RESEARCH

The U-shaped correlation between serum VD concentration and systemic immune-inflammatory index: results from the NHANES database prospective cohort study

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Abstract

Background Vitamin D (VD) plays a critical role in regulating systemic inflammation, but its correlation with the systemic immune-inflammatory index (SII) remains unclear. This study aimed to explore the relationship between serum VD concentration, dietary VD intake, and SII using data from the National Health and Nutrition Examination Survey (NHANES).

Methods Data from NHANES 2007–2018 and NHANES 2007–2020 were analyzed for serum VD levels and dietary VD intake, respectively. Restricted cubic splines (RCS) and logistic regression were used to assess associations between VD and SII. Mediation analysis was conducted to evaluate the role of SII in VD-related disease outcomes and mortality.

Results Serum VD concentration exhibited a U-shaped correlation with SII (P-overall = 0.005; P-non-linear = 0.002). Severe VD deficiency significantly elevated SII levels compared to insufficiency or sufficiency groups. No association was observed between dietary VD intake and SII. Mediation analysis revealed that SII mediated the effects of VD on all-cause and cardiovascular disease-related mortality, but not on cancer, hypertension, or diabetes development.

Conclusion A U-shaped relationship exists between serum VD and SII, with VD supplementation potentially reducing systemic inflammation and improving cardiovascular outcomes. Future studies should explore VD's role in systemic inflammation and its clinical implications.

Keywords Vitamin D, Systemic immune-inflammatory index, NHANES, U-shaped correlation, Cardiovascular mortality

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Background

Vitamin D (VD), a fat-soluble secosteroid, is well-recognized for its critical role in bone health, including regulating calcium and phosphate homeostasis to promote bone mineralization [1, 2].This vitamin can promote the absorption of calcium and phosphate in the intestines and renal tubules, further increasing the levels of these microelements in the blood; VD also works synergistically with parathyroid hormone and calcitonin to promote bone matrix calcification, thereby strengthening the bones [3, 4].

Beyond its classical roles, VD has garnered considerable attention for its regulatory effects on the immune system and inflammation. Acting through the vitamin D receptor, VD modulates gene expression pathways that influence immune cell function, inflammatory cytokine production, and systemic inflammation [5–7]. Deficiency in VD has been linked to numerous diseases, including cardiovascular disorders, diabetes, and cancer, where inflammation plays a pivotal role in disease progression [8, 9].

In recent years, the role of inflammation in the occurrence and development of diseases has been continuously recognized in both local and systemic inflammation. Among them, the level of systemic inflammation mainly depends on the proportion and function of various immune cells in peripheral blood. Systemic inflammation can represent the ability to generate and maintain the immune response, and is associated with the prognosis of cancer, cardiovascular diseases, and respiratory diseases [10–13]. For decades, researchers have been committed to exploring indicators to evaluate systemic inflammation, including conventional single indicators such as C-reactive protein (CRP), PCT, and IL1 and innovative combined factors such as the neutrophil/lymphocyte ratio, the monocyte/lymphocyte ratio, and the systemic inflammation response index.

The systemic immune-inflammatory index (SII), a composite marker derived from platelet, neutrophil, and lymphocyte counts, has emerged as a robust and clinically relevant indicator of systemic inflammation [14]. SII has demonstrated strong predictive power in evaluating disease prognosis, severity, and survival, particularly in cancers and cardiovascular diseases [15–17]. Despite the established roles of VD in immune regulation and SII in reflecting systemic inflammation, the precise relationship between VD levels and SII remains poorly understood.

Existing studies exploring the link between VD and inflammation often focus on single inflammatory markers, such as CRP or ILs, with inconsistent findings. For instance, while some research suggests that lower VD levels correlate with elevated inflammatory markers, others report non-linear or negligible associations [18, 19]. The limited scope of these studies, which fail to capture the complexity of systemic inflammation, highlights a significant research gap. The potential U-shaped relationship between VD and inflammation, where both deficiency and excess of VD may drive inflammatory processes, has been hypothesized but remains inadequately explored.

Investigating the association between serum VD and SII, a comprehensive indicator of systemic inflammation, can provide deeper insights into the interplay between VD status and inflammatory pathways. Moreover, understanding whether SII mediates the effects of VD on disease outcomes and mortality can shed light on VD's broader role in chronic disease management and prevention. Using data from the National Health and Nutrition Examination Survey (NHANES), a large, representative database, this study aims to address these gaps by systematically analyzing the relationship between serum VD concentration, dietary VD intake, and SII.

By clarifying the dose-response relationship and potential mediating role of SII, this study contributes to the growing body of literature on VD and inflammation. The findings have implications for public health policies and clinical practices, particularly regarding VD supplementation strategies to mitigate systemic inflammation and improve disease outcomes.

