Journal of Cardiovascular Nursing
Vol. 00, No. 0, pp. 00–00 | Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

The Association Between Vitamin D Levels and the 10-Year Risk of Atherosclerotic Cardiovascular Disease

A Population-Based Study

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Background: The association between vitamin D levels and atherosclerotic cardiovascular disease (ASCVD) risk remains unclear. In this study, the association between serum 25(OH)D and 10-year ASCVD risk was examined in a national sample of middle-aged and older adults. **Methods:** Cross-sectional data from the 2009–2014 National Health and Nutrition Examination Survey were analyzed. The Pooled Cohort Equations were used to estimate the risk of a first ASCVD event in 10 years. An adjusted multiple linear regression model was used to investigate the association between serum 25(OH)D and ASCVD risk. In addition, we performed sensitivity analysis and interactive analysis to assess the robustness of associations across different subgroups. **Results:** A total of 3354 participants were included in this study. The linear regression model indicated that the risk of ASCVD decreased with the increase in serum 25(OH)D. When analyzed as a continuous variable, serum 25(OH)D was significantly associated with the estimated 10-year risk of ASCVD. In the fully adjusted model, each 10-nmol/L increase in serum 25(OH)D reduced the estimated 10-year ASCVD risk by 0.172% ($P < .001$). Individuals in the moderate, insufficient, and sufficient vitamin D deficiency groups had a 0.449% ($P = .362$), 0.957% ($P = .046$), 1.475% ($P = .003$) decrease in ASCVD risk, respectively, when a severe vitamin D deficiency group was set as a reference in the fully adjusted model. **Conclusion:** Our data suggest a negative association between vitamin D levels and the predicted 10-year risk of ASCVD. Further studies are required to investigate whether vitamin D supplements could reduce the risk of ASCVD.

KEY WORDS: atherosclerotic cardiovascular disease, pooled cohort equations, serum 25(OH)D, vitamin D

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in developed countries. Atherosclerotic cardiovascular disease risk includes coronary heart disease death, nonfatal myocardial infarction, or fatal/nonfatal stroke,[1] which cause significant health and financial burden worldwide.[2] Thus, identifying a high-risk ASCVD population

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This study was supported by the National Key Research and Development Program of China (no. 2019YFA0210100), China International Medical Foundation (Z-2019-42-1908), and Postgraduate Research & Practice Innovation Program of Jiangsu Province (SJCX21_0626).

The authors have no conflicts of interest to disclose.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jcnjournal.com).

DOI: 10.1097/JCN.0000000000000943

is important for primary prevention.[3,4] Recently, a predictive model named Pooled Cohort Equations has been developed to estimate the 10-year primary risk of ASCVD.[1,5] Pooled Cohort Equations has been applied by multiple guidelines to assist decision making in primary ASCVD prevention, such as lifestyle management, blood pressure control, and blood cholesterol regulation.[6–8]

Vitamin D is a secosteroid that consists of 2 forms: D_2 (ergocalciferol) and D_3 (cholecalciferol).[9] Vitamin D_3 is mainly synthesized through ultraviolet B light in the skin or consumption of oily fish, whereas vitamin D_2 is obtained by digesting plants containing ergosterol.[10] Accumulating studies highlighted the significant role of $1,25(OH)_2D_3$ in preventing cardiovascular diseases via multiple mechanisms, including pancreatic β cell function,[11] blood pressure,[12] dyslipidemia, obesity,[13] renin-angiotensin system activity,[14] endothelial cell function,[15] arterial stiffness,[16] and vascular dysfunction[17]; yet, the function of vitamin D in cardiovascular diseases remains controversial. Moreover, vitamin D deficiency has been recently recognized as a global problem, with a prevalence of 40.4%, 36.8%, and 24.0% in Europe, Canada, and the United States, respectively.[18,19]

In some cross-sectional studies, a close association was observed between serum 25(OH)D levels and the prevalence of cardiovascular diseases,[20–22] whereas in another study, authors revealed inconsistent results.[23] In addition, cohort studies showed that individuals with low serum 25(OH)D levels were more likely to develop hypertension.[24,25] However, it remains unclear whether 25(OH)D levels are associated with the risk of future ASCVD.

The purpose of this study was to determine the connection between serum 25(OH)D and the 10-year ASCVD risk according to a national sample of middle-aged and older adults.

