Optimal vitamin D status attenuates the age-associated increase in systolic blood pressure in white Americans: results from the third National Health and Nutrition Examination Survey[1–3]

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ABSTRACT

Background: The prevalences of both hypertension and vitamin D insufficiency are high in the United States. Recent clinical trials and animal studies have suggested that vitamin D insufficiency may be associated with elevated blood pressure.

Objective: With cross-sectional data, we sought to determine whether vitamin D concentrations were related to systolic blood pressure (SBP) in the third National Health and Nutrition Examination Survey (1988–1992).

Design: Blood pressure was classified with 5 categories from the Joint National Committee 7 with a sixth category added to distinguish participants with normotensive SBP (<110 mm Hg) from those with high-normal SBP (110–119 mm Hg). We used predicted marginals to estimate the conditional means of serum 25 hydroxyvitamin D [25(OH)D] and to test for trend across blood pressure categories. We used linear regression to explore the association between vitamin D, blood pressure, and age.

Results: Lower 25(OH)D concentrations were associated with a higher blood pressure category in whites ($P < 0.001$); however, when controlling for age, the association was no longer significant. Concentrations of 25(OH)D > 80 nmol/L decreased the age-related increase in SBP by 20% compared with participants having 25(OH)D concentrations < 50 nmol/L ($P < 0.001$). Only 8% of blacks had 25(OH)D concentrations > 80 nmol/L.

Conclusions: SBP is inversely associated with serum vitamin D concentrations in nonhypertensive white persons in the United States. This observation provides a rationale for studies on the potential effects of vitamin D supplementation as a method to reduce SBP in persons at risk of hypertension. *Am J Clin Nutr* 2008;87:136–41.

KEY WORDS Systolic blood pressure, vitamin D, hypovitaminosis D, hypertension, aging, NHANES

INTRODUCTION

Hypertension is a multifaceted disease with an estimated prevalence in US adults of 30% (1, 2). The cause of hypertension is unknown in most persons, leaving open the possibility for novel treatment strategies (3). Adiposity and the dietary intake of sodium, potassium, calcium, and magnesium are all aspects of nutrient status that may have important effects on blood pressure levels in our society (4–8).

Vitamin D is one important nutrient that has been postulated as a contributing factor to the development of hypertension, possibly through inhibition of the renin angiotensin system (9–15). Li et al (15) showed that 1α, 25-hydroxyvitamin D [1α,25$(OH)_2$D], the active steroid hormone form of vitamin D, inhibits renin gene expression in vitamin D receptor knockout mice. These mice develop hypertension that can be reversed with treatment with captopril, an angiotensin-converting enzyme inhibitor as well as treatment with 1α,25$(OH)_2$D. Although, Li et al (15) studied 1α,25$(OH)_2$D, it is thought that higher concentrations of 25-hydroxyvitamin D [25(OH)D] are needed for extrarenal synthesis of 1α,25$(OH)_2$D to occur (16).

Vitamin D can be produced in the skin (vitamin D_3) or obtained from the diet (vitamin D_2 or D_3), which is converted to 25(OH)D, the serum marker for vitamin D status (16). More than one-third of the US population exhibits vitamin D deficiency, defined as 25(OH)D < 50 nmol/L (17). Higher concentrations of 25(OH)D (>80 nmol/L) were proposed for optimal skeletal health (18). The concentration of 25(OH)D needed for cardiovascular benefits may be even higher than that needed for skeletal benefits and may differ by race, but data are limited in this regard (17–19). In the present study, we examined whether an association existed between blood pressure and circulating 25(OH)D in black and white adults who participated in the third National Health and Examination Survey (NHANES III; 1988–1994).