Methods

Data selection and study design

NHANES is a nationwide public database focusing on the health and nutrition status of the US population (https://www.cdc.gov/nchs/nhanes/index.htm), involving demographic data, dietary data, laboratory data, and questionnaire data. The protocols of the NHANES study were authorized by the Research Ethics Review Board of the National Center for Health Statistics (NCHS), and participants signed informed consent forms. We selected individuals with complete serum VD (NHANES 2007–2018) or dietary VD intake (NHANES 2007–2020) data to analyze the correlation between serum VD (or VD intake) and SII. The SII was calculated as follows: platelet count × neutrophil count / lymphocyte count. Specimen collection and processing adhered to the NHANES Laboratory Procedures Manual. Complete blood count analysis was conducted using the Beckman Coulter DxH 800 in the NHANES mobile examination center. The Coulter method reliably counts and sizes cells by detecting changes in electrical resistance as each particle (e.g., a cell) in a conductive solution passes through a narrow aperture.

Exclusion criteria for this part included: (a) age under 18 years; (b) lack of data on serum VD or dietary VD intake; (c) lack of data for calculating SII; (d) lack of data on covariates, including BMI, physical activity, smoking history, alcohol consumption history, hypertension

history, and diabetes history. The corresponding research flow chart is shown in Fig. 1.

Measurement of serum vitamin D and vitamin D intake

In this study, serum VD concentrations were measured as the total VD concentration, calculated by VD2 and VD3. High-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) conducted by the National Center for Environmental Health was used to measure the total VD levels. Vitamin D levels were assessed using a single baseline serum sample collected from participants in the NHANES study. The samples were processed, stored at −30 °C, and sent to the Nutritional Biomarkers Branch of the Division of Laboratory Sciences at the National Center for Environmental Health. Researchers quantified vitamin D concentration by measuring total serum 25-hydroxyvitamin D [25(OH)D], which includes both 25(OH)D2 and 25(OH)D3 components. More detailed information on the 25(OH)D measurement method can be found on the NHANES website. Serum VD levels were divided into four groups based on the Endocrine Society Clinical Practice guidelines: severe deficiency group, deficiency group, insufficiency group, and sufficiency group [20].

The data on dietary VD intake were obtained from two 24-hour diet recall interviews in NHANES. According to the dietary VD Recommended Nutrient Intakes (RNIs) from the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), individuals with a vitamin D intake ≤5.00 μg/d were considered as a reference group, and those with a vitamin D intake > 5.00 μg/d were further divided into two groups based on the median number (9.90 μg/d) [21].

Based on serum VD levels, 27,305 individuals were divided into four groups: 1,243 in the severe deficiency group (VD ≤ 25 nmol/L), 7,482 in deficiency group (25 < VD ≤ 50 nmol/L), 10,030 in insufficiency group (50 < VD ≤ 75 nmol/L), and 8,550 in sufficiency group (VD > 75 nmol/L).

Assessment of covariates

Based on previous reports, parameters that might affect SII were included as covariates in this study, including sex, age, race, BMI, physical activity, smoking history, alcohol consumption history, hypertension history, and diabetes history. Some covariates groupings were as follows: (a) Sex (male, female); (b) Race (Non-Hispanic white, Mexican American, Other Hispanic, Non-Hispanic black, and Other races); (c) Smoking history (Never smoke, Quit smoke, Current smokers); (d) Alcohol history (No, Yes); (e) Physical activity (Sedentary, Insufficient, Moderate, and High); (f) Hypertension history (No, Yes); (g) Diabetes history (No, Yes). Body mass index (BMI) was calculated as weight (kg)/height (m^2). Physical activity was defined as total metabolic equivalent (MET) minutes per week according to all physical activity questions. MET scores were calculated based on the PAQ files from the NHANES database. The PAQ files provided suggested MET scores for each type of activity and the duration per week that each activity type was performed. Leisure-time physical activity was categorized into 4 groups based on MET-minutes per week: sedentary (MET = 0), insufficient (0 < MET ≤ 500), moderate (500 < MET ≤ 1000), and high (MET > 1000).

Statistical methods

The data for this study were derived from the National Health and NHANES 2007−2018 and 2007−2020
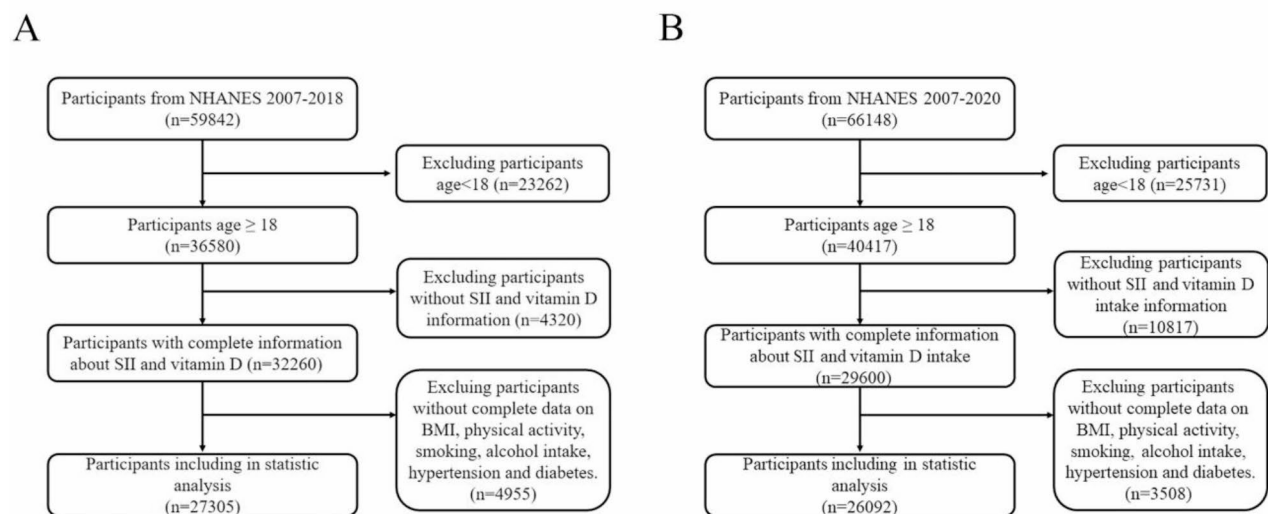
Fig. 1 Flow chart for study population selection. (**A**) Flow chart for serum vitamin D analysis; (**B**) Flow chart for dietary VD intake analysis

