Serum Vitamin D Level and Prehypertension among Subjects Free of Hypertension

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Key Words

Vitamin D • Blood pressure • Prehypertension

Abstract

Background: Low serum vitamin D levels are associated with high blood pressure (BP). Prehypertension is a preclinical stage where primary prevention efforts have been recommended for delaying or preventing the onset of hypertension. However, the majority of studies examining the association between vitamin D and BP have not accounted for kidney function or systemic inflammation. **Methods:** Participants of the 3rd National Health and Nutrition Examination Survey >20 years of age and free of hypertension (n = 9,215, 53.5% women) and clinical cardiovascular disease were examined. Serum vitamin D levels were analyzed as quartiles. Prehypertension (n = 3,712) was defined as systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg. **Results:** Lower serum vitamin D levels were found to be associated with prehypertension independent of potential confounders including body mass index (BMI), serum cholesterol, C-reactive protein and estimated glomerular filtration rate. Compared to the highest quartile of serum vitamin D (referent), the odds ratio (95% confidence interval) of prehypertension associated with the lowest quartile was 1.48 (1.16–1.90; p trend

<0.0001). This association persisted in subgroup analyses by gender, race-ethnicity and BMI. **Conclusion:** Lower serum vitamin D levels are associated with prehypertension in a representative sample of US adults.

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A prevalence of low vitamin D status is common in the US [1]. Low serum levels of vitamin D are associated with an increased risk of diabetes and cardiovascular disease (CVD) [2, 3]. Recent epidemiological studies also suggest an inverse association between dietary or serum vitamin D measures and hypertension or high blood pressure (BP) [4–10]. However, these studies focused on specific population groups [4, 6, 7], or were limited by the use of self-reported hypertension as the outcome [4, 5] or incomplete adjustment for lifestyle factors including smoking and alcohol consumption [8]. Reduced kidney function is an important confounder in the association between vitamin D and BP as it has been shown to be associated with both vitamin D [11] and high BP [12]. Similarly, markers of inflammation have been shown to be associated with both vitamin D [13, 14] and BP [13]. However, the majority of studies examining the association between vitamin D and BP have not accounted for kidney

function or systemic inflammation. Also, the previous literature is not entirely consistent as some recent studies did not find an independent association between vitamin D and BP after adjustment for potential confounders [15, 16].

Prehypertension is an earlier stage in the continuum of hypertension where prevention efforts have been recommended for delaying or preventing the onset of hypertension [17]. Prehypertension is shown to be associated with a twofold higher risk of CVD [18–20] in addition to a higher risk of developing hypertension [21]. In this context, we examined the association between serum vitamin D and prehypertension in a representative sample of US adults who were free of clinical CVD and hypertension after adjusting for important confounders, including estimated glomerular filtration rate (eGFR) and C-reactive protein (CRP) levels.

Methods

The data for the current study are derived from the 3rd National Health and Nutrition Examination Survey (NHANES III). Detailed description of the complex survey design and methods have been published elsewhere and are available online [22, 23]. In brief, NHANES employed a stratified, multistage, probability sample representative of the civilian non-institutionalized US population with oversampling of non-Hispanic blacks and Mexican Americans to ensure adequate representation of these groups. Eligible participants were required to sign an informed consent form and ethics approval was obtained from the Human Subjects Committee in the US Department of Health and Human Service.

The current study sample consisted of participants aged >20 years who were randomly assigned to be examined in the morning after an overnight fast. Serum vitamin D levels were measured in 18,883 participants who were examined in the morning after an overnight fast who had surplus sera available. We further excluded participants with hypertension ($n = 6,059$), self-reported CVD ($n = 378$), missing information on BP measurements ($n = 2,957$) and other relevant covariates included in the multivariable model ($n = 274$), leaving 9,215 participants for the current analysis of whom 3,712 had prehypertension.

Measurement of Prehypertension

Systolic and diastolic BP measurements were taken 3 times using a mercury sphygmomanometer according to the American Heart Association's recommendations during evaluation at the medical examination center [24]. The average of the 3 measures were taken as the systolic and diastolic BP. Patients were considered to have hypertension if they reported using current BP-reducing medication and/or had systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg [17]. We excluded those with hypertension in the current analysis. Prehypertension was defined as systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg based on the 7th Report of the Joint National Committee on prevention, Detection, Evaluation, and treatment of High Blood Pressure recommendations [17].