Methods

Data Source and Study Population

The National Health and Nutrition Examination Survey (NHANES) is conducted by the US Centers for Disease Control and Prevention to assess the population's health and nutritional status. The flow chart of eligible participants' selection is shown in Figure S1, http://links.lww.com/JCN/A174.

First, we collected 17598 participants from NHANES 2007–2014. Then, we selected 11761 individuals with complete information, including demographics (age, gender, race/ethnicity, and poverty to income ratio level), laboratory indicators (serum 25[OH]D, total and high-density cholesterol, triglyceride, glycosylated hemoglobin, and serum creatinine), ASCVD risk factors (hypertension, diabetes, smoking status, drinking status, energy intake, and sodium intake), and the history of self-reported cardiovascular diseases (stroke, angina, coronary heart disease, congestive heart failure, or heart attack). Participants with a history of stroke, angina, coronary heart disease, congestive heart failure, or heart attack were excluded (n = 1285). In addition, participants who were pregnant (n = 99) or whose estimated glomerular filtration rate was less than 60 mL/min per 1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration equation (n = 690) were also excluded. Importantly, because Pooled Cohort Equations was designed for non-Hispanic African American and non-Hispanic White men and women from 40 to 79 years old, we also screened for age (n = 2670) and race (n = 2852). A final sample of 4165 participants was included in the analyses.

The study was approved by the National Center for Health Statistics Research Ethics Review Board.

The Evaluation of Serum 25(OH)D

Serum 25(OH)D was measured using the standardized liquid chromatography-tandem mass spectrometry method.[26] According to the NHANES protocol document, the database code-named LBXVIDMS was used as the serum 25(OH)D level. Serum 25(OH)D is the sum of 25-hydroxyvitamin D_3 and 25-hydroxyvitamin D_2, reported in nanomoles per liter. According to the Endocrine Society's Clinical Guidelines Subcommittee, serum 25(OH)D less than 25 nmol/L, 25 to 50 nmol/L, 50 to 74 nmol/L, and 75 nmol/L or greater represent a severe deficiency, moderate deficiency, insufficient deficiency, and sufficient levels, respectively.[27–29]

The Calculation of 10-Year Estimated Atherosclerotic Cardiovascular Disease Risk

The outcomes were ASCVD events, including fatal stroke, nonfatal stroke, fatal coronary heart disease, and nonfatal myocardial infarction. The Pooled Cohort Equations was calculated based on 7 variables, including age (years), total cholesterol (milligrams per deciliter), high-density lipoprotein cholesterol (milligrams per deciliter), systolic blood pressure (millimeters of mercury) of treated or untreated status, diabetes mellitus, and current smoking status (yes/no).[1] The equation was calculated as 1 minus the 10-year survival rate, which was raised to the power of the exponent of the "Coefficient-Value" sum minus the sex- and race-specific overall mean "Coefficient × Value" sum. According to the guideline by the American College of Cardiology/American Heart Association,[1] the Pooled Cohort Equations was simplified as follows:

$$\textit{Estimated } 10\textit{–year risk of ASCVD} = 1 - S_{10}^{\left(lndX'B - MeanX'B\right)}$$

According to Goff et al,[1] participants whose estimated 10-year risk of ASCVD is less than 1% or greater than

30% should be excluded because the results are unstable when approaching the limits of the sample data. Therefore, participants were grouped according to the estimated 10-year risk of ASCVD as low-risk (1%–4.9%), borderline-risk (5% to <7.5%), intermediate-risk (7.5% to <20%), and high-risk (20%–30%) groups.[30]

Covariates

We included multiple covariates in the analysis, including demographics, 24-hour diet recall, examination, laboratory, and questionnaire information. Demographic variables included gender, age, race/ethnicity, education level, and income. Race/ethnicity was classified as non-Hispanic Black and non-Hispanic White. Education level was categorized as lower than high school, high school, or higher than high school. According to the qualification criterion for the US federal Supplemental Nutrition Assistance Program, PIR (PIR = family income/federal poverty level) was classified as less than 1.33, 1.33 to 3.50, and 3.50 or greater to evaluate household poverty. Cardiometabolic risk factors, such as lipid profiles, plasma glucose, history of chronic kidney disease, alcohol consumption, smoking status, total energy intake, and sodium intake, were also included. Hypertension was regarded as mean systolic blood pressure of 130 mm Hg or greater and/or diastolic blood pressure of 80 mm Hg or greater,[31] self-reported history of hypertension, and/or using antihypertensive drugs. Diabetes was defined as hemoglobin A_{1c} of 6.5% or greater, fasting plasma glucose of 126 mg/dL or greater, and/or self-reported history of diabetes. Smoking refers to someone who smoked more than 100 cigarettes in their lifetime. Alcohol consumption was defined as drinking more than 12 alcoholic drinks per year.

