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The Role Of Vitamin D In Inflammatory Responses Among Adolescents: Nhanes 2021–2023

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Abstract

Background: *Vitamin D is known for its antioxidant and anti-inflammatory properties, playing a key role in regulating immune responses. However, research on its effects in adolescent populations remains limited, despite this group being at increased risk for deficiency due to reduced sun exposure, poor diet, and lifestyle factors.*

Objective: *This study aimed to examine the relationship between vitamin D levels and markers of inflammation—specifically high-sensitivity C-reactive protein (hsCRP) and white blood cell count (WBCs)—in the U.S. adolescents aged 10–19 years.*

Methods: *A cross-sectional analysis was conducted using data from the National Health and Nutrition Examination Survey (NHANES) 2021–2023. Data were analyzed using RStudio software. General linear regression was performed, and inflammatory biomarkers were assessed separately, with statistical significance set at $p < 0.05$.*

Results: *The analysis included initially 2,069 participants (M: 1,041; F: 1,028), with a mean age of 14.43 years (SD = 2.94). Serum vitamin D levels were suboptimal (<50 nmol/L) in 79% of adolescents, while only 21% achieved sufficient levels (≥75 nmol/L). A weak positive correlation was observed between $25(OH)D_2$ + $25(OH)D_3$ and hsCRP ($r = 0.015$) and WBCs ($r = 0.002$), though these were not statistically significant. However, inflammation was significantly predicted by gender, BMI, ethnicity, and general health status (all $p < 0.0001$).*

Conclusion: *Although vitamin D levels were not directly associated with inflammation in this adolescent population, the high prevalence of suboptimal vitamin D remains a significant public health concern. These findings underscore the importance of ongoing monitoring of vitamin D status in adolescents and suggest that other factors may play a more prominent role in inflammation. Further research with larger samples and a broader range of inflammatory biomarkers is recommended.*

INTRODUCTION

Inflammation is a critical immune response that protects the body against infections, injuries, and harmful stimuli (Zhang et al., 2021). It is generally classified into two types: acute inflammation, a short-term response characterized by the involvement of neutrophils and pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β; and chronic inflammation, a prolonged condition associated with the

development of autoimmune diseases, obesity, and cardiovascular disorders (Zhang et al., 2021). Recent research highlights a significant association between Vitamin D status and inflammatory processes, with Vitamin D deficiency linked to elevated inflammatory markers, particularly in individuals with immune-related conditions (Djalalinia et al., 2024).

Vitamin D is acquired through sunlight exposure, diet, and supplementation. It undergoes hydroxylation in the liver and kidneys to become its active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], which binds to the Vitamin D receptor (VDR) expressed in various immune cells (Aranow et al., 2011). This active form of Vitamin D plays a vital role in modulating both innate and adaptive immune responses. It enhances the production of antimicrobial peptides, regulates T-cell activity, and helps suppress excessive inflammation (Aranow et al., 2011). Studies have demonstrated that Vitamin D deficiency is associated with increased levels of inflammatory markers in diseases such as COVID-19 and asthma (Jain et al., 2022; Naseem et al., 2024).

Despite growing recognition of Vitamin D's immunomodulatory functions, research focused on adolescents remains limited. This age group is particularly vulnerable to Vitamin D deficiency due to decreased sun exposure, poor dietary habits, and sedentary lifestyles (Pludowski, 2021). Although supplementation has shown positive effects on vascular function in obese adolescents, its impact on healthy, normal-weight adolescents is still not well understood (Barbarawi et al., 2019). Furthermore, Vitamin D deficiency has been implicated in inflammatory conditions such as eosinophilic esophagitis and tic disorders among children and adolescents (Zhao, 2020). Ensuring adequate Vitamin D levels during adolescence may be crucial in reducing the long-term risk of chronic inflammatory diseases, including autoimmune and cardiovascular conditions (Aranow et al., 2011). Given the increasing prevalence of Vitamin D deficiency, further investigation is warranted to explore its long-term effects on immune function and inflammation, particularly in healthy adolescent populations.