SUBJECTS AND METHODS

Data from the NHANES III represent the noninstitutionalized US population ≥ 2 mo of age and were collected by the National Center for Health Statistics, Centers for Disease Control and Prevention, with the use of field clinic visits at mobile examination centers and household interviews. The survey was approved

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by the Centers for Disease Control and Prevention Institutional Review Board, and written consent was received from participants. A detailed description of the NHANES III plan, operation, and sample design are described elsewhere (20). Briefly, after being interviewed in their home, participants were invited to attend 1 of 3 physical examination sessions. Blood samples were centrifuged, and serum was divided into aliquots and frozen to −70 °C on site during examination. The aliquots were then shipped on dry ice to central laboratories where they were stored at −70 °C until analysis. A radioimmunoassay kit from DiaSorin (Stillwater, MN) was used to measure 25(OH)D, with a lower limit of detection of 20 nmol/L. Reliable 25(OH)D concentrations and systolic blood pressure (SBP) measures were available on 16 135 participants aged ≥ 19 y.

Three sets of blood pressure measurements were taken in the examination center by trained personnel. The average of the 3 measures was used for analysis. Blood pressure measurements were taken at both the home interview and the mobile examination center with the use of a mercury sphygmomanometer (WA Baum Co, Inc, Copiague, NY) according to the standardized blood pressure measurement protocols recommended by the American Heart Association. To examine mean circulating 25(OH)D across various classifications of blood pressure, we divided blood pressure into 6 categories. Five categories were based on the recommendations from the Joint National Committee 7 (normotensive: <120 mm Hg; prehypertensive: 120–129 mm Hg; borderline: 130–139 mm Hg; stage 1 hypertension: 140–159 mm Hg; and stage 2 hypertension: ≥160 mm Hg) (21). The Joint National Committee 7 classifies normotensive SBP as < 120 mm Hg; however, we divided this category into 2 separate groups (normotensive: <110 mm Hg; high normal: 110–119 mm Hg) to create the sixth category.

We conducted data analyses only in participants who identified themselves as white or black and who had never been told they had hypertension ($n = 7699$). We excluded persons who had been previously told they had hypertension to minimize the potential that participants in the current study had made lifestyle modifications to improve blood pressure. To account for the complex NHANES sampling design we used weighted data to provide accurate variance estimates. Analyses were done with the use of SAS version 9.1 (SAS Institute, Cary, NC) and SAS-callable SUDAAN software version 9.0 (Research Triangle Park, NC). PROC REGRESS was used for all linear regression and conditional means estimation. The use of predicted marginals is a method within PROC REGRESS used for direct standardization of means (22). Predicted marginals were used to estimate the conditional means of 25(OH)D within each of the 6 blood pressure categories and to test for trends across these strata. We tested for interaction between 25(OH)D and age, race, and sex. We tested age, body mass index (BMI; in kg/m^2), sex, season when blood was drawn, physical activity, and smoking status as possible covariates. Statistical significance was set at $P < 0.05$ for all comparisons.

RESULTS

The analytic sample was balanced in terms of sex (47% men and 53% women) and race (39% black and 61% white) (**Table 1**). The majority of the sample was <50 y of age (63% of whites and 79% of blacks). Distribution of SBP between the 2 races was similar. The season during which 25(OH)D was measured differed between the races, with more white participants being tested in the spring ($P < 0.01$) and more black participants tested in the fall ($P < 0.01$).

TABLE 1
Demographic characteristics of white and black adults without a diagnosis of hypertension who had a serum vitamin D measurement 25(OH)D available in the third National Health and Nutrition Examination Survey NHANES (1988–1994)[1]

	Total (n = 7699)	White (n = 4663)	Black (n = 3036)
Sex			
Men	3613 (47)	2198 (47)	1415 (47)
Women	4086 (53)	2465 (53)	1621 (53)
Age (y)[2]			
18–49	4818 (63)	2413 (52)	2405 (79)
≥50	2881 (37)	2250 (48)	631 (21)
BMI (kg/m^2)[2]			
Normal and underweight (<25)	3692 (48)	2362 (51)	1330 (44)
Overweight (25–29.9)	2514 (33)	1572 (34)	942 (31)
Obese (≥30)	1493 (19)	729 (16)	764 (25)
Season of measurement[2]			
January–March	1167 (15)	724 (16)	443 (15)
April–June	1987 (26)	1386 (30)	601 (20)
July–September	2485 (32)	1535 (33)	950 (31)
October–December	2060 (27)	1018 (22)	1042 (34)
Systolic blood pressure (mm Hg)[2]			
<110 (normotensive)	1957 (25)	1123 (24)	834 (27)
110–119 (high normal)	2133 (28)	1218 (26)	915 (30)
120–129 (prehypertensive)	1654 (21)	983 (21)	671 (22)
130–139 (borderline)	919 (12)	595 (13)	324 (11)
140–159 (stage 1 hypertension)	793 (10)	568 (12)	225 (7)
≥160 (stage 2 hypertension)	243 (3)	176 (4)	67 (2)