Measurement of Exposure

Information on participant's demographic characteristics, educational attainment, cigarette smoking, alcohol consumption, physical activity, history of diabetes, hypertension and use of oral hypoglycemic drug or insulin administration, and antihypertensive medication use were assessed using a standardized questionnaire. Individuals who had smoked <100 cigarettes during their lifetime were considered never smokers, those who had smoked ≥ 100 cigarettes lifetime and currently not smoking were considered former smokers, and those who had smoked ≥ 100 cigarettes lifetime and currently smoking were considered current smokers. Current alcohol drinking was defined as consumption of ≥ 1 alcoholic drink in the past month. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Overweight was defined as a BMI between 25–29.9 and obesity as a BMI ≥ 30 .

Detailed descriptions of the blood collection, processing and quality control checks are provided in the Laboratory Procedures Manual [25]. Serum 25-hydroxy vitamin D was measured using a radioimmunoassay kit (Diasorin, Stillwater, Minn., USA) at the National Center for Environmental Health, CDC, Atlanta, Ga., USA [25]. The interassay CV was 15–25% for lower values (20–62 nmol/l) and 14–18% for higher values (86–143 nmol/l). Serum total cholesterol was measured enzymatically. Serum glucose was measured using the modified hexokinase method by the Diabetes Diagnostic Laboratory at University of Missouri. Diabetes was defined as a serum glucose ≥ 126 mg/dl after fasting for a minimum of 8 h, a serum glucose ≥ 200 mg/dl for those who fasted <8 h before their NHANES visit, or a self-reported current use of oral hypoglycemic medication or insulin based on the recommendations of the American Diabetes Association [26]. CRP was analyzed using a modification of the Behring Latex-Enhanced CRP assay on the Behring Nephelometer Analyzer System. Serum creatinine was measured using a modified kinetic Jaffé reaction and GFR was estimated from serum creatinine using the Modification of Diet in Renal Disease equation [26].

Statistical Analysis

Serum levels of vitamin D were categorized into quartiles (≤ 17.7 , 17.8–24.6, 24.7–32.4 and >32.4 ng/ml). We compared selected baseline characteristics of the study population across quartiles of vitamin D by χ^2 test or analysis of variance as appropriate. We calculated the odds ratio (OR) and 95% confidence interval (CI) of prehypertension associated with quartiles of vitamin D using the highest quartile (quartile 4) as referent in two multivariable logistic regression models. In the first model, we adjusted for age (years) and gender (women, men) and in the second multivariable model, we additionally adjusted for race-ethnicity (non-Hispanic whites, non-Hispanic blacks, Mexican Americans, others), smoking (never smoker, former smoker, current smoker), current alcohol intake (absent, present), body mass index, physical inactivity (absent, present), diabetes mellitus (absent, present), serum total cholesterol to high-density lipoprotein (HDL) cholesterol ratio, CRP (mg/dl), and eGFR (ml/min/1.73 m²). Tests for linear trend were performed by modeling vitamin D quartiles as an ordinal variable in the corresponding multivariable logistic regression models. We also analyzed vitamin D as a continuous variable (per standard deviation [SD] change). To examine the consistency of the asso-

Table 1. Baseline characteristics of the study population by quartiles of vitamin D