We used the Chronic Kidney Disease Epidemiology Collaboration equation to calculate the estimated glomerular filtration rate,[32] and chronic kidney disease was defined as eGFR less than 60 mL/min per 1.73 m^2. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). In addition, indicators associated with vitamin D metabolism were included, such as albumin, blood calcium, and blood phosphorus. Methods and protocols for laboratory tests, questionnaires, and examinations are presented on the NHANES website.

Statistical Analysis

We performed weighted data analyses following NHANES analytic guidelines to minimize the basis caused by nonresponse, oversampling, and post-stratification. We used multivariate multiple imputation strategies based on 5 replications to impute missing covariates to minimize the selection bias and maximize the statistical power.

Continuous variables were expressed by mean ± standard deviation; categorical variables were expressed by percentages. Baseline characteristics were described across vitamin D levels, and the differences among groups were compared by the Wilcoxon test for continuous variables and the χ^2 test for categorical variables. We first described the missingness and consistency of different variables by the mice package. The distributions of serum 25(OH)D and the estimated 10-year risk of ASCVD were illustrated by applying kernel density estimation with Gaussian kernels.

A linear regression model was applied to illustrate the relationship of serum 25(OH)D with the estimated 10-year risk of ASCVD. Then, 3 different regression models were used to determine the association between serum 25(OH)D and the estimated 10-year risk of ASCVD: (1) model 1 was unadjusted; (2) model 2 (minimally adjusted model) was adjusted for gender, age, and race; and (3) model 3 (fully adjusted model) was additionally adjusted for eGFR, blood calcium, blood phosphorus, albumin, body mass index, sodium intake, diabetes history, and total cholesterol based on model 2. To further demonstrate the robustness of the association, we performed sensitivity analysis and interactive analysis under unmeasured confounding in different subgroups, including gender (male/female), age (<60 years, ≥60 years), hypertension (yes/no), diabetes (yes/no), and body mass index (<30 kg/m^2, ≥30 kg/m^2). The associations were adjusted for gender, age, race, eGFR, blood calcium, blood phosphorus, albumin, body mass index, sodium intake, diabetes history, and total cholesterol. Importantly, the specific variable was not adjusted when analyzing each subgroup.

All statistical analyses were performed in R software (version 4.1.1). $P < .05$ was considered as statistically significant.

Results

Characteristics of the Study Population

A total of 4165 participants were included in the analysis. As previously described, we excluded 811 participants because their estimated 10-year risk of ASCVD was outside the 1% and 30% ranges (Figure S1, http://links.lww.com/JCN/A174). The final sample included 3354 participants (mean age, 56.2 years; 47.5% female).

The serum 25(OH)D levels ranged from 12.3 to 318.0 nmol/L with a median of 68.0 nmol/L. In addition, 27.2% of participants had deficient vitamin D (<50 nmol/L), and 62.7% of them had insufficient levels (<75 nmol/L). The median estimated 10-year risk of ASCVD was 9.17%. Among the participants, 1269 (37.9%) were considered to be at a low risk, 493 (14.7%) were at a borderline risk, 1242 (37%) were at an intermediate risk, and 350 (10.4%) were at a high

risk. A small percentage were missing data on body mass index (0.13%) and education (0.03%) (Figure S2, http://links.lww.com/JCN/A175), which did not affect the analyses.

Table 1 summarizes the demographic characteristics of the study population. Participants who had high serum 25(OH)D were more likely to be non-Hispanic White and have a higher family income level compared with those with low serum 25(OH)D. Individuals with higher serum 25(OH)D tended to have a lower estimated 10-year risk of ASCVD, systolic blood pressure, and hemoglobin A_{1c}, and lower prevalence of obesity and smoking. The distributions of serum 25(OH)D and the estimated 10-year risk of ASCVD by kernel density estimation with Gaussian kernels are shown in Figure 1.