[1] All values are *n;* weighted percentage in parentheses.
[2] P value comparing number of whites and blacks in each category was <0.01 (Mantel-Haenszel chi-square test).

A statistically significant inverse association was observed between circulating 25(OH)D and blood pressure category in the white men and women (**Figure 1**; $P < 0.001$). When controlling for age, this linear relation was no longer present. The interaction between race and 25(OH)D was significant at the 5% level, so we stratified the analysis by race. Black men and women had significantly lower concentrations of 25(OH)D at all blood pressure classifications than did whites. When stratified by race, the inverse association between 25(OH)D and blood pressure classification was not present in either black men or women. However, 92% of black participants had 25(OH)D concentrations < 80 nmol/L.

We examined the linear regression coefficients between age, BMI, sex, 25(OH)D concentration, season when blood was drawn, physical activity, and smoking status in white participants. The interaction between age in 3 categories as classified by the Institute of Medicine [18–49 y (young), 50–64 y (middle-aged), and ≥65 y (elderly)] and 25(OH)D was statistically significant, so we stratified by age (**Table 2**). A 3-factor interaction was present between 25(OH)D, age, and race, so we also stratified on race. Linear regression coefficients for 25(OH)D were negative for elderly and middle-aged whites but positive for young whites, although the final models were not statistically significant. Age was associated with an increase in SBP (0.82 mm Hg/y in elderly white participants, $P < 0.001$; 0.16 mm Hg/y