Characteristics	Quartile 4 (>32.4 ng/ml)	Quartile 3 (24.7–32.4 ng/ml)	Quartile 2 (17.8–24.6 ng/ml)	Quartile 1 (≤17.7 ng/ml)	p value
Unweighted sample size, n	2,282	2,318	2,306	2,309	
Age, years	37.3 ± 0.4	39.8 ± 0.5	40.4 ± 0.5	39.7 ± 0.6	<0.0001
Female, %	34.5 ± 1.6	26.4 ± 1.0	21.8 ± 0.9	17.3 ± 1.1	<0.0001
Smoking categories, %					<0.0001
Never smoker	45.1 ± 1.8	48.9 ± 1.6	52.0 ± 1.8	49.8 ± 2.0	
Former smoker	22.9 ± 1.2	21.8 ± 1.3	20.3 ± 1.4	16.3 ± 1.4	
Current smoker	32.0 ± 1.7	29.3 ± 1.5	27.7 ± 1.7	33.9 ± 1.8	
Current drinker, %	42.0 ± 1.4	28.2 ± 1.2	18.3 ± 1.0	11.5 ± 0.8	<0.0001
Body mass index categories, %					<0.0001
Normal	59.8 ± 1.4	51.9 ± 1.6	45.2 ± 1.8	43.5 ± 1.9	
Overweight	29.8 ± 1.3	32.7 ± 1.3	34.7 ± 1.6	32.1 ± 1.7	
Obesity	10.4 ± 0.8	15.4 ± 1.1	20.0 ± 1.7	24.4 ± 1.4	
Race-ethnicity, %					<0.0001
Non-Hispanic whites	91.5 ± 0.9	80.3 ± 1.4	65.7 ± 2.1	42.4 ± 2.5	
Non-Hispanic blacks	1.9 ± 0.2	4.8 ± 0.4	13.5 ± 0.9	34.2 ± 2.0	
Mexican Americans	3.0 ± 0.4	6.2 ± 0.7	8.2 ± 0.9	8.8 ± 0.8	
Others	3.7 ± 0.8	8.7 ± 1.1	12.6 ± 1.6	14.6 ± 1.8	
Diabetes mellitus, %	20.8 ± 3.6	29.6 ± 3.4	26.9 ± 3.9	22.7 ± 3.9	0.0001
Physical inactivity, %	41.0 ± 1.2	27.9 ± 0.9	19.2 ± 0.8	12.0 ± 0.9	<0.0001
Systolic blood pressure, mm Hg	113.9 ± 0.3	114.9 ± 0.3	115.2 ± 0.3	115.1 ± 0.4	0.04
Diastolic blood pressure, mm Hg	71.1 ± 0.3	71.9 ± 0.2	72.0 ± 0.3	71.6 ± 0.3	0.7
Total cholesterol, mg/dl	196.0 ± 1.2	195.3 ± 1.4	199.8 ± 1.5	196.2 ± 1.5	0.0017
HDL cholesterol, mg/dl	58.6 ± 3.6	59.1 ± 4.5	56.6 ± 3.0	56.6 ± 2.5	0.84
Serum C-reactive protein, mg/dl	0.3 ± 0.01	0.4 ± 0.02	0.4 ± 0.01	0.4 ± 0.02	0.0004
Estimated glomerular filtration rate ml/min/1.73 m ²	94.3 ± 0.7	96.4 ± 0.6	97.8 ± 0.9	104.1 ± 1.4	<0.0001

HDL = High-density lipoprotein.

Data presented are row percentages or mean values ± SE.

p value represents differences in means (SD) or proportions, using analysis of variance or χ^2 test.

ciation between vitamin D and prehypertension, we then performed subgroup analyses stratified by gender, race-ethnicity and BMI. Interactions were formally evaluated by including cross-product interaction terms in the corresponding multivariable models. To examine the dose-response relationship of the observed association between serum vitamin D level and prehypertension without linearity assumptions, we used flexible non-parametric logistic regression employing the generalized additive modeling approach [R system for statistical computing, available from Comprehensive R Archive Network (<http://www.CRAN.R-project.org>)] to calculate odds of prehypertension, adjusting for all covariates in the multivariable model; the predicted odds of prehypertension were then plotted against increasing vitamin D levels (on the log scale). All analyses were conducted by including sampling weights [23] to account for unequal probabilities of selection, oversampling, and non-response using SUDAAN (version 8.0; Research Triangle Institute, Research Triangle Park, N.C., USA) and SAS (version 9.2; SAS Institute, Cary, N.C., USA) software. Standard errors (SEs) were estimated using the Taylor series linearization method.

Results

Table 1 shows the baseline characteristics of the study population. Those in the lowest quartile of vitamin D were more likely to be older, current smokers, obese, have higher levels of systolic BP, total cholesterol, CRP, eGFR; and less likely to be female, non-Hispanic white, current drinkers and physically inactive.

Table 2 shows the association between serum vitamin D levels and prehypertension. Lower levels of vitamin D were positively associated with prehypertension in both the age- and gender-adjusted and the multivariable model. Models evaluating trend in this association were also statistically significant ($p < 0.001$). This positive association persisted when serum vitamin D was analyzed as a continuous variable.