The Association Between Serum 25(OH)D and the Atherosclerotic Cardiovascular Disease Risk

As shown in Figure 2, the linear regression model revealed a negative association between serum 25(OH)D and the estimated 10-year risk of ASCVD. A consistent relationship was observed in regression analysis (Table 2). When analyzed as a continuous variable, serum 25(OH)D was significantly associated with the estimated 10-year risk of ASCVD in all 3 models. In the fully adjusted model, each 10-nmol/L increase in serum 25(OH)D was associated with a 0.172% ($P < .001$) reduction in ASCVD risk. In addition, individuals in the moderate, insufficient, and sufficient vitamin D deficiency groups had a 0.449% ($P = .362$), 0.957% ($P = .046$), and 1.475% ($P = .003$) decrease in ASCVD risk, respectively, when setting the severe vitamin D deficiency group as a reference in the fully adjusted model.

Subgroup Analysis

Table 3 shows a robust association between serum 25(OH)D and the ASCVD risk when participants were classified by gender (male/female), hypertension (yes/no), and body mass index (<30 kg/m^2, ≥30 kg/m^2). Participants who were male, with a lower body mass index, and without a history of hypertension were more likely to have a lower risk of ASCVD risk. Interestingly, no

TABLE 1 Demographic Characteristics of the Participants Across Serum 25(OH)D Levels

Variables	Severe Deficiency [0, 25] nmol/L	Moderate Deficiency [25, 50] nmol/L	Insufficient Deficiency [50, 75] nmol/L	Sufficient [75, 318] nmol/L	*P*
No. participants	136	776	1191	1251	
Estimated 10-y risk of ASCVD, %	8.9 ± 0.5	8.3 ± 0.3	8.0 ± 0.2	7.7 ± 0.2	.009
Serum 25(OH)D	20.6 ± 0.4	39.3 ± 0.4	63.3 ± 0.3	96.9 ± 0.9	<.001
Serum calcium, mg/dL	9.4 ± 0.1	9.4 ± 0.0	9.4 ± 0.0	9.5 ± 0.0	<.001
Age, y	54.2 ± 0.8	54.0 ± 0.4	54.5 ± 0.3	56.5 ± 0.3	<.001
Gender (female), %	56.6	49.0	37.3	49.6	<.001
Race/ethnicity, %					<.001
Non-Hispanic White	41.1	70.3	90.5	95.7	
Non-Hispanic Black	58.9	29.7	9.5	4.3	
PIR level, n (%)					<.001
<1.33	36.0	21.8	12.9	10.5	
1.33–3.5	40.4	34.6	31.7	25.1	
≥3.5	23.6	43.6	55.4	64.4	
Education, %					.001
Lower than high school	21.3	16.0	12.0	8.5	
High school	21.2	25.4	22.4	24.5	
Higher than high school	57.5	58.6	65.6	67.0	
Blood pressure					
Hypertension, %	60.3	50.2	43.0	45.7	.014
SBP, mm Hg	129.2 ± 1.7	127.8 ± 1.1	123.8 ± 0.5	123.4 ± 0.5	<.001
DBP, mm Hg	71.9 ± 1.6	74.3 ± 0.9	73.6 ± 0.4	72.1 ± 0.4	<.001
Blood glucose					
Diabetes, %	10.0	12.3	7.4	8.3	.124
Serum glucose, mmol/L	6.3 ± 0.3	6.0 ± 0.1	5.6 ± 0.1	5.5 ± 0.1	.010
HbA_{1c}, %	6.0 ± 0.1	5.9 ± 0.1	5.7 ± 0.0	5.6 ± 0.0	<.001
Lipid profile					
Cholesterol level, mmol/L	5.2 ± 0.1	5.2 ± 0.1	5.3 ± 0.0	5.3 ± 0.0	.100
Triglyceride level, mg/dL	139.7 ± 12.0	163.2 ± 6.8	170.0 ± 4.9	155.7 ± 3.5	.017
Health behavior					
Body mass index, kg/m^2	32.8 ± 1.2	32.0 ± 0.4	30.0 ± 0.3	28.6 ± 0.2	<.001
Smoking status (yes), %	57.2	50.3	50.7	48.3	.569
Alcohol consumption (yes), %	13.7	11.8	7.9	8.4	.088

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; DBP, diastolic blood pressure; HbA_{1c}, hemoglobin A_{1c}; PIR, Poverty to income ratio level; SBP, systolic blood pressure.