The study of Vitamin D among adolescents is particularly important for several reasons, especially in the context of its relationship with inflammation. This research underscores the need to assess Vitamin D levels in adolescents as part of comprehensive preventive health programs, particularly for those suffering from immune-related conditions (Ourania Kolokotroni et al., 2015). Despite the recognized role of Vitamin D in modulating inflammation, several limitations and research gaps remain.

A study by Mohamed M. Meghil et al. (2019) was limited by a small sample size and only examined short-term effects, without addressing potential long-term outcomes. Similarly, the study conducted by Amir Ghorbanzadeh-Moghaddam et al. (2015) lacked randomization in sample selection, introducing bias and limiting the generalizability of the findings. These limitations highlight the need for further robust, large-scale, and longitudinal studies to explore the effects of Vitamin D on inflammation.

This research also contributes to the growing body of evidence on the long-term implications of Vitamin D deficiency and its role in inflammatory processes. It encourages future studies to delve deeper into this relationship and supports the development of more effective treatments for inflammation-related conditions. Additionally, it emphasizes the importance of public health education, promoting the use of Vitamin D supplements and raising awareness of its benefits for immune function.

In the long term, adequate Vitamin D levels play a critical role in reducing inflammation, strengthening immunity, and potentially lowering healthcare costs associated with chronic inflammatory diseases that require continuous and costly treatment. Moreover, Vitamin D has been shown to enhance the effectiveness of certain therapeutic medications, such as those used in treating respiratory infections like asthma (Ermias Sisay et al., 2024).

METHODOLOGY

This study utilizes data from the National Health and Nutrition Examination Survey (NHANES) dataset, collected between August 2021 and August 2023, in a cross-sectional design. It focuses on adolescents aged 10–19 years and aims to examine the association between vitamin D levels and inflammatory biomarkers, with the hypothesis that lower vitamin D levels are associated with higher levels of inflammatory markers.

NHANES Methodology

The National Health and Nutrition Examination Survey (NHANES) is a program conducted by the National Center for Health Statistics (NCHS), a division of the Centers for Disease Control and Prevention (CDC). NHANES is designed to evaluate the health and nutritional status of adults and children in the United States. It integrates interviews, physical examinations, and laboratory tests to collect data on a wide range of health topics.

The NHANES dataset collects comprehensive data to evaluate the health and nutritional status of the U.S. population, including adolescents aged 10 to 19 years. Although specific data from the 2021–2023 cycle are not yet publicly available, previous cycles have provided valuable insights into vitamin D status among adolescents.

The survey covers demographic, socioeconomic, dietary, and health-related information. Physical examinations include medical, dental, and physiological assessments, along with laboratory testing conducted by trained healthcare professionals. The data gathered through NHANES is essential for monitoring the prevalence of major diseases and risk factors, shaping public health policies, and establishing national benchmarks for health indicators.

NHANES 2021–2023 Survey

The 2021–2023 NHANES cycle resumed following a temporary suspension due to the COVID-19 pandemic. This cycle incorporated methodological updates to address pandemic-related constraints. Key features of the NHANES 2021–2023 cycle include:

- **Timeframe**: August 2021 – August 2023
- **Population**: A nationally representative sample, including adolescents aged 10–19 years
- **Data Collection Components**:
  - Demographic Data: Age, gender, race/ethnicity, and socioeconomic factors
  - Dietary Data: Nutritional intake and supplement usage
  - Examination Data: Physical health assessments
  - Laboratory Data: Biomarkers, including serum 25-hydroxyvitamin D and inflammatory markers such as C-reactive protein (CRP) and white blood cell count
  - Questionnaire Data: Self-reported health status and lifestyle behaviors

This dataset is particularly valuable for analyzing the relationship between vitamin D status and inflammatory responses among adolescents. It provides essential biomarkers and health metrics necessary to evaluate the proposed research hypotheses.

a. **Demographic Data (NHANES 2021–2023)**

The demographic dataset from NHANES 2021–2023 includes information collected during household interviews and examinations. It provides key variables such as sample weights, masked variance units, interview and exam status, six-month data collection periods, and various demographic and socioeconomic details.