datasets, which are publicly available and include a wide range of demographic, laboratory, and survey data. All statistical analyses were performed using R version 4.3.1 and the "mediation" package for mediation analysis. A significance level of $p < 0.05$ (two-sided) was considered statistically significant.

Descriptive statistics

Continuous variables, such as age and body mass index (BMI), were expressed as mean±standard deviation (SD). Categorical variables, including sex, smoking history, and hypertension status, were presented as counts and percentages. The baseline characteristics of the study population were compared across the serum VD concentration and dietary VD intake groups using ANOVA for continuous variables and Chi-square tests for categorical variables.

Association between vitamin D and SII

The relationship between serum VD concentration and SII was assessed using restricted cubic splines (RCS) to model the non-linear association. RCS is a flexible approach that allows for the detection of both linear and non-linear relationships between continuous variables and outcomes. The statistical significance of the overall association and the non-linear component was tested using likelihood ratio tests.

For examining the association between VD and SII, logistic regression models were applied, adjusting for potential confounders. These models were run in the following steps:

Model 1 adjusted for age, gender, race, and BMI. Model 2 adjusted for age, gender, race, BMI, smoking history, alcohol consumption, hypertension history, diabetes history, and physical activity.

Regression coefficients (β) along with their 95% confidence intervals (CIs) were reported for each group based on serum VD levels and dietary VD intake categories.

Mediation analysis

To assess whether SII mediated the association between VD and disease outcomes or mortality, mediation analysis was conducted using the "mediation" package in R. This package implements a counterfactual framework for causal inference, decomposing the direct and indirect effects of VD on health outcomes through the mediator (SII). The bootstrap method was used to estimate the confidence intervals for the Average Causal Mediation Effect (ACME) and Average Direct Effect (ADE) to assess the strength and significance of mediation.

Sensitivity analyses

To assess the robustness of the findings, sensitivity analyses were conducted using different model specifications, including testing for interactions between VD and key covariates such as age, BMI, and physical activity. Stratified analyses were also performed to assess the relationship between VD and SII in specific subgroups, such as males and females, and individuals with and without hypertension or diabetes.

Results

Baseline characteristics of participants

As shown in Table 1, a total of 27,305 individuals were selected to analyze the association between serum VD and SII. The cohort included 13,512 men and 13,793 women, with an average age and BMI of 48.96±18.13 years and 29.22±7.00 kg/m², respectively. Among these individuals, 4,215 (15.4%) were Non-Hispanic White, 2,886 (10.6%) were Mexican American, 11,530 (42.2%) were Other Hispanic, 5,573 (20.4%) were Non-Hispanic Black, and 3,101 (11.4%) were of Other races. Non-smokers accounted for 14,641 (56.1%), non-drinkers for 8,664 (33.2%), individuals without hypertension for 15,879 (58.2%), and those without diabetes for 23,618 (86.5%) in this cohort.

Based on serum VD levels, 27,305 individuals were divided into four groups. Differences in covariates among the groups were shown in Table 1, including age, sex, race, BMI, smoking history, alcohol consumption history, hypertension history, and diabetes history.

As shown in Table 2, a total of 26,092 individuals were selected to analyze the association between dietary VD intake and the SII. This cohort included 12,670 men and 13,422 women, with an average age of 49.25±17.99 years and an average BMI of 29.43±7.11 kg/m², respectively. Among these individuals, 3,747 (14.4%) were Non-Hispanic White, 2,703 (10.4%) were Mexican American, 11,310 (43.3%) were Other Hispanic, 5,641 (21.6%) were Non-Hispanic Black, and 2,691 (10.3%) were of Other races. Non-smokers accounted for 14,641 (56.1%), non-drinkers for 8,664 (33.2%), individuals without hypertension for 15,419 (59.1%), and those without diabetes for 22,557 (86.5%) in this cohort. Based on dietary VD intake levels, 26,092 individuals were divided into three groups: 12,466 (VD intake≤5.00 μg/d), 6,816 (5.00<VD intake≤9.90 μg/d), and 6,810 (VD intake>9.90 μg/d). Differences in covariates among the groups were also shown in Table 2.