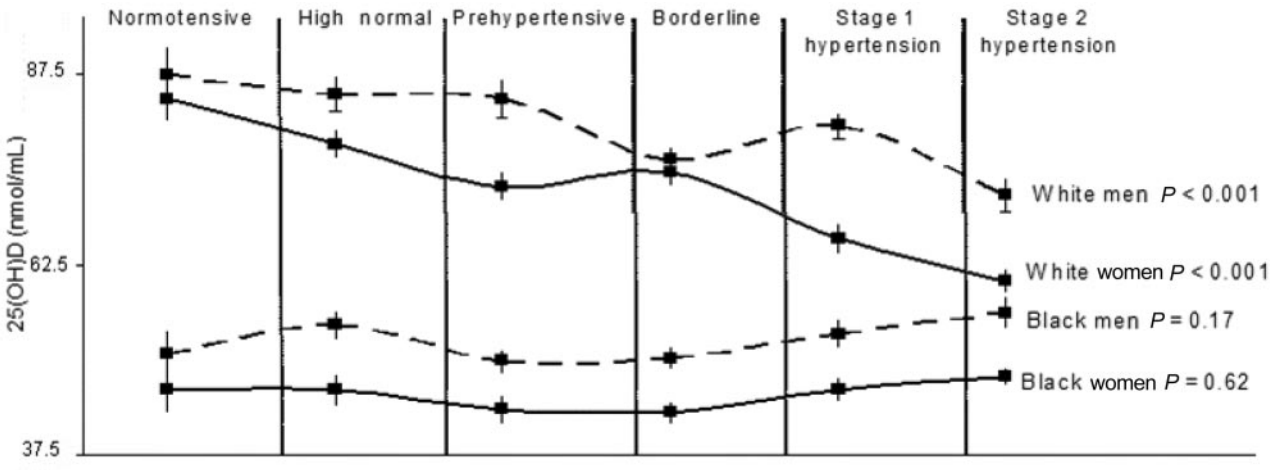

FIGURE 1. Concentrations of 25-hydroxyvitamin D [25(OH)D] by systolic blood pressure with the use of the Joint National Committee 7 (JNC 7) hypertension classifications among adults in the third National Health and Nutrition Examination Survey (NHANES III; 1988–1994). Persons studied in the NHANES III who were not previously known to have hypertension were subdivided into 6 categories. Five categories were based on the recommendations from the JNC 7 (normotensive: <120 mm Hg; prehypertensive: 120–129 mm Hg; borderline: 130–139 mm Hg; stage 1 hypertension: 140–159 mm Hg; and stage 2 hypertension: ≥160 mm Hg). The normotensive categories was further divided into normotensive (<110 mm Hg) and high normal (110–119 mm Hg). Concentrations of 25(OH)D significantly ($P < 0.001$) decreased when moving from JNC 7 blood pressure category normotensive to stage 2 hypertension in the total population and in the subgroup of both white men and women. No significant change was observed in 25(OH)D concentration when moving across blood pressure category when examined in either black men or black women. Analysis was done in PROC REGRESS to estimate the conditional mean concentration of 25(OH)D with the use of appropriate sample weights. Error bars represent SEs.

in young white participants, $P < 0.001$). This trend was not present in black participants; however, there were only 287 elderly black participants. BMI was associated with increased blood pressure in young and middle-aged participants but not in elderly participants. Sex was strongly associated with SBP in both races in young participants but not in old participants. Season when blood was drawn, physical activity, and smoking status were not significantly associated with SBP.

To explore the interaction between age and vitamin D on SBP, we examined the age-related increase in SBP by stratifying the analysis into 3 classifications of 25(OH)D [vitamin D deficient: <50 nmol/L ($n = 876$); vitamin D insufficient: 50–80 nmol/L ($n = 1959$); and vitamin D sufficient: ≥80 nmol/L ($n = 1991$)] (**Figure 2**). This interaction was statistically significant at the 5% level. In participants with 25(OH)D concentrations < 50 nmol/L, the age-related increase in SBP was 0.50 mm Hg/y. In comparison the age-related increase in SBP was 0.48 mm Hg/y in participants with 25(OH)D concentrations between 50 and 79 nmol/L. This decreased to 0.40 mm Hg/y in participants with 25(OH)D concentrations > 80 nmol/L. Participants who were vitamin D deficient and insufficient had significantly higher age-associated increases in SBP than did participants who were vitamin D sufficient ($P = 0.01$). Because of the small number of black participants with sufficient vitamin D status [only 8% of the participants had 25(OH)D concentrations > 80 nmol/L], we were only able to conduct this analysis in white participants.

DISCUSSION

In our analysis, a statistically significant inverse association was observed between circulating 25(OH)D concentrations and SBP classification (ranging from normotensive to mildly hypertensive). This association was not statistically significant when age was included in the model, nor was it significant in the black subpopulation. However, the age-associated rise in SBP was 20% ($P < 0.001$) lower in white participants who had sufficient circulating concentrations of 25(OH)D (>80 nmol/L) than in their deficient counterparts [25(OH)D < 50 nmol/L].

Previous studies have indicated that vitamin D insufficiency is common in the United States (23, 24). We found that with a 25(OH)D cutoff of <80 nmol/L to define vitamin D insufficiency, 61% of whites and 92% of blacks, respectively, were vitamin D insufficient in the NHANES III. Blacks with sufficient concentrations of 25(OH)D were largely absent in this analysis of the US black population, thus limiting the range of values with which to detect an association. This was particularly concerning in this population because 65% of black participants had 25(OH)D concentrations tested in the summer or the fall when 25(OH)D concentrations should have been the highest.

Despite a high prevalence of vitamin D insufficiency, we found an inverse association between 25(OH)D and blood pressure in white participants. Epidemiologic studies support this finding and suggest a pathophysiologic link (25–30). For example, others have reported that residents of higher latitudes experience decreased UV light exposure, reduced vitamin D production, and higher SBP and diastolic blood pressure (29). In addition, blood pressure is known to increase in the winter in the northern hemisphere when vitamin D production is low (25–28).