Table 2. Association between vitamin D and prehypertension

Vitamin D quartiles	n (cases) ^a	Age-, gender-adjusted OR (95% CI) ^b	Multivariate OR (95% CI) ^{b, c}
Quartile 4 (>32.4 ng/ml)	2,282 (923)	1.00 (referent)	1.00 (referent)
Quartile 3 (24.7–32.4 ng/ml)	2,318 (928)	1.20 (0.97–1.48)	1.14 (0.91–1.43)
Quartile 2 (17.8–24.6 ng/ml)	2,306 (955)	1.36 (1.17–1.58)	1.25 (1.06–1.48)
Quartile 1 (≤17.7 ng/ml)	2,309 (906)	1.58 (1.29–1.93)	1.48 (1.16–1.90)
p (trend)		<0.0001	<0.0001
Per SD decrease in vitamin D (11.4 ng/ml)	9,215 (3,712)	1.18 (1.09–1.27)	1.14 (1.05–1.24)

^a Unweighted sample size.^b OR (95% CI) = Odds ratio (95% confidence interval) from weighted analysis.^c Adjusted for age (years), gender (women, men), race-ethnicity (non-Hispanic whites, non-Hispanic blacks, Mexican Americans, others), smoking categories (never, former, current), current drinker (absent, present), body mass index categories (<25, 25–29, ≥30), physical inactivity (absent, present), diabetes (absent, present), total to high-density lipoprotein cholesterol ratio, C-reactive protein level (mg/dl), and estimated glomerular filtration rate (ml/min/1.73 m²).**Table 3.** Association between vitamin D and prehypertension by gender

Vitamin D quartiles	n (cases) ^a	Age-, gender-adjusted OR (95% CI) ^b	Multivariate OR (95% CI) ^{b, c}
Men (n = 4,289)			
Quartile 4 (>32.4 ng/ml)	1,242 (657)	1.00 (referent)	1.00 (referent)
Quartile 3 (24.7–32.4 ng/ml)	1,207 (629)	1.06 (0.79–1.43)	1.07 (0.80–1.44)
Quartile 2 (17.8–24.6 ng/ml)	1,040 (566)	1.27 (1.02–1.57)	1.28 (0.98–1.66)
Quartile 1 (≤17.7 ng/ml)	800 (459)	1.47 (1.10–1.95)	1.53 (1.13–2.07)
p (trend)		0.001	0.004
Women (n = 4,926)			
Quartile 4 (>32.4 ng/ml)	1,067 (249)	1.00 (referent)	1.00 (referent)
Quartile 3 (24.7–32.4 ng/ml)	1,099 (326)	1.42 (1.07–1.88)	1.19 (0.89–1.61)
Quartile 2 (17.8–24.6 ng/ml)	1,278 (362)	1.53 (1.18–1.99)	1.23 (0.93–1.62)
Quartile 1 (≤17.7 ng/ml)	1,482 (464)	1.75 (1.31–2.34)	1.44 (1.03–2.00)
p (trend)		<0.0001	0.03

^a Unweighted sample size.^b OR (95% CI) = Odds ratio (95% confidence interval) from weighted analysis.^c Adjusted for age (years), race-ethnicity (non-Hispanic whites, non-Hispanic blacks, Hispanic-Americans, others), smoking categories (never, former, current), current drinker (absent, present), body mass index categories (<25, 25–29, ≥30), physical inactivity (absent, present), diabetes (absent, present), total to high-density lipoprotein cholesterol ratio, C-reactive protein (mg/dl), and estimated glomerular filtration rate (ml/min/1.73 m²); p interaction (vitamin D quartiles × female) was 0.84.

In subgroup analyses, the positive association between lower levels of vitamin D and prehypertension was consistently present among categories of gender (table 3), race-ethnicity (table 4) and BMI (table 5). No significant interactions were detected between vitamin D and gender, race-ethnicity or BMI (p interaction >0.1). When we employed nonparametric models to graphically examine

the dose-response relationship between serum vitamin D levels and prehypertension without linearity assumptions involved in traditional regression models, we observed a continuous inverse association between serum vitamin D level and prehypertension without any threshold effect (fig. 1).