Relationship between serum vitamin D, dietary vitamin D intake, and SII

Tables 3 and 4 present the relevant results of the weighted multivariate linear regression model: the crude model did not adjust for covariates; model 1 adjusted for age, gender, ethnicity, and BMI; and model 2 adjusted for age, gender, ethnicity, BMI, smoking history, alcohol history, hypertension history, diabetes history, and physical

Table 1 Baseline characteristics of participants for serum VD analysis

Characteristic		Serum Vitamin D, nmol/L					P-value
		overall	Vitamin D ≤ 25	25 < Vitamin D ≤ 50	50 < Vitamin D ≤ 75	75 ≤ Vitamin D	
Weighted, n		189,897,106	5,601,117	39,817,868	70,387,178	74,090,943	
Age [year], mean (SD)		47.12 (17.20)	41.90 (16.43)	42.77 (16.23)	44.99 (16.49)	51.89 (17.30)	<0.001
Gender, n (%)	Male	93,035,099 (49.0)	2,431,945 (43.4)	20,222,488 (50.8)	38,427,096 (54.6)	31,953,571 (43.1)	<0.001
	Female	96,862,007 (51.0)	3,169,173 (56.6)	19,595,381 (49.2)	31,960,082 (45.4)	42,137,372 (56.9)	
Race, n (%)	Non-Hispanic white	16,424,525 (8.6)	787,421 (14.1)	6,284,790 (15.8)	7,111,194 (10.1)	2,241,120 (3.0)	<0.001
	Mexican American	11,116,248 (5.9)	318,710 (5.7)	3,276,682 (8.2)	5,230,178 (7.4)	2,290,678 (3.1)	
	Other Hispanic	128,467,767 (67.7)	1,277,153 (22.8)	16,902,315 (42.4)	47,552,072 (67.6)	62,736,226 (84.7)	
	Non-Hispanic black	19,840,704 (10.4)	2,670,587 (47.7)	9,183,226 (23.1)	5,147,745 (7.3)	2,839,145(3.8)	
	Other races	14,047,863 (7.4)	547,246 (9.8)	4,170,855 (10.5)	5,345,989 (7.6)	3,983,774 (5.4)	
BMI [kg/m2], mean (SD)		29.08 (6.88)	31.55 (9.27)	30.69 (7.74)	29.26 (6.70)	27.86 (6.07)	<0.001
Smoke status, n (%)	Never smoke	105,785,024 (55.7)	3,157,358 (56.4)	23,250,806 (58.4)	38,334,112 (54.5)	41,042,747 (55.4)	<0.001
	Quit smoke	47,083,831 (24.8)	839,015 (15.0)	7,218,942 (18.1)	17,782,286 (25.3)	21,243,588 (28.7)	
	Current smokers	37,028,252 (19.5)	1,604,745 (28.7)	9,348,120 (23.5)	14,270,780 (20.3)	11,804,607 (15.9)	
Alcohol intake, n (%)	No	50,901,454 (26.8)	1,865,146(33.3)	12,102,234 (30.4)	18,417,626 (26.2)	18,516,447 (25.0)	<0.001
	Yes	138,995,653 (73.2)	3,735,971 (66.7)	27,715,634 (69.6)	51,969,552 (73.8)	55,574,495 (75.0)	
Physical activity, n (%)	Sedentary	69,368,430 (36.5)	2,847,223 (50.8)	17,057,312 (42.8)	25,437,579 (36.1)	24,026,317 (32.4)	<0.001
	Insufficient	30,074,727 (15.8)	788,743 (14.1)	6,476,954(16.3)	10,917,873 (15.5)	11,891,157 (16.0)	
	Moderate	25,686,199 (13.5)	586,033 (10.5)	4,616,010 (11.6)	9,483,252 (13.5)	11,000,906 (14.8)	
	High	64,767,750 (34.1)	1,379,119 (24.6)	11,667,593 (29.3)	24,548,475 (34.9)	27,172,564 (36.7)	
Hypertension, n (%)	No	119,123,233 (62.7)	3,340,112 (59.6)	25,465,387 (64.0)	46,855,350 (66.6)	43,462,386 (58.7)	<0.001
	Yes	70,773,873 (37.3)	2,261,006 (40.4)	14,352,482 (36.0)	23,531,829 (33.4)	30,628,557 (41.3)	
Diabetes, n (%)	No	170,817,162 (90.0)	4,919,659 (87.8)	35,549,482 (89.3)	64,204,457 (91.2)	66,143,565 (89.3)	<0.001
	Yes	19,079,945 (10.0)	681,458 (12.2)	4,268,387 (10.7)	6,182,722 (8.8)	7,947,378 (10.7)	