A recent analysis that examined the relation between 25(OH)D and blood pressure in this same population was published by Scragg et al (30). Similar to our findings, they found when comparing quintiles of 25(OH)D that mean SBP and diastolic blood pressure were lower in the highest quintile of 25(OH)D (>85.7 nmol/L) than in the lowest quintile (<40.4 nmol/L) after adjustment for sex, age, ethnicity, and physical activity. They reported significant negative regression coefficients in SBP after adjustment for age, sex, and physical activity in non-Hispanic whites and blacks; however, regression coefficients after adjustment for BMI were not reported.

TABLE 2
Linear regression coefficients modeling systolic blood pressure (SBP) compared with vitamin D [25(OH)D] concentrations stratified by age in whites in the third National Health and Nutrition Examination Survey [NHANES III] (1988–1994)[1]

	Model A[2]	Model B[3]	Model C[4]	Model D[5]	Model E[6]	Model F[7]	Model G[8]
Whites							
Ages 19–49 y (n = 2407)							
25(OH)D (nmol/L)	−0.32	—	−0.09	−0.47	0.29	0.42[9]	0.21
Age (y)	—	0.21[9]	0.21[9]	—	—	0.15[9]	0.16[9]
BMI (kg/m^2)	—	—	—	—	0.77[9]	0.73[9]	0.61[9]
Sex	—	—	—	−9.39[9]	—	—	−8.56[9]
Ages 50–64 y (n = 882)							
25(OH)D (nmol/L)	−0.61	—	−0.49	−0.76[9]	−0.24	−0.11	−0.26
Age (y)	—	0.51[9]	0.46[9]	—	—	0.47[9]	0.47[9]
BMI (kg/m^2)	—	—	—	—	0.60[9]	0.60[9]	0.61[9]
Sex	—	—	—	−2.12[9]	—	—	−2.14[9]
Ages ≥65 y (n = 1364)							
25(OH)D (nmol/L)	−0.12[9]	—	−0.42	−0.1	−0.11[9]	−0.41	−0.32
Age (y)	—	0.79[9]	0.81[9]	—	—	0.82[9]	0.82[9]
BMI (kg/m^2)	—	—	—	—	−0.02	0.12	0.13
Sex	—	—	—	1.55	—	—	0.80
Blacks							
Ages 19–49 y (n = 2401)							
25(OH)D (nmol/L)	−0.01	—	0.11	−0.90[9]	0.39	0.44	−0.42
Age (y)	—	0.39[9]	0.39[9]	—	—	0.35[9]	0.32[9]
BMI (kg/m^2)	—	—	—	—	0.45[9]	0.39[9]	0.48[9]
Sex	—	—	—	−8.81[9]	—	—	−9.30[9]
Ages 50–64 y (n = 341)							
25(OH)D (nmol/L)	1.43	—	1.31	1.39	2.03	1.92	1.91
Age (y)	—	1.05[9]	1.11[9]	—	—	1.13[9]	1.12[9]
BMI (kg/m^2)	—	—	—	—	0.58[9]	0.61[9]	0.62[9]
Sex	—	—	—	−0.84	—	—	−2.06
Ages ≥65 y (n = 287)							
25(OH)D (nmol/L)	−0.98	—	−0.89	−1.13	−1.17	−1.09	−1.28
Age (y)	—	0.24	0.22	—	—	0.30	0.32
BMI (kg/m^2)	—	—	—	—	0.03	0.08	0.13
Sex	—	—	—	−2.08	—	—	−2.57