Key demographic variables include Gender: Male/female, Age: Age in years at the time of screening, used to determine examination eligibility and for most analyses. Race/Ethnicity: Categories include: 1 = Mexican American, 2 = Other Hispanic, 3 = Non-Hispanic White, 4 = Non-Hispanic Black, 6 = Non-Hispanic Asian, 7 = Other Non-Hispanic, including multiracial. Education Level: Recoded into three categories: 1 = Less than high school, 2 = High school graduate/GED or some college/associate degree, 3 = College graduate or higher. Marital Status Recoded into three categories:, 1 = Married or living with partner, 2 = Widowed, divorced, or separated, 3 = Never married. (CDC Report).

The dataset focuses on participants aged 0–19 years and includes household reference person data relevant to this group. For analyses using NHANES 2021–2023 data, researchers should apply the appropriate 2-year sample weights—: WTINT2YR: For interview data, WTMEC2YR: For examination data. These weights ensure that findings are nationally representative and account for NHANES's complex sampling design (CDC Report).

b. **Dietary Data (NHANES 2021–2023)**

Dietary data are collected through 24-hour dietary recall interviews, providing information on nutrient intake, including vitamin D. This helps examine the relationship between diet and serum vitamin D levels (CDC Report).

The National Health and Nutrition Examination Survey (NHANES) 2021–2023 dataset includes detailed information on dietary intake and supplement use. Among the nutrients tracked is Vitamin D (D2 + D3), identified by the variable DSQIVD. The 30-day dietary supplement questionnaire, previously administered in person, was conducted via telephone interviews following the first 24-hour dietary recall. Participants were asked whether they had taken any dietary supplements in the past 30 days. Based on their responses, individuals were categorized by supplement use and type (prescription vs. non-prescription). (CDC Report).

Key Variables in the Supplement Dataset: DSD010: Use of any vitamins, minerals, or supplements in the past 30 days, DSD090: Duration of supplement use (e.g., how long the product has been taken), DSD103:

Number of days the supplement was taken in the past 30 days, DSD122Q / DSD122U: Quantity of the supplement typically taken per day (CDC Report).
NHANES integrates this data with the 24-hour dietary recall to calculate total nutrient intake. The average daily nutrient intake from supplements (over 30 days) is combined with intake from foods and beverages reported during recall interviews. Nutrient composition is calculated using the USDA FNDDS 2021–2023 database, allowing researchers to estimate dietary nutrient intake with high precision (CDC Report).

c. **Examination Data (NHANES 2021-2023)**

The National Health and Nutrition Examination Survey (NHANES) provides data on various health metrics, including blood pressure (BP) and pulse measurements. Additionally, body measurements were collected from participants between August 2021 and August 2023, with no medical or safety exclusions (CDC Report). These measurements include height, weight, Body Mass Index (BMI), waist circumference, and hip circumference, providing a comprehensive assessment of overall health, nutrition, and obesity.
For children and adolescents aged 2 to 19 years, BMI was analyzed using BMI-for-age charts based on CDC standards. Participants were categorized into the following BMI groups: **Underweight**: Below the 5th percentile, **Normal weight**: Between the 5th and 85th percentiles, **Overweight**: Between the 85th and 95th percentiles, and **Obese**: Above the 95th percentile. These data are crucial for monitoring trends in obesity and its impact on adolescent health (CDC Report). Obesity is linked to increased chronic inflammation, which plays a significant role in the development of metabolic and cardiovascular diseases therefore BMI will be always controlled in the analysis part as it might affect the model.

d. **Laboratory Data (NHANES 2021–2023)**

1) High-Sensitivity C-Reactive Protein (hs-CRP): hs-CRP is an acute-phase protein produced by the liver. 2) White Blood Cell (WBC): WBC was reported in NHANES and estimated using a hematology flow cytometer. It was measured within a complete blood count (CBC) data and used to evaluate overall health and detect the infection. 3) Serum Vitamin D (25-hydroxyvitamin D2 and D3 (nmol/L): NHANES measures serum 25-hydroxyvitamin D concentrations using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Vitamin D status is categorized as follows: Deficient: <30 nmol/L, Insufficient: 30–50 nmol/L, Sufficient: 50–125 nmol/L, and Possibly Harmful: >125 nmol/L (CDC Report).

e. **Questionnaire Data (NHANES 2021–2023)**

Physical activity is assessed using the Physical Activity Questionnaire (PAQ), which records the frequency, duration, and intensity of various physical activities. Physical activity is important as it can influence vitamin D status through increased outdoor sunlight exposure (CDC Report).