Table 2 Baseline characteristics of participants for dietary VD intake analysis

Characteristic		Vitamin D intake, ug/d				P-value
		overall	VD Intake ≤ 5.00	5.00 < VD Intake ≤ 9.90	VD Intake > 9.90	
Weighted, n		205,638,253	93,550,829	52,572,481	59,514,944	
Age [year], mean (SE)		47.15 (17.23)	43.25 (16.25)	46.48 (17.11)	53.86 (16.82)	< 0.001
Gender, n (%)	Male	99,616,081 (48.4)	45,188,934 (48.3)	28,201,841 (53.6)	26,225,306 (44.1)	< 0.001
	Female	106,022,173 (51.6)	48,361,895 (51.7)	24,370,640 (46.4)	33,289,638 (55.9)	
Race, n (%)	Non-Hispanic white	17,766,203 (8.6)	9,843,621 (10.5)	4,769,359 (9.1)	3,153,223 (5.3)	< 0.001
	Mexican American	12,310,991 (6.0)	6,602,731 (7.1)	3,174,702 (6.0)	2,533,558 (4.3)	
	Other Hispanic	138,231,221 (67.2)	57,508,944 (61.5)	35,431,191 (67.4)	45,291,086 (76.1)	
	Non-Hispanic black	21,935,567 (10.7)	12,554,995 (13.4)	5,171,314 (9.8)	4,209,258 (7.1)	
	Other races	15,394,272 (7.5)	7,040,537 (7.5)	4,025,916 (7.7)	4,327,819 (7.3)	
BMI [kg/m2], mean (SE)		29.17 (6.90)	29.43 (7.05)	29.02 (6.83)	28.90 (6.70)	0.005
Smoke status, n (%)	Never smoke	115,818,452 (56.3)	50,974,343 (54.5)	30,438,122 (57.9)	34,405,987 (57.8)	< 0.001
	Quit smoke	51,464,878 (25.0)	20,375,233 (21.8)	13,109,288 (24.9)	17,980,356 (30.2)	
	Current smokers	38,354,924 (18.7)	22,201,252 (23.7)	9,025,072 (17.2)	7,128,600 (12.0)	
Alcohol intake, n (%)	No	57,527,601 (28.0)	25,322,062 (27.1)	13,939,945 (26.5)	18,265,594 (30.7)	< 0.001
	Yes	148,110,652 (72.0)	68,228,766 (72.9)	38,632,536 (73.5)	41,249,350 (69.3)	
Physical activity, n(%)	Sedentary	72,518,579 (35.3)	35,140,926 (37.6)	17,921,682 (34.1)	19,455,970 (32.7)	< 0.001
	Insufficient	329,885,679 (16.0)	14,783,481 (15.8)	8,049,654 (15.3)	10,155,433 (17.1)	
	Moderate	277,472,089 (13.5)	11,139,808 (11.9)	7,595,576 (14.4)	9,011,825 (15.1)	
	High	72,383,899 (35.2)	32,486,613 (34.7)	19,005,569 (36.2)	20,891,717 (35.1)	
Hypertension, n(%)	No	133,059,566 (64.7)	64,526,144 (69.0)	34,240,404 (65.1)	34,293,018 (57.6)	< 0.001
	Yes	72,578,688 (35.3)	29,024,685 (31.0)	18,332,077 (34.9)	25,221,926 (42.4)	
Diabetes, n (%)	No	20,610,764 (10.0)	8,229,605(8.8)	4,849,232 (9.2)	7,531,927 (12.7)	< 0.001
	Yes	185,027,489 (90.0)	85,321,224 (91.2)	47,723,249 (90.8)	51,983,016 (87.3)	

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Table 3 Association of serum vitamin D with SII in NHANES 2007–2018 participants

	crude model		model 1		model2	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
VD≤25	-0.60 (-27.96, 26.76)	0.97	45.08 (17.73, 72.43)	0.002	26.05 (-0.65, 52.75)	0.06
25 <VD ≤50	2.49 (-10.34, 15.31)	0.70	23.57 (10.92, 36.22)	<0.001	12.78 (0.68, 24.89)	0.04
50 <VD ≤75	1.00	-	1.00	-	1.00	-
VD>75	14.95 (2.03, 27.88)	0.02	-5.50 (-18.17, 7.17)	0.39	5.43 (-6.97, 17.83)	0.39

crude model: unadjust

model 1: adjust for age, gender, race and BMI;

model 2: adjust for age, sex, race, BMI, smoking history, alcohol consumption history, hypertension history, and diabetes history

activity. In models 1 and 2, setting the insufficiency group as the baseline, SII levels were significantly higher in the severe deficiency group (for model 1, β=45.08, 95% CI, 17.73–72.43, P=0.002; for model 2, β=26.05, 95% CI, -0.65–52.75, P=0.06) and the deficiency group (for model 1, β=23.57, 95% CI, 10.92–36.22, $P<0.001$; for model 2, β=12.78, 95% CI, 0.68–24.89, P=0.04), but there was no significant difference in SII levels in the sufficiency group: (for model 1, β = -5.50, 95% CI, -18.17–7.17, P=0.39; for model 2, β=5.43, 95% CI, -6.97–17.83, P=0.39). Additionally, across all three models, there was no significant association between dietary VD intake and SII. Compared to the VD intake≤5.00 μg/d group, SII levels did not significantly increase or decrease in the other two groups (Table 4). We then used the RCS curve to evaluate the nonlinear relationship between serum VD (or dietary VD intake) and SII. As shown in Fig. 2, a U-shaped relationship existed between serum VD and SII (P-overall=0.005, P-non-linear=0.002). In the contrast, no relationship existed between dietary VD intake and SII (P-overall=0.472, P-non-linear=0.902).