[1] Linear regression was conducted with PROC REGRESS. The 25(OH)D × age × race interaction was significant. Season when blood was drawn, latitude, smoking status, and physical activity were also tested as covariates and were neither significant predictors of systolic blood pressure nor confounders (did not change point estimates by >10% in model G).
[2] Adjusted for 25(OH)D only; regression coefficient represents the change in SBP (1 mm Hg) for every 10-ng/mL change in 25(OH)D.
[3] Adjusted for age (continuous) only; regression coefficient represents the change in SBP (1 mm Hg) for every additional year in age.
[4] Adjusted for 25(OH)D and age (continuous).
[5] Adjusted for 25(OH)D and sex; negative regression coefficient represents lower average blood pressure in women than in men because women were coded as 2 and men as 1.
[6] Adjusted for 25(OH)D and BMI (continuous); regression coefficient represents the change in SBP (1 mm Hg) for every additional increase in BMI.
[7] Adjusted for 25(OH)D, age (continuous), and BMI (continuous).
[8] Adjusted for 25(OH)D, age (continuous), BMI (continuous), and sex.
[9] Coefficient was significant at the 5% level.

In previous epidemiologic studies, blood pressure was not associated with reported dietary vitamin D intake; however, those investigations did not include 25(OH)D determinations (31, 32). When circulating 25(OH)D has been examined, low 25(OH)D concentrations (<37.5 nmol/L) were associated with increased risk of incident hypertension, suggesting a potential role for vitamin D in the cause of hypertension (33). It is not known whether correcting vitamin D deficiency retards the development of hypertension in persons without a history of hypertension.

In the cross-sectional study presented here, the inverse association between blood pressure and 25(OH)D concentration was not significant after controlling for age. Because vitamin D production decreases in older adults because of lower skin concentrations of 7-dehydrocholesterol (the precursor to D_3), increasing age is associated with decreased concentrations of 25(OH)D (34). Thus, the effect of increased age overwhelmed the association of 25(OH)D with SBP in our study. Because statistically significant interaction existed between age and 25(OH)D, we examined the effect of 25(OH)D in 3 different age classifications as well as the effect of age in 3 different 25(OH)D classifications. Participants who were vitamin D deficient had the strongest association of age with SBP, and, although nonsignificant, the strongest negative linear association of 25(OH)D was observed in participants >65 y of age. Therefore, the effect of 25(OH)D may be more relevant to elderly persons. Forman et al (33) showed that those who had 25(OH)D concentrations < 37.5 nmol/L were at increased risk of developing hypertension.

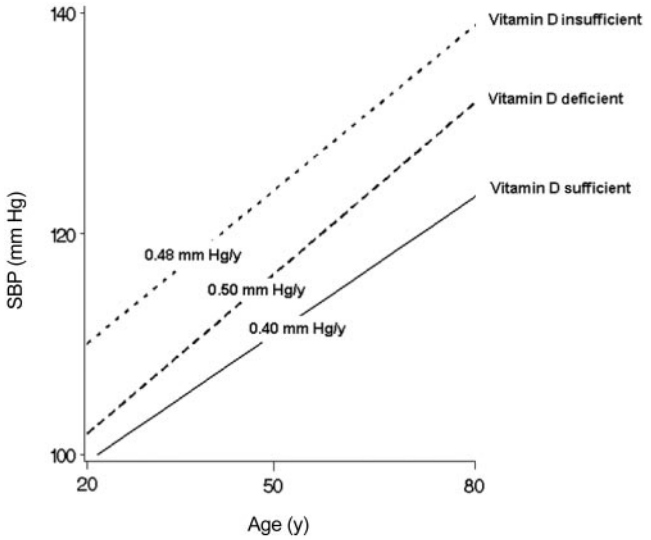

FIGURE 2. Age-related increase in systolic blood pressure (SBP) is shown in white participants not currently using medication to lower blood pressure, stratified by 3 concentrations of 25-hydroxyvitamin D [25(OH)D]. The interaction of age and vitamin D on SBP was significant ($P < 0.05$). Vitamin D sufficiency [25(OH)D > 80 nmol/L] attenuated the predicted age-related rise in SBP by 20% compared with participants with vitamin D deficiency [25(OH)D < 50 nmol/L] ($P < 0.001$) in white participants participating in the third National Health and Nutrition Examination Survey (1988–1994). Vitamin D sufficiency reduced the predicted age-related rise in SBP by 16% ($P < 0.001$) and reduced the average SBP at age 20 y by 9.1 mm Hg ($P = 0.008$) compared with participants with vitamin D insufficiency [25(OH)D: 50.1–79.9 nmol/mL]. The model controlled for BMI, sex, physical activity, and smoking status. Analysis was done in PROC REGRESS in SUDAAN with the use of appropriate sample weights.