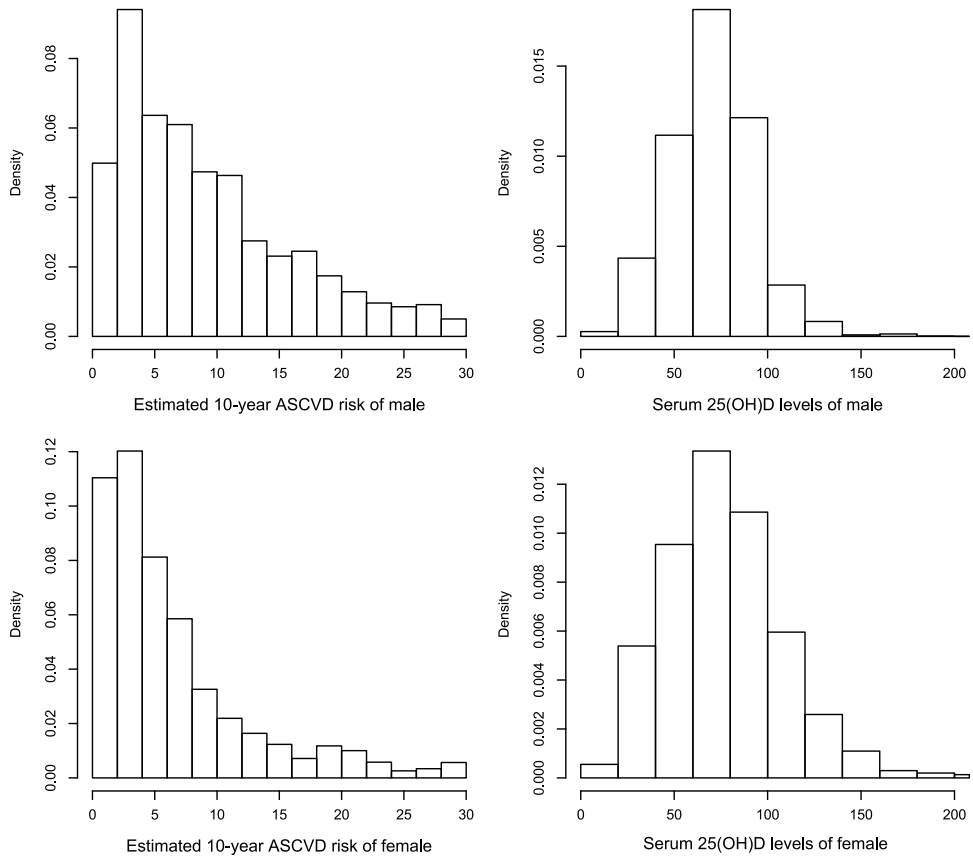

FIGURE 1. *Distribution of the estimated 10-year risk of ASCVD and serum 25(OH)D in men and women by kernel density estimation. ASCVD, atherosclerotic cardiovascular disease.*

significant ASCVD-inducing effect was observed when classifying participants by age (<60 years, ≥60 years) and history of diabetes mellitus (yes/no). The interaction test suggested no significant difference between serum 25(OH)D and ASCVD risk in all subgroups (all *P*s for interaction > .05), which further demonstrated the robust association between serum 25(OH)D and the ASCVD risk.

Discussion

Although accumulating studies highlighted the significant role of $1,25(OH)_2D_3$ in preventing cardiovascular diseases,[11–17] the association between vitamin D and cardiovascular disease outcomes remains unclear. Whereas some researchers reported no association between 25(OH)D level and cardiovascular events,[23] others showed inconsistent results.[20,22,33] For example, cross-sectional research revealed that serum 25(OH)D less than 50 nmol/L was a risk factor for cardiovascular diseases, including angina, myocardial infarction and stroke.[22] In addition, a higher degree of vitamin D deficiency has been related to more severe coronary heart disease.[34–36] Interestingly, a J-shaped relationship was observed between serum 25(OH)D and cardiovascular events, with the lowest risk in 50 to 60 nmol/L.[37] In another study, it was suggested that serum 25(OH)D of 50 to 90 nmol/L may lead to the least risk of death for patients having acute coronary syndrome (U-shaped association).[38] Dudenkov et al[39] achieved a similar trend with the cutoff interval of 50 to 125 nmol/L in cardiovascular disease, whereas no significant association was discovered when serum 25(OH)D is greater than 125 nmol/L.