RESULTS

Statistical Analyses:

Data cleaning and analysis conducted using RStudio-2024.12 for Windows 10/11. In total 849 participants information was included for the analysis after removing the outliers and incomplete information participants. To convert the variables HsCRP, WBC, and Vitamin D into a common scale, Z-transformation implemented using standard deviations from their mean. Descriptive statistics for quantitative variables and frequency and percentages for qualitative variables were used. Regression Analysis was employed to understand the associations between dependent variables HsCRP (mg/L), WBCs (1000 cells/uL) and independent variable-25OHD2+25OHD3 (nmol/L) further confounding factors such as gender, age, race, income and BMI were controlled and a significance level of $P<0.05$ was set for all statistical tests.

Table 1: Background and health characteristics of the participants

	Characteristics	Category	Participants n = 849 (Mean ± SD)	(%)
1	RIAGENDR	1	412	48.53%
		2	437	51.47%
2	RIDAGEYR		13.57 ± 2.33	
		10	112	13.19%
		11	98	11.54%
		12	97	11.43%
		13	110	12.96%

		14	95	11.19%
		15	109	12.84%
		16	115	13.55%
		17	113	13.31%
3	RIDRETH3		3.22 ± 1.70	
		1	129	15.19%
		2	138	16.25%
		3	335	39.46%
		4	118	13.90%
		6	50	5.89%
		7	79	9.31%
9	BMDBMIC	1	26	3.06%
		2	458	53.95%
		3	142	16.73%
		4	223	26.27%
10	WTPH2YR		39006.08 ± 24084.53	
11	LBXHSCRP		1.77 ± 4.35	
12	LBDHRPLC	0	759	89.40%
		1	90	10.60%
13	LBXWBCSI		6.91 ± 1.91	
14	LBXVIDMS		59.21 ± 23.83	

Table 1 shows cross-sectional sample of 849 adolescents that was analyzed from the NHANES 2021–2023 dataset. The gender distribution was relatively balanced, with 48.53% male (n = 412) and 51.47% female (n = 437). The average age of participants was 13.57 years (± 2.33), with participants ranging from 10 to 19 years old. The distribution across individual ages was relatively even, with each age group comprising approximately 11% to 13.5% of the sample.

In terms of race and ethnicity, participants had a mean coded value of 3.22 (± 1.70), indicating a diverse population. The most represented group was coded as "3" (39.46%), followed by codes "2" (16.25%) and "1" (15.19%). Smaller proportions fell under codes "4" (13.90%), "7" (9.31%), and "6" (5.89%). The NHANES codebook can be referenced for precise category labels corresponding to these codes.

Various survey design and weighting variables were included to account for the complex sampling design, including the interview weight (WTINT2YR), the mobile examination center (MEC) weight (WTMEC2YR), the stratification variable (SDMVSTRA), the Primary Sampling Units (SDMVPSU).

Regarding BMI categories, the majority of participants (53.95%) were in category 2, likely representing the normal weight range. About 26.27% were in category 4 (likely obese), 16.73% in category 3 (likely overweight), and a small percentage (3.06%) in category 1 (likely underweight), though exact labels should be confirmed through NHANES documentation.

The mean 2-year exam weight (WTPH2YR) was 39,006.08 (± 24,084.53), another indicator used for appropriate statistical weighting in NHANES analyses. Among the biomarkers, the mean level of high-sensitivity C-reactive protein (HS-CRP) was 1.77 mg/L (± 4.35), and white blood cell (WBC) count was 6.91 (± 1.91) x 1000 cells/μL. Serum vitamin D (25-hydroxyvitamin D) levels averaged 59.21 nmol/L (± 23.83), and about 10.60% of participants reported using vitamin D supplements, while 89.40% did not. Lastly, the mean score for physical activity frequency (PAQ706) was 4.42 (± 5.68), reflecting self-reported activity levels among adolescents. This combination of demographic, biochemical, and behavioral data provides a comprehensive overview of the health status of the adolescent population included in the study.