Table 4. Association between vitamin D and prehypertension by race-ethnicity

Vitamin D quartiles	n (cases) ^a	Age-, gender-adjusted OR (95% CI) ^b	Multivariate OR (95% CI) ^{b, c}
Non-Hispanic whites (n = 3,503)			
Quartile 4 (>32.4 ng/ml)	1,525 (583)	1.00 (referent)	1.00 (referent)
Quartile 3 (24.7–32.4 ng/ml)	1,009 (454)	1.24 (0.95–1.62)	1.15 (0.87–1.51)
Quartile 2 (17.8–24.6 ng/ml)	654 (302)	1.44 (1.20–1.74)	1.22 (1.00–1.48)
Quartile 1 (≤17.7 ng/ml)	315 (151)	1.72 (1.19–2.50)	1.44 (0.96–2.16)
p (trend)		<0.0001	0.02
Non-Hispanic blacks (n = 2,407)			
Quartile 4 (>32.4 ng/ml)	175 (75)	1.00 (referent)	1.00 (referent)
Quartile 3 (24.7–32.4 ng/ml)	337 (132)	0.87 (0.62–1.22)	0.83 (0.58–1.19)
Quartile 2 (17.8–24.6 ng/ml)	694 (281)	1.08 (0.82–1.43)	1.02 (0.76–1.36)
Quartile 1 (≤17.7 ng/ml)	1,201 (472)	1.35 (1.02–1.80)	1.25 (0.94–1.68)
p (trend)		0.001	0.004
Other race-ethnicities (n = 3,305)			
Quartile 4 (>32.4 ng/ml)	609 (248)	1.00 (referent)	1.00 (referent)
Quartile 3 (24.7–32.4 ng/ml)	960 (369)	1.17 (0.73–1.89)	1.23 (0.80–1.91)
Quartile 2 (17.8–24.6 ng/ml)	970 (345)	1.32 (0.82–2.13)	1.38 (0.82–2.32)
Quartile 1 (≤17.7 ng/ml)	766 (300)	1.43 (0.93–2.19)	1.50 (0.92–2.43)
p (trend)		0.14	0.14

^a Unweighted sample size.^b OR (95% CI) = Odds ratio (95% confidence interval) from weighted analysis.^c Adjusted for age (years), gender (women, men), smoking categories (never, former, current), current drinker (absent, present), body mass index categories (<25.25–29, ≥30), physical inactivity (absent, present), diabetes (absent, present), total to high-density lipoprotein cholesterol ratio, C-reactive protein (mg/dl), and estimated glomerular filtration rate (ml/min/1.73 m²); p interaction (vitamin D quartiles × race-ethnicity) was 0.71.**Table 5.** Association between vitamin D and prehypertension by body mass index categories

Vitamin D quartiles	n (cases) ^a	Age-, gender-adjusted OR (95% CI) ^b	Multivariate OR (95% CI) ^{b, c}
Body mass index <25 (n = 7,638)			
Quartile 4 (>32.4 ng/ml)	2,027 (748)	1.00 (referent)	1.00 (referent)
Quartile 3 (24.7–32.4 ng/ml)	1,886 (730)	1.15 (0.93–1.42)	1.13 (0.91–1.41)
Quartile 2 (17.8–24.6 ng/ml)	1,798 (670)	1.30 (1.08–1.56)	1.27 (1.03–1.57)
Quartile 1 (≤17.7 ng/ml)	1,657 (606)	1.43 (1.13–1.83)	1.50 (1.14–1.97)
p (trend)		0.0003	0.001
Body mass index ≥25 (n = 1,847)			
Quartile 4 (>32.4 ng/ml)	282 (158)	1.00 (referent)	1.00 (referent)
Quartile 3 (24.7–32.4 ng/ml)	420 (225)	1.09 (0.65–1.83)	1.16 (0.68–1.98)
Quartile 2 (17.8–24.6 ng/ml)	520 (258)	1.03 (0.64–1.66)	1.13 (0.69–1.86)
Quartile 1 (≤17.7 ng/ml)	625 (317)	1.20 (0.75–1.91)	1.40 (0.85–2.32)
p (trend)		0.52	0.23

^a Unweighted sample size.^b OR (95% CI) = Odds ratio (95% confidence interval) from weighted analysis.^c Adjusted for age (years), gender (women, men), race-ethnicity (non-Hispanic whites, non-Hispanic blacks, Hispanic-Americans, others), smoking categories (never, former, current), current drinker (absent, present), physical inactivity (absent, present), diabetes (absent, present), total to high-density lipoprotein cholesterol ratio, C-reactive protein (mg/dl), and estimated glomerular filtration rate (ml/min/1.73 m²); p interaction (vitamin D quartiles × body mass index categories) was 0.56.

