871 (96.79)	5841 (96.15)	5841 (95.79)	5735 (94.26)	
Stroke, *n* (%)					< 0.001
Yes	210 (3.46)	174 (2.86)	214 (3.51)	332 (5.46)	
No	5856 (96.54)	5901 (97.14)	5884 (96.49)	5752 (94.54)	
Cancer, *n* (%)					< 0.001
Yes	351 (5.79)	405 (6.67)	625 (10.25)	1016 (16.70)	
No	5715 (94.21)	5670 (93.33)	5473 (89.75)	5068 (83.30)	
BMI (kg/m^2)	29.60 (25.10,35.20)	28.82 (25.04,33.36)	27.80 (24.40,31.80)	26.97 (23.60,31.05)	< 0.001
FPG (mg/dL)	93.00 (85.00,105.00)	93.00 (86.00,105.00)	93.00 (86.00,104.00)	93.00 (86.00,104.00)	0.570

Table 2 (continued)

Variables	Vitamin D				
	Quartile 1 (*n* = 6066)	Quartile 2 (*n* = 6075)	Quartile 3 (*n* = 6098)	Quartile 4 (*n* = 6084)	*P*
HbA1c (%)	5.60 (5.20,6.00)	5.50 (5.20,5.90)	5.50 (5.20,5.90)	5.60 (5.30,5.90)	< 0.001
TC (mg/dL)	187.00 (161.00,215.00)	188.00 (163.00,217.00)	191.00 (165.00,219.00)	191.00 (165.00,220.00)	< 0.001
TG (mg/dL)	113.00 (76.00,178.75)	127.00 (84.00,197.00)	125.00 (84.00,191.00)	120.00 (82.00,181.00)	< 0.001
HDL-c (mg/dL)	49.00 (40.25,60.00)	48.00 (40.00,58.00)	50.00 (41.00,61.00)	54.00 (44.00,67.00)	< 0.001
Creatinine (mg/dL)	0.82 (0.69,0.99)	0.84 (0.70,0.99)	0.87 (0.73,1.02)	0.89 (0.75,1.05)	< 0.001
BUN (mg/dL)	11.00 (9.00,14.00)	12.00 (10.00,16.00)	13.00 (11.00,17.00)	14.00 (11.00,18.00)	< 0.001
Uric acid (mg/dL)	5.40 (4.50,6.50)	5.40 (4.50,6.40)	5.40 (4.50,6.30)	5.30 (4.40,6.30)	0.004
Total Calcium (mg/dL)	9.30 (9.10,9.60)	9.40 (9.10,9.60)	9.40 (9.20,9.60)	9.40 (9.20,9.70)	< 0.001
Vitamin D (nmol/L)	34.43 (27.45,39.96)	54.23 (49.85,58.35)	70.75 (66.35,75.55)	95.45 (87.15,110.45)	< 0.001
Kidney stones, *n* (%)					< 0.001
Yes	477 (7.86)	593 (9.76)	659 (10.81)	661 (10.86)	
No	5589 (92.14)	5482 (90.24)	5439 (89.19)	5423 (89.14)	

Data are shown as median (25th, 75th percentiles) or percentages, $p < 0.05$ considered statistically significant

PIR, Poverty-to-income ratio; BMI, Body mass index; FPG, Fasting plasma glucose; HbA1c, Hemoglobin A1c; TC, Total cholesterol; TG, Triglyceride; HDL-c, High-density lipoprotein cholesterol; BUN: Blood urea nitrogen

Table 3 Relationship between Vitamin D and kidney stones in different models

Variables	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Vitamin D (nmol/L)	1.01 (1.01 ~ 1.01)	< 0.001	1.00 (1.00 ~ 1.00)	0.066	1.00 (1.00 ~ 1.00)	0.186
Categories						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.27 (1.12 ~ 1.44)	< 0.001	1.04 (0.91 ~ 1.18)	0.572	1.07 (0.94 ~ 1.22)	0.286
Quartile 3	1.42 (1.25 ~ 1.61)	< 0.001	1.01 (0.89 ~ 1.15)	0.842	1.06 (0.93 ~ 1.21)	0.387
Quartile 4	1.43 (1.26 ~ 1.62)	< 0.001	0.88 (0.77 ~ 1.00)	0.054	0.91 (0.80 ~ 1.05)	0.198

Model 1: crude

Model 2: adjusted for gender, age, race

Model 3: adjusted for gender, age, race, education level, marital status, family PIR, smoke, alcohol, physical activity, diabetes mellitus, hypertension, coronary heart disease, stroke, cancer