GENERAL MODEL

Table 2: Association between HS C-Reactive Protein (mg/L) (SPSS FILE Variable 14) and 25OHD2+25OHD3 (nmol/L)b (SPSS Variable 17) among US adolescents (N = 849)

Dependent Variable	Confounding factors	B	SE	β	SSE	95% CI	P-value	STAND P VALUE

Model 1	-	-0.004	0.01	-0.02	0.03	[-0.09, 0.04]	0.50	0.50
Model 2	Gender	-0.06	0.04	-0.02	0.03	[-0.09, 0.04]	0.10	0.50
Model 3	Gender+ Age in years at screening	-0.06	0.04	-0.02	0.03	[-0.09, 0.04]	0.10	0.48
Model 4	Gender+ Age in years at screening+ Race/Hispanic origin w/ NH Asian	-0.06	0.04	-0.02	0.03	[-0.09, 0.04]	0.10	0.50
Model 5	Gender+ Age in years at screening+ Race/Hispanic origin w/ NH Asian+ Ratio of family income to poverty	-0.06	0.04	-0.02	0.03	[-0.09, 0.05]	0.10	0.50
Model 6	Gender+ Age in years at screening+ Race/Hispanic origin w/ NH Asian+ Ratio of family income to poverty+ BMI Category - Children/Youth	-0.04	0.04	0.02	0.03	[-0.05, 0.08]	0.30	0.66

Dependent variable-HS C-Reactive Protein (mg/L); Independent variable-25OHD2+25OHD3 (nmol/L); B = Unstandardized coefficient; β = Standardized coefficient; SE = Standard error; CI = 95% Confidence interval; P-value = t-test significance value; **P<0.01 *P<0.05. Model 1-regression function without confounding factors; Model 2- gender controlled; Model 3-gender and age controlled; Model 4-gender, age and race controlled; Model 5-gender, age, race and ratio of family income to poverty controlled; Model 6- gender, age, race, ration of family income and BMI confounding factors are controlled.

Table 2 explores the association between HS C-Reactive Protein (HS-CRP) levels and 25OHD2+25OHD3 concentrations among US adolescents, considering different confounding factors across models. Model 1, simple linear regression without confounding factors. The adjusted regression coefficient (β =-0.02) is very small, suggesting negative association between HS-CRP levels for every unit increase in 25OHD2+25OHD3. Model 2 to 5 adjusted the confounding factors gender, age, race and ratio of family income to poverty controlled Adjusted Gender. Regression coefficient becomes slightly larger (B = -0.06), shows a weak negative association. Model 3, (Adjusted for Gender + Age): Coefficient remains stable (B = -0.06), indicating no meaningful change. Slight drop in p-value (0.48), but association is still not significant. Model 4, (Adjusted for Gender + Age + Race/Ethnicity) - Coefficient and significance (B = -0.06, p = 0.50) remain unchanged. Model 5, (Added Family Income-to-Poverty Ratio): - Coefficient stays consistent (B = -0.06), and p-value (0.50) indicates no significant association. Model 6, (Added BMI Category): Coefficient changes direction (B = -0.04), indicating a weak positive association. Higher p-value (0.30) highlights lack of statistical significance.

Overall, interpretation, across all six models, the association between HS-CRP and 25OHD2+25OHD3 remains **statistically insignificant** (p-values > 0.05), regardless of adjustments for confounding factors. The confidence intervals also consistently include 0, reinforcing that no meaningful relationship exists between these variables in this analysis.