Fig. 1. Vitamin D and prehypertension. Multivariable-adjusted odds of prehypertension according to serum vitamin D level (ng/ml). The solid thick line represents the predicted odds of prehypertension from nonparametric logistic regression; the dashed lines indicate 95% confidence limits for the nonparametric logistic regression estimates. The nonparametric logistic regression was adjusted for age (years), gender (men, women), race-ethnicity (non-Hispanic whites, non-Hispanic blacks, Mexican Americans, others), smoking categories (never, former, current), current drinker (absent, present), body mass index categories (<25, 25–29, ≥30), physical inactivity (absent, present), diabetes (absent, present), total to high-density lipoprotein cholesterol ratio, C-reactive protein level (mg/dl), and estimated glomerular filtration rate (ml/min/1.73 m²). X axis = Serum vitamin D level (ng/ml); Y1 axis = predicted odds of prehypertension plotted in log scale; Y2 axis = participant number for each serum vitamin D level.

Discussion

Lower serum levels of vitamin D were found to be positively associated with prehypertension in a nationally representative sample of US adults free of hypertension and CVD. This association was independent of age, gender, race-ethnicity, smoking, alcohol consumption, physical inactivity, BMI, diabetes, total cholesterol to HDL ratio, CRP and eGFR, and was consistently present within categories of gender, race-ethnicity and BMI. Further, the association between low vitamin D and prehypertension was present without a threshold effect when vitamin D was analyzed as a continuous variable in nonparametric graphical models. In addition, we were able to adjust for low kidney function and systemic inflammation, factors that could potentially confound the association between vitamin D and BP.

Serum 25-hydroxy vitamin D, the active metabolite of circulating vitamin D, reflects the cumulative exposure to sunlight and dietary vitamin D [27]. Our finding of an association between low serum vitamin D and prehypertension is largely consistent with previous cohort and cross-sectional studies that examined the association between vitamin D and hypertension or BP in the US [4–6, 8] and Europe [28–31] and extend the association to prehypertension, an earlier stage when primary prevention is effective. In the US, Zhao et al. [9] in a recent study reported a positive association between vitamin D and hypertension, and prehypertension. Forman et al. [4, 5] reported a significant positive association

between dietary vitamin D and self-reported incident hypertension among 38,388 men from the Health Professional Follow-Up Study and 77,531 women from the Nurses' Health Study; a positive association was also reported between serum vitamin D and incident hypertension in a subsample of participants. Further, a nested case-control study from the 2nd Nurses' Health Study reported a positive association between serum vitamin D and incident hypertension among 1,484 healthy, young, white women [4]. In the NHANES, systolic BP was shown to be inversely associated with vitamin D among 12,644 participants [8] and in a subgroup of white participants [6]. However, not all studies have shown a consistent positive association between low vitamin D and BP. In a prospective study conducted in the UK, Forouhi et al. [15] did not find a significant association between serum vitamin D and BP in a middle-aged cohort of 524 non-diabetic men and women in a 10-year follow-up. In another prospective study conducted by Jorde et al. [31] serum vitamin D levels were strongly associated with systolic BP but had no predictive value for the development of hypertension or changes in BP. Few intervention trials have reported that vitamin D supplementation did not reduce BP in specific populations including postmenopausal [32] and overweight subjects [33].

Several mechanisms have been proposed to explain the association between low levels of vitamin D and prehypertension. Animal studies have shown increased activation of the renin-angiotensin-aldosterone system in

vitamin D receptor and 1-hydroxylase knockout mice [34, 35]. Low vitamin D also promotes insulin resistance [36], endothelial dysfunction [37], proinflammatory cytokine production [38], and secondary hyperparathyroidism and hypocalcemia affecting vascular smooth muscles [39]. Our finding of an association between low vitamin D and prehypertension is also analogous to an association between low vitamin D and preeclampsia among pregnant women [40].

The main strengths of the study include its population-based nature, rigorous methodology, and rich information on covariates. The cross-sectional nature of the study limits making causal inferences. Further, we do not have information on parathyroid hormone which could confound the observed association.

In summary, in a representative sample of US adults, low serum levels of vitamin D were found to be positively associated with prehypertension independent of potential confounding factors, including BMI, serum cholesterol, CRP, and eGFR. Since prehypertension is a stage in the disease continuum where hypertension prevention has been shown to be effective [17], future intervention trials could clarify if vitamin D supplementation at this stage can prevent or delay the onset of hypertension in the general population.

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