OR, Odds ratio; CI, Confidence interval

associated with an elevated risk of kidney stones in a cohort of female nurses aged 25 to 42 years [13]. Furthermore, two randomized clinical trials of postmenopausal women demonstrated that daily oral vitamin D3 plus calcium supplementation resulted in a notable increase in the incidence of kidney stones compared to the placebo group [14, 15]. A Mendelian randomization study also corroborated the correlation between long-term elevated levels of circulating 25-hydroxyvitamin D and blood calcium and an increased risk of kidney stones [16]. Nevertheless, other studies have yielded disparate results. A cross-sectional study based on the Third National Health and Nutrition Examination Survey (NHANES III) found no association between high serum 25(OH)D levels and prevalent kidney stone disease [17]. Similarly, a recent study utilizing data from the UK Biobank did not identify a significant association between high 25(OH)D levels and kidney stone incidence [18]. Notably, the results of a randomized, placebo-controlled, double-blind clinical trial demonstrated that high-dose vitamin D therapy (100,000 IU/month) did not elevate the risk of stone formation or hypercalcemia in the general population [22].

In conclusion, the relationship between serum vitamin D and the risk of kidney stones is a complex and significant research topic. The results of the current study are inconsistent, which may be attributed to many factors, including limitations inherent to the study design, dose–effect relationships, and the influence of confounding

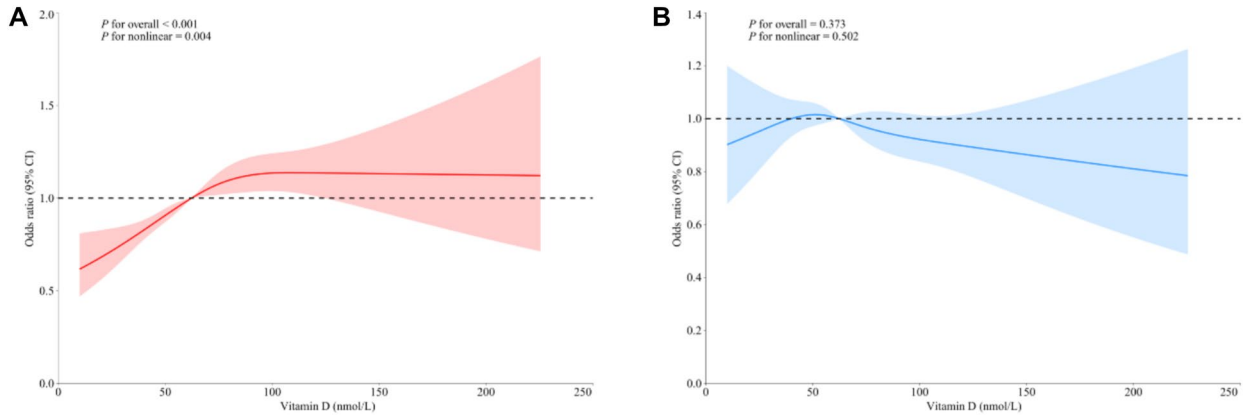

Fig. 2 Non-linear relationship of vitamin D levels and the risk of kidney stones. **A**: Unadjusted; **B**: Adjusted for gender, age, race, education level, marital status, family PIR, smoking, alcohol, physical activity, diabetes, hypertension, coronary heart disease, stroke, and cancer. The solid line displays the odds ratio, with the 95% CI represented by shading

factors. The results of the present study indicate a significant positive association when not adjusted for potential confounders; however, this association became non-significant after adjustment for multiple confounders. These findings also suggest that vitamin D levels' impact on kidney stone risk may not be a standalone phenomenon but a function of a complex interplay between multiple factors.