Table 3: Association between White blood cell count (1000 cells/uL) (SPSS FILE Variable 16) and 25OHD2+25OHD3 (nmol/L)b (SPSS Variable 17) among US adolescents (N = 849)

Dependent Variable	Confounding factors	B	SE	β	SSE	95% CI	P-value	STAND P VALUE
Model 1	-	-0.0006	0.003	-0.01	0.03	[-0.08, 0.06]	0.83	0.83

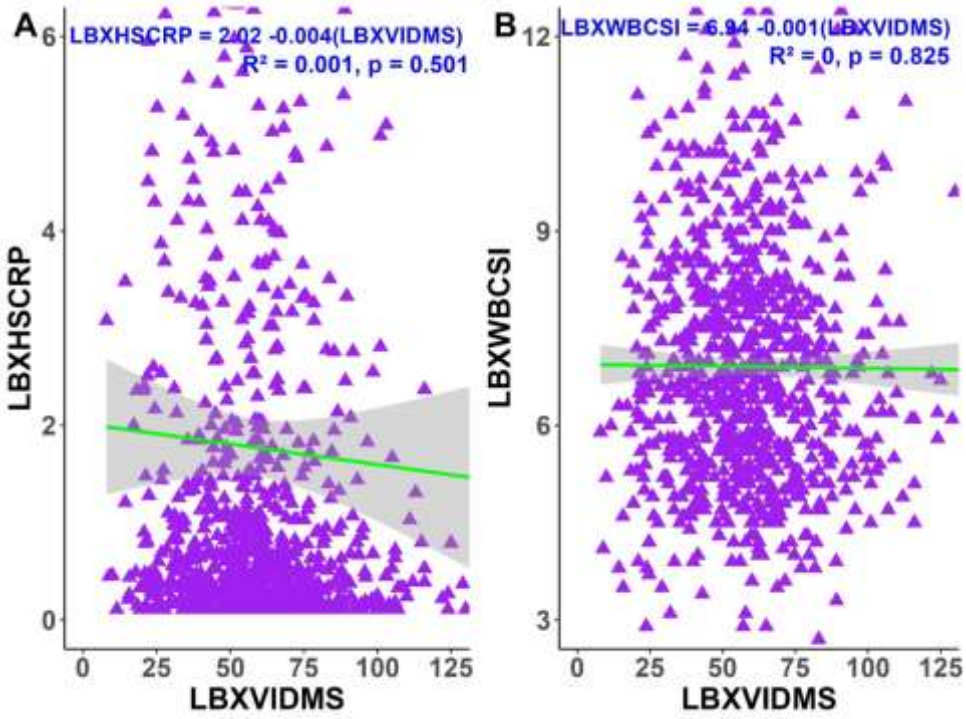
Model 2	Gender	-0.03	0.02	-0.01	0.03	[-0.08, 0.06]	0.04	0.73
Model 3	Gender+ Age in years at screening	-0.03	0.02	-0.01	0.03	[-0.08, 0.06]	0.05	0.80
Model 4	Gender+ Age in years at screening+ Race/Hispanic origin w/ NH Asian	-0.03	0.02	-0.01	0.03	[-0.08, 0.06]	0.05	0.77
Model 5	Gender+ Age in years at screening+ Race/Hispanic origin w/ NH Asian+ Ratio of family income to poverty	-0.03	0.02	-0.01	0.03	[-0.08, 0.06]	0.05	0.78
Model 6	Gender+ Age in years at screening+ Race/Hispanic origin w/ NH Asian+ Ratio of family income to poverty+ BMI Category - Children/Youth	-0.02	0.02	0.04	0.03	[-0.03, 0.10]	0.22	0.29

Dependent variable-White blood cell count (1000 cells/uL); Independent variable-25OHD2+25OHD3 (nmol/L); B = Unstandardized coefficient; β = Standardized coefficient; SE = Standard error; CI = 95% Confidence interval; P-value = t-test significance value; **P<0.01 *P<0.05. Model 1-regression function without confounding factors; Model 2- gender controlled; Model 3-gender and age controlled; Model 4-gender, age and race controlled; Model 5-gender, age, race and ratio of family income to poverty controlled; Model 6- gender, age, race, ration of family income and BMI confounding factors are controlled.

Table 3 shows the association between WBCs (1000 cells/μL) and combined serum 25OHD2 + 25OHD3 levels (nmol/L) was analyzed using a series of regression models, adjusting for potential confounding factors across six models.