The subgroup analysis revealed the association between serum VD and SII, including age, gender, BMI, smoking history, alcohol history, hypertension history, diabetes history, and physical activity: the effect of serum VD on SII was consistent in most subgroups, except for BMI, physical activity, and diabetes history (Supplementary Table 1, P-interaction=0.015, 0.024, and 0.023).

Mediation analysis

Considering the key roles of the inflammatory and VD in disease development, we applied mediation analysis to further assess whether VD could influence the occurrence of cancer, hypertension, diabetes, and coronary heart disease through SII. In this analysis, the package relies on the bootstrap method to estimate the confidence intervals for both the Average Causal Mediation Effect (ACME) and Average Direct Effect (ADE). The mediation package uses a counterfactual framework for causal inference, enabling a precise decomposition of the mediation and direct effects. Based on the theoretical hypothesis, we constructed two regression models: the first model used SII as the dependent variable, VD as the independent variable, and other covariates to analyze the effect of VD on SII. The second model used disease or mortality as the dependent variable, with VD and SII as independent variables, to analyze both direct and indirect effects of VD on disease or mortality.

Based on these models, we used the mediate function to calculate ACME and ADE. To ensure robust effect estimates, the mediate function employs the bootstrap method for repeated sampling, calculating confidence intervals for both the mediation and direct effects. This bootstrap method enhances the reliability of estimates,

Table 4 Association of dietary VD intake with SII in NHNES 2007–2020 particanpants crude model: unadjust

	crude model		model 1		model2	
	β(95% CI)	P value	β(95% CI)	P value	β(95% CI)	P value
VD intake ≤ 5.00	1.00	-	1.00	-	1.00	-
5.00 < VD intake ≤ 9.90	6.99 (-7.64, 21.62)	0.35	3.07 (-11.46, 17.59)	0.68	6.69 (-7.67, 21.04)	0.36
9.90 < VD intake	6.82 (-7.36, 21.00)	0.34	-11.50 (-26.14, 3.14)	0.12	-4.99 (-19.10, 9.13)	0.48

model 1: adjust for age, gender, race and BMI

model 2: adjust for age, sex, race, BMI, smoking history, alcohol consumption history, hypertension history, and diabetes history
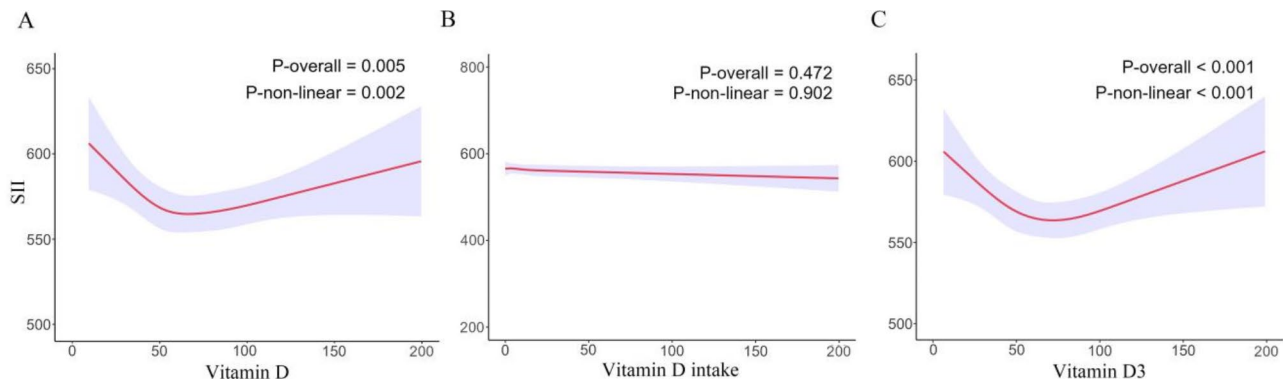
Fig. 2 RCS results for VD and SII. (**A**) RCS results for total VD and SII; (**B**) RCS results for dietary VD intakeand SII; (**C**) RCS results for serum VD3 and SII

particularly when data do not meet the normality assumption.

As shown in the Table 5, we report the estimated values of ACME and ADE along with their 95% confidence intervals. ACME reflects the indirect effect of VD on disease or mortality mediated through SII, while ADE indicates the direct effect of VD on disease or mortality. These results reveal the extent of SII's mediating role between VD and disease. The table also includes total effects with their confidence intervals, as well as the mediation proportion, quantifying SII's contribution as a mediator to the total effect. Together, VD did not influence the occurrence of above diseases through SII. Moreover, SII was a mediator for vitamin D affected all-cause mortality and cardiovascular disease-related mortality (Table 5).