The role of serum vitamin D levels in kidney stone risk is a complex and multidimensional topic, potentially influencing kidney stone formation through various mechanisms. These include calcium and phosphorus metabolism, oxalate metabolism, urinary pH regulation, and inflammatory responses. Specifically, enhanced activity of vitamin D, a critical factor in promoting calcium absorption and reabsorption, may lead to an increase in urinary calcium ion levels, which is a recognized risk factor for kidney stone formation [23]. This is because elevated levels of calcium ions readily combine with oxalic acid, phosphate, and other components in the urine to form crystals, promoting kidney stones' development. The process of regulating the absorption and excretion of oxalate, a primary element of calcium stones, is paramount in preventing stone formation. Vitamin D may indirectly contribute to a hyperoxaluria state by enhancing intestinal absorption of oxalate, elevating calcium oxalate saturation, and exacerbating the risk of stone formation [24, 25]. Furthermore, vitamin D may exert a regulatory influence on the pH of urine, which in turn affects the solubility of minerals in urine [26]. The pH of the urine is a significant factor in the formation of kidney stones, as there are notable differences in the solubility of various minerals in acidic and alkaline environments. For example, uric acid stones are more likely to form in acidic environments, while calcium phosphate stones are more likely to precipitate in alkaline environments. It is noteworthy that evidence indicates that vitamin D deficiency may indirectly influence the process of kidney stone formation by inducing oxidative stress and overexpression of inflammatory mediators in renal tissues [27]. Inflammatory responses may damage renal tubular epithelial cells, which provide attachment sites for crystalline components in the urine and promote their deposition on the tubular wall, thereby contributing to kidney stone formation. In conclusion, the evidence suggests that vitamin D affects the risk of kidney stones through a number of mechanisms that are intertwined and work together in the process of kidney stone formation.

In addition, subgroup analyses were conducted to investigate the influence of population characteristics, lifestyle, and health status on the relationship between vitamin D levels and kidney stone risk. Although slight statistical associations were observed in the subgroups of individuals who engaged in vigorous exercise and those with diabetes, the overall differences did not reach statistical significance. This finding lends further support to the multivariable nature of the risk of kidney stone development, suggesting that vitamin D levels may not be a major determinant of kidney stone risk or that other, more potent risk factors may mask their effect. It is noteworthy that some studies have indicated that vitamin D deficiency may be a contributing factor in the development of kidney stones [27–29]. In the present study, the lowest quartile of vitamin D was found to be 45.15 nmol/L, below the generally accepted diagnostic threshold of 50 nmol/L for vitamin D deficiency [30]. However, no increased risk of kidney stones was identified in this group.