In Model 1 (unadjusted), no significant association was observed between WBCs and vitamin D levels (B = -0.0006, SE = 0.003, β = -0.01, p = 0.83; 95% CI: [-0.08, 0.06]). In Model 2, adjusting for gender, the association remained statistically non-significant (B = -0.03, SE = 0.02, β = -0.01, p = 0.04), although the p-value dropped slightly below 0.05, the standardized p-value was 0.73, indicating no meaningful effect. Models 3 to 5 progressively adjusted for additional confounders, including age, race/ethnicity, and family income-to-poverty ratio. Across these models, the association remained non-significant (p-values ranging from 0.04 to 0.05), and all 95% confidence intervals consistently crossed zero. In the fully adjusted Model 6, which included BMI category alongside previous covariates, the association slightly shifted (B = -0.02, SE = 0.02, β = 0.04), but remained statistically non-significant (p = 0.22; p = 0.29; 95% CI: [-0.03, 0.10]). Overall, no significant relationship was found between white blood cell count and serum 25OHD2+25OHD3 levels among U.S. adolescents, even after adjusting for key demographic and socioeconomic factors.

Figure 1: Regression Plots Showing the Relationship Between 25OHD2+25OHD3 (nmol/L) and (A) HS C-Reactive Protein (mg/L) and (B) White Blood Cell Count (1000 cells/µL)



Scatter plots (A & B) demonstrate that the both variables LBXHSCRP and LBXWBCSI have a negative linear association with the variable LBXVIDMS with a regression coefficient -0.004 and -0.001 respectively. It was shown that increasing 25(OH) vitamin D levels are associated with decreasing CRP levels and White blood cell count (1000 cells/uL).

DISCUSSION

In the present study, we examined the association between serum vitamin D levels and systemic inflammatory biomarkers: hs-CRP and WBCs, among adolescents aged 10–19 years using data from the NHANES Survey. Despite the well-established immunomodulatory roles of vitamin D reported in previous studies (Holick MF, 2007; Bikle DD, 2009; Chun RF; 2014), our findings revealed no statistically significant association between serum 25(OH)D concentrations and hs-CRP or WBC levels, even after adjusting for covariates such as age, gender, ethnicity, socioeconomic status, and BMI.

Vitamin D has been hypothesized to modulate immune responses by enhancing anti-inflammatory pathways and suppressing pro-inflammatory cytokine production (Bikle DD, 2009; Chun RF; 2014). Several experimental and clinical studies in adults have demonstrated inverse relationships between vitamin D levels and inflammatory markers such as IL-6, TNF-α, and CRP (Wang TJ, 2008; Ganji V, 2013; Peterson CA 2008). However, our findings are in agreement with other studies focusing on adolescent populations, which often report weak or non-significant associations.

Several studies have investigated the relationship between vitamin D status and systemic inflammatory markers, supporting for the current study findings. For instance, Wang et al. (2022) analyzed data from the NHANES Survey 2007–2018 and reported a significant inverse association between serum 25-hydroxyvitamin D levels and hs-CRP concentrations among adolescents, indicating that lower vitamin D status may contribute to a pro-inflammatory state.

Similarly, Song et al. (2021) found that serum 25-hydroxyvitamin D concentrations were negatively associated with multiple inflammatory markers, in a representative sample of adolescents, suggesting that vitamin D may play a protective role against systemic inflammation. In addition, Zhao et al. (2023) conducted a systematic review and meta-analysis and demonstrated that lower vitamin D levels were associated with higher serum concentrations of several pro-inflammatory cytokines, such as hs-CRP, IL-6, and TNF-α, among children and adolescents, reinforcing the hypothesis that vitamin D exerts anti-inflammatory effects.

The findings of these recent studies collectively support the notion that vitamin D deficiency is linked to elevated inflammatory responses, aligning with the biological plausibility that vitamin D acts as a modulator of immune function. Although some differences exist in the specific inflammatory markers

assessed, the consistent inverse relationships reported across studies strengthen the rationale for exploring similar associations within adolescent populations.