Relationship between serum vitamin D3 and SII

Given that VD3 is the main component and active form of VD, we further analyzed the relationship between serum VD3 and SII. As shown in Table 6, there was no significant difference in SII levels among the normal group (VD3 ≥ 50 nmol/L), the insufficient group (30 ≤ VD3 < 50 nmol/L), and the deficient group (D3 < 30 nmol/L) in the crude model; in models 1 and 2, compared to the normal group, SII levels were significantly higher in the insufficient group (for model 1, β=29.54, 95% CI, 16.40-42.68, $P<0.001$; for model 2, β=15.80, 95% CI, 3.53–28.08, $P=0.01$) and deficient group (for model 1, β=44.41, 95% CI, 29.45–59.36, $P<0.001$; for model 2, β=21.50, 95% CI, 7.16–35.84, $P=0.004$) RCS curve

analysis showed a U-shaped relationship between serum VD3 and SII Fig. 2. Subgroup analysis indicated that the effect of serum VD3 on SII was consistent in most subgroups, except for BMI, physical activity, and diabetes history (P-interaction=0.021, 0.02, and 0.028; Supplementary Table 2). The trends of serum VD3 results were consistent with those of total VD.

Discussion

To our knowledge, this study first and systematically explored the relationship between vitamin D (VD) and systemic inflammation index (SII) from multiple perspectives. We found no significant association between dietary VD intake and SII, but there existed a U-shaped relationship between serum VD and SII. Additionally, SII was a mediator for the effect of serum VD on all-cause mortality and cardiovascular disease-related mortality, but not on the occurrence of diabetes, cancer, or cardiovascular disease.

In recent years, the relationship between VD and inflammation has garnered widespread attention, with researchers continuously employing various inflammation markers to establish connections between them. An observational study found a negative correlation between serum VD and some inflammation markers (such as WBC and fibrinogen) in adults, while a U-shaped correlation with CRP [22]. A meta-analysis indicated that the decrease in VD levels was accompanied by the increase in inflammation markers in elderly populations [23]. A cross-sectional study revealed a negative correlation between VD levels and certain inflammatory

Table 5 Mediation analysis for serum vitamin D, SII, and disease

	ACME				ADE				Total effect				Proportion mediated			
	Estimate	95% CI lower	95% CI upper	P	Estimate	95% CI lower	95% CI upper	P	Estimate	95% CI lower	95% CI upper	P	Estimate	95% CI lower	95% CI upper	P
Cancer	-0.00000082	-0.0000035	0	0.39	0.000249	0.000164	0	<0.001	0.000249	0.000164	0	<0.001	-0.00331	-0.0147	0.01	0.39
CHD	0.000000266	-0.000000722	0	0.64	-0.000191	-0.000334	0	<0.001	-0.00019	-0.000334	0	<0.001	-0.0014	-0.0122	0	0.64
Hypertension	-0.00000309	-0.0000124	0	0.45	0.000382	0.000197	0	<0.001	0.000379	0.000196	0	<0.001	-0.00817	-0.0409	0.01	0.45
Diabetes	-0.000000978	-0.0000042	0	0.44	0.00018	0.0000366	0	0.02	0.000179	0.0000339	0	0.02	-0.00545	-0.035	0.02	0.46
All-cause mortality	-0.1371	-0.2049	-0.0841	<0.001	5.6844	3.7518	7.9896	<0.001	5.5471	3.6065	7.8438	<0.001	-0.0247	-0.044	-0.0139	<0.001
CVD mortality	-0.6912	-1.2491	-0.3335	<0.001	39.456	17.6415	70.0899	<0.001	38.7647	17.052	69.2018	<0.001	-0.0173	-0.0408	-0.0087	<0.001
Cancer mortality	-0.3667	-0.6381	-0.1824	<0.001	6.3073	-4.3436	16.6769	0.27	5.9407	-4.8876	16.3519	0.25	-0.0436	-0.6791	0.4479	0.27

markers (CRP, A1GPA) in patients with cystic fibrosis [24]. Another cross-sectional study demonstrated weak and inconsistent correlations between VD levels and inflammation markers (CRP and AGP) in preschool children and adult women [25]. A study based on the UK Biobank showed a negative correlation between VD deficiency and systemic inflammation markers based on blood cells, but not with CRP based markers [26]. Innovatively, our analytic data revealed a U-shaped association between serum VD and SII, and the result indicated that the effect of VD on systemic inflammation is bidirectional and concentration-dependent.

Previous studies have shown that the impact of exogenous VD supplementation on systemic inflammation is also unclear. Some research suggests no correlation between VD supplementation and inflammation levels. For example, supplementing with VD did not significantly affect systemic inflammation levels in knee osteoarthritis patients [27]; a meta-analysis of RCT studies indicated no significant correlation between VD3 supplementation and some serum inflammation markers (IL6, IL10, and CRP) in cancer and precancerous patients [28]; a randomized, double-blind RCT study showed that combined magnesium and vitamin D supplementation did not influence serum inflammation marker levels [29]. Other studies suggested that VD supplementation could effectively reduce systemic inflammation levels. For example, an RCT study focused on Parkinson's disease found a downward trend in inflammation levels in the VD supplementation group [30]; an RCT study involving type 2 diabetes showed that VD supplementation could reduce platelet-mediated inflammatory responses, and the levels of several inflammation factors (such as IL18, TNF-α, and IFN-γ) [31]; The VITAL study demonstrated that exogenous VD3 supplementation could effectively decrease high-sensitivity CRP levels in peripheral blood by 19% [32]. In this study, we further analyzed the correlation between dietary VD intake and SII. Unlike serum VD results, no correlation was found between dietary VD intake and SII levels. These results suggest that the dosage and duration of VD supplementation should be based on real-time monitoring of serum VD levels.