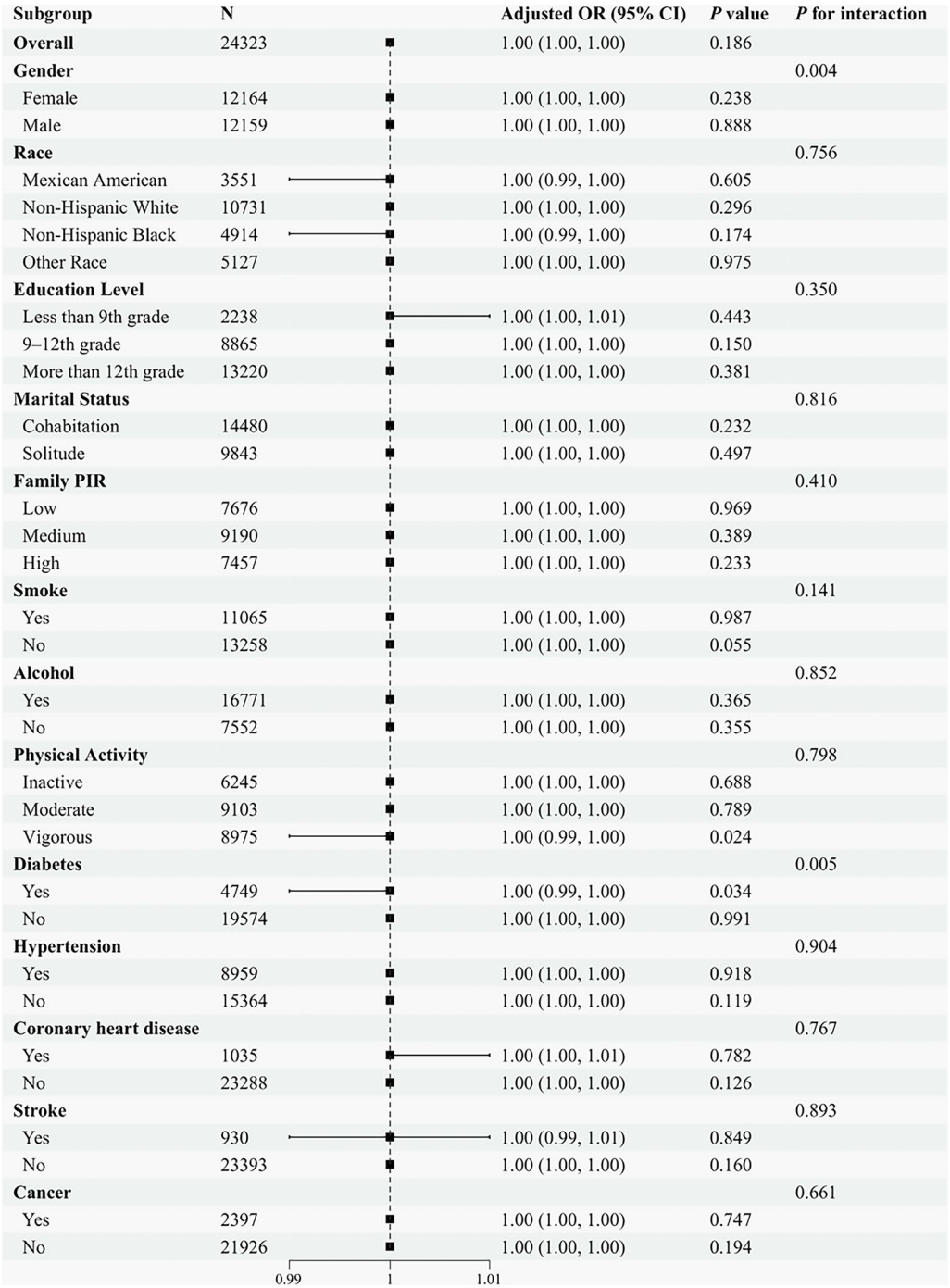

Fig. 3 Subgroup analysis of the correlation between vitamin D levels and the risk of kidney stones. Adjusted variables: gender, age, race, education level, marital status, family PIR, smoking, alcohol, physical activity, diabetes, hypertension, coronary heart disease, stroke, and cancer. The model was not adjusted for the stratification variables themselves in the corresponding stratification analysis

The findings of this study contribute to the existing body of knowledge in this field. First, we present novel evidence for an association between vitamin D levels and the risk of kidney stones through large-scale data analysis and underscore the necessity of controlling confounding factors. Secondly, our study demonstrates the intricate and multifaceted nature of the risk of developing kidney stones, indicating that the combined effects of multiple factors must be considered when developing pertinent preventive strategies. Ultimately, while this study did not

substantiate the hypothesis that vitamin D levels are an independent predictor of kidney stone risk, the findings indicate that caution should be exercised when supplementing with vitamin D, particularly in patients with a history of kidney stones. It is recommended that physicians consider the risk of kidney stones in their patients when developing clinical practice guidelines and provide appropriate monitoring and intervention when necessary.

However, it should be noted that the present study has limitations. First, as this study employed a cross-sectional design, it was impossible to ascertain a causal relationship. The relationship between vitamin D levels and kidney stone risk may be reciprocal or influenced by other factors not considered in this study. Secondly, despite considering many potential confounding variables, there may still be unidentified or uncontrolled confounding factors, such as vitamin D receptor activity within the kidney and levels of vitamin D metabolites. Therefore, future studies should continue to explore and incorporate a more significant number of possible confounders. Furthermore, the data for this study were obtained from the NHANES database. While this is a large and representative sample, the survey methodology and sample selection limitations may have affected the data collection and analysis. It is also important to note that the sample for this study was primarily drawn from the US population. As a result, the applicability of its findings to populations in other countries and regions requires further validation.

Conclusion

In conclusion, the present study illustrates that the relationship between serum vitamin D levels and the risk of kidney stones is intricate and subject to many factors. Although the initial analysis indicated a positive correlation between the two variables, this association became non-significant after controlling for multiple confounding factors. Consequently, further high-quality studies are required to elucidate how vitamin D contributes to kidney stone formation and consider the combined effects of various factors. Furthermore, future studies should concentrate on the dose effect of vitamin D, genetic polymorphisms, and the potential synergistic effects with other factors to gain a more comprehensive understanding of the relationship between vitamin D and kidney stone risk.

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Author contributions
Conceptualization and methodology, F.Z. and W.L.; project administration, data curation, and investigation, F.Z.; formal analysis, F.Z. and W.L.; visualization and supervision, W.L.; Writing—original draft, F.Z.; Writing—review and editing, W.L.; funding acquisition, F.Z.; All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials
The National Health and Nutrition Examination Survey dataset is publicly available at the National Center for Health Statistics of the Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes/index.htm).

Declarations

Ethics approval and consent to participate
The studies involving humans were approved by the National Center for Health Statistics Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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