Supporting evidence for the role of vitamin D in reducing blood pressure can be found in 2 randomized clinical trials. One randomized, placebo-controlled study in 145 elderly women showed that 400 IU of vitamin D_3 plus 600 mg of calcium significantly reduced blood pressure by 9.3% after 8 wk, whereas treatment with 600 mg of calcium alone reduced blood pressure by only 4.0% ($P = 0.02$) (35). Because supplemental calcium was used as an active intervention group in that study, the investigators suggested that vitamin D repletion may improve blood pressure control independent of dietary calcium intake. A second randomized, placebo-controlled trial that compared UVB (needed for de novo synthesis of vitamin D from skin) with UVA light (which is unable to initiate endogenous vitamin D production) in 18 persons found that increasing serum 25(OH)D concentrations from an average of 50 to 152 nmol/L resulted in a significant reduction in SBP (6 mm Hg) after 6 wk of treatment (36).

Several in vivo studies have shown that $1\alpha,25(OH)_2D$ has an important role in the regulation of plasma renin activity (15). However, there are limited clinical data to determine the potential mechanisms by which vitamin D may influence blood pressure. A case study in Japan found that after 2 wk of therapy with $1\alpha,25(OH)_2D$ SBP and diastolic blood pressure and plasma renin activity decreased significantly (37). Other suggested potential mechanisms of $1\alpha,25(OH)_2D$ action on blood pressure include direct action of the nutrient on the arterial wall (38) and reduction in inflammation (19, 39), leading to arteriosclerosis. Many in vivo studies have examined $1\alpha,25(OH)_2D$ and blood pressure. However, 25(OH)D is the best biomarker of vitamin D status because $1\alpha,25(OH)_2D$ has a short half-life. It is believed that, because 25(OH)D is the substrate for $1\alpha,25(OH)_2D$, higher concentrations of 25(OH)D are needed for production of extrarenal $1\alpha,25(OH)_2D$ (16, 19).

We have shown a reduction in the age-related rise in blood pressure in white participants who are vitamin D sufficient, but our analyses have limitations. First, the NHANES III is a cross-sectional study, and a causal relation cannot be inferred from these results. However, these data do concur with reports from prospective studies that have consistently described an inverse relation between concentrations of 25(OH)D and blood pressure. Second, the NHANES III was conducted in the early 1990s, and the results may not indicate current vitamin D status in the United States. This is the most recent NHANES survey to measure 25(OH)D concentrations, so more recent data are currently unavailable from this national survey. Third, because blood pressure was only measured at one appointment, it is possible that some participants were misclassified as having elevated blood pressure when they were truly normotensive or vice versa. It is unlikely that this misclassification would change the mean 25(OH)D concentrations in a way that would bias the results, given the number of participants studied. We limited our analyses to white and black adults and persons who had not been told they had hypertension; thus, generalizability to Mexican American and persons of other race or ethnic groups is limited.

Although the epidemiologic evidence suggests an association between 25(OH)D and blood pressure, determining this association in the US population presents a challenge because vitamin D insufficiency is so common. Our data suggest the need for improved detection and treatment of vitamin D insufficiency in US adults, especially in blacks. Future studies that examine the effects of optimizing vitamin D status on blood pressure in both white and black adults appear to be warranted.

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The author's responsibilities were as follows—SEJ: contributed to the study design and concept, statistical analysis, and writing of manuscript; MSN and TRZ: contributed to the writing and editing of the manuscript; PWFW: contributed to the statistical design and analysis of the data in the manuscript and writing of the manuscript; VT: contributed to the study design concept and writing of the manuscript. None of the authors had a personal or financial conflict of interest.

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