As mentioned in the background, VD and systemic inflammation play critical roles in the occurrence and development of various diseases. Some studies have evaluated whether VD affects disease progression through systemic inflammation. For example, some mechanistic studies indicated that VD could affect inflammation processes to promote cancer progression, involving COX-2, NF-κB, TNF-α, IL1β, and IL6 [33, 34]; Vitamin D has been reported to play important roles in cardiovascular disease by regulating immune and inflammation functions [35, 36]; VD could also prevent high glucose-induced pancreatic β cell dysfunction through the

Table 6 Association of Serum vitamin D3 with SII in NHNES 2007–2018 participants

	crude model		model 1		model 2	
	β(95% CI)	P value	β(95% CI)	P value	β(95% CI)	P value
D3 < 30	2.26 (-13.62, 18.14)	0.78	44.41 (29.45, 59.36)	< 0.001	21.50 (7.16, 35.84)	0.004
30 ≤ D3 < 50	4.10 (-9.83, 18.03)	0.56	29.54 (16.40, 42.68)	< 0.001	15.80 (3.53, 28.08)	0.01
D3 ≥ 50	1.00		1.00		1.00	

crude model: unadjusted

model 1: adjust for age, gender, race and BMI

model 2: adjust for age, sex, race, BMI, smoking history, alcohol consumption history, hypertension history, and diabetes history

AMPK/NLRP3 inflammatory pathway [37]. In this study, we found that SII is not a mediator for the influence of VD on the incidence of these diseases, which might be due to the strong disease-promoting effect of VD. Additionally, we found that VD might affect all-cause mortality and cardiovascular disease-related mortality through SII. In general, we demonstrated that vitamin D affected disease prognosis, especially cardiovascular disease prognosis through systemic inflammation levels by using large-scale data.

One of the key strengths of this study is its use of the NHANES database, a large, nationally representative dataset that includes diverse demographic groups and allows for robust generalizability of the findings. The study employs a comprehensive approach by analyzing both serum Vitamin D levels and dietary intake, along with SII, a well-established marker of systemic inflammation. The use of RCS and logistic regression models enabled the detection of non-linear relationships between Vitamin D and SII, offering a more nuanced understanding of their correlation. Additionally, mediation analysis provided valuable insights into the role of SII in the relationship between Vitamin D and mortality outcomes, contributing to the current body of knowledge on inflammation and disease prognosis.

However, this study also has some limitations. First, the results based on database analysis only revealed the association type between VD and SII, but did not directly prove a causal relationship. This causal relationship requires supplementary evidence from earlier studies. Secondly, VD levels in this study were mostly based on single measurements rather than continuous results, which might not accurately reflect long-term vitamin D status. Thirdly, this study only selected SII as a marker for systemic inflammation, possibly leading to the omission of more representative inflammation markers. Fourthly, the study did not include the potential impact of the COVID-19 pandemic on vitamin D intake, and the use of anti-inflammatory and immunosuppressive drugs that may influence the generalizability of our findings. Fifthly, the results were derived from a single cross-sectional nature of the NHANES database, lacking external data validation and related animal model validation. Therefore, well-designed, large-sample prospective cohort studies are needed to clarify the relationship between VD, systemic inflammation, and specific disease progression. Additionally, animal studies are needed to explore the mechanisms of how VD influences disease occurrence and progression through systemic inflammation.

Conclusion

In this study, we found a U-shaped correlation between serum VD and SII based on the NHANES database for the first time. However, dietary VD intake did not affect SII levels. Furthermore, SII was a mediator for the impact of VD on all-cause mortality and cardiovascular disease mortality. This study reveals a U-shaped relationship between serum Vitamin D and systemic inflammation, highlighting the potential role of Vitamin D in regulating inflammation-related health outcomes. Future research should focus on randomized controlled trials to explore the causal relationship between Vitamin D and systemic inflammation, while clinical strategies should consider personalized Vitamin D supplementation to optimize inflammation control and improve cardiovascular health.

Author contributions
Peng Yunpeng: Formal analysis, Investigation, Writing original draftDai Shangnan: Data curation, Formal analysis, Project administrationWu Di: Data curation, Formal analysisHou Chaoqun: Methodology, SoftwareGe Wanli: Data curation, SoftwareLi Qiang: Conceptualization, Supervision, Writing – review & editingGuo Feng: Conceptualization, Data curation, Project administration, Writing – review & editing.

Data availability
Data are available at the NHANES website, https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate
Ethical review and approval were waived for this study due to prior ethical clearance from regulatory institutions. Informed consent was obtained from all subjects involved in the study.

Consent for publication
Not Applicable.

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Not Applicable.

Competing interests
The authors declare no competing interests.

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