An interesting observation in our study is the trend toward negative associations between vitamin D and inflammation, although these associations did not reach statistical significance. This suggests that vitamin D may exert subtle anti-inflammatory effects that are difficult to capture with general biomarkers like hs-CRP and WBC alone. Given that hs-CRP and WBCs are broad indicators of systemic inflammation, it is plausible that vitamin D's effects are more apparent at the level of specific cytokines or within certain tissues (Chun RF, 2014), rather than at the systemic level in otherwise healthy adolescents.

Additionally, our study highlights a concerning public health issue: the high prevalence of vitamin D insufficiency among adolescents, with nearly 80% of participants displaying serum 25(OH)D levels below the optimal threshold. Vitamin D deficiency during adolescence—a critical period for skeletal growth and immune system development—may have lasting implications on long-term health outcomes, including increased susceptibility to autoimmune diseases, cardiovascular diseases, and metabolic disorders later in life (Wang TJ, 2008; Amer M, 2012; Dhibar DP).

There are several possible explanations for the absence of a significant association in our study. First, the cross-sectional design limits causal inferences and captures only a single snapshot of vitamin D status and inflammation, without considering temporal variations. Second, the inflammatory markers chosen (hs-CRP and WBC) are relatively nonspecific and may not sensitively reflect subtle immune alterations linked to vitamin D. Future studies incorporating a wider range of inflammatory biomarkers, including interleukin-10 (IL-10), tumor necrosis factor receptors (TNFR-1 and TNFR-2), and interleukin-6 (IL-6), could provide more nuanced insights.

Furthermore, several confounding factors that can influence both vitamin D status and inflammation were not fully controlled for in this study, such as physical activity levels, sun exposure habits, skin pigmentation, and nutritional intake beyond vitamin D. Seasonal variation is particularly relevant, as serum vitamin D levels fluctuate throughout the year depending on sunlight exposure (Holick, 2007), and this was not accounted for in the current analysis. Another important consideration is the potential genetic variability in vitamin D metabolism and immune response, which could modulate the observed associations.

Finally, adolescence represents a period of dynamic physiological changes, including hormonal shifts, growth spurts, and neuroimmune development, all of which may interact in complex ways with vitamin D status and inflammatory processes (Wang TJ, 2008; Ganji V, 2012). This complexity underscores the need for longitudinal studies to track changes over time and better understand the interplay between vitamin D and inflammation during adolescence.

Overall, while our study did not demonstrate significant associations between vitamin D levels and systemic inflammation, the findings contribute to the growing body of evidence (Holick, 2007; Bikle, 2009; Ganji, 2012) suggesting that vitamin D may have subtle, context-dependent effects on immune regulation in adolescents. Further research is warranted to elucidate these relationships and to explore the potential benefits of improving vitamin D status during this critical developmental window.

CONCLUSION

In conclusion, this cross-sectional study found no significant association between serum vitamin D levels and systemic inflammatory biomarkers (hs-CRP and WBC) among healthy U.S. adolescents aged 10–19 years. Despite the lack of a direct relationship, the high prevalence of vitamin D insufficiency among adolescents remains a significant public health concern that necessitates attention.

Vitamin D plays an essential role not only in bone health but also in immune function and the prevention of various chronic diseases (Bikle, 2009; Chun, 2014). Although its direct impact on systemic inflammation in healthy adolescents appears limited based on the markers assessed, maintaining adequate vitamin D levels is crucial for supporting overall health and reducing potential future health risks.

Future research should focus on prospective longitudinal studies to better clarify the temporal relationships between vitamin D status and inflammatory markers. Including a broader range of specific cytokines and considering seasonal variation, genetic factors, and lifestyle behaviors will be essential to uncovering the full extent of vitamin D's immunomodulatory effects in adolescents (Chun, 2014; Schleithoff, 2006). Intervention studies examining the impact of vitamin D supplementation on immune function and inflammatory profiles in deficient adolescent populations are also warranted. Ultimately, ensuring sufficient vitamin D levels during adolescence may represent an important, modifiable factor in promoting health and preventing the early onset of inflammation-related diseases later in life.

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