According to our knowledge, this is the first study in which authors analyzed the association between serum 25(OH)D levels and the 10-year risk of ASCVD estimated by Pooled Cohort Equations. Our data indicated a significant adverse effect of insufficient serum 25(OH)D on the 10-year risk of ASCVD, which was still present after adjusting for gender, age, race, eGFR, blood calcium, blood phosphorus, albumin, body mass index, sodium intake, diabetes history, and total cholesterol. The ASCVD risk for subjects in the vitamin D sufficient group (≥75 nmol/L) was lowest (*B* coefficient = –1.475, *P* = .003), whereas the vitamin D severe and moderate deficiency groups had a higher ASCVD risk in the fully adjusted model. Consistently, a previous secondary analysis of the Framingham Offspring Study also demonstrated low serum 25(OH)D levels (<37.5 nmol/L) as an adverse factor for 5-year cardiovascular events (hazard ratio, 1.62; 95% confidence interval, 1.11–2.36).[21]

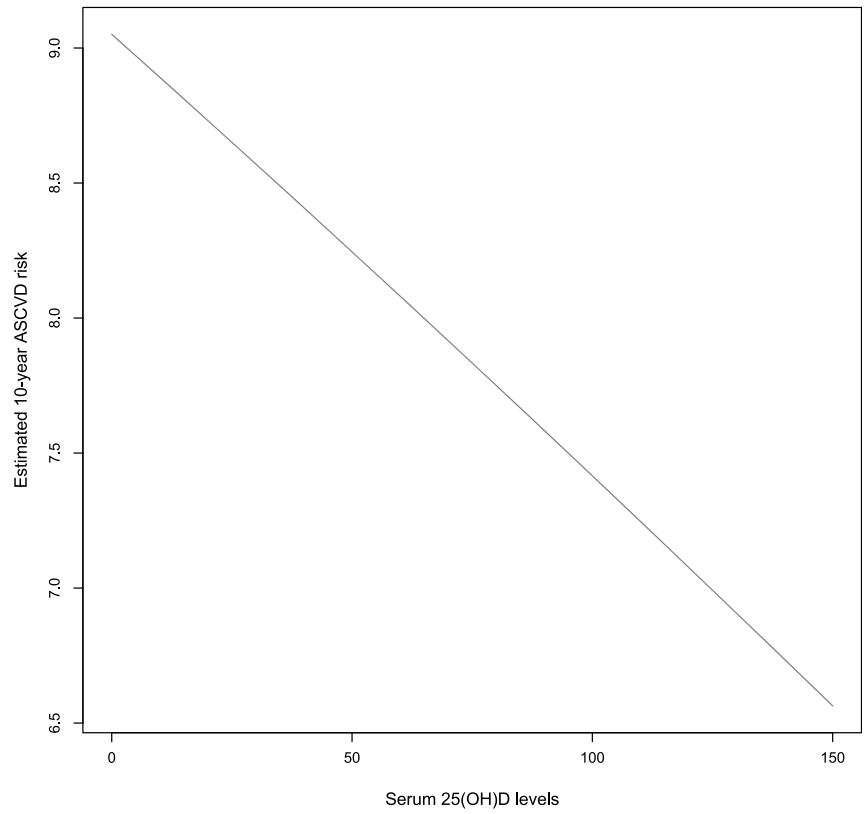

FIGURE 2. *Fitting diagram of the linear regression model in the analysis of the association between serum 25(OH)D and the estimated 10-year risk of ASCVD. ASCVD, atherosclerotic cardiovascular disease.*

Although observational studies sustained a relationship between increased serum 25(OH)D and lower risk of cardiovascular disease, interventional studies regarding vitamin D supplementation provide no positive results.[23,40–44] A meta-analysis involving 83000 individuals showed that vitamin D supplementation was not associated with reduced cardiovascular adverse events and all-cause mortality.[45] Interestingly, Sheerah et al[46] conducted a prospective population-based study including 58646 healthy adults with a mean follow-up of 19.3 years in Japan. The results indicated that vitamin D intake was related to decreased risk of stroke-induced death (hazard ratio, 0.70; 95% confidence interval, 0.54–0.91), but not coronary heart disease–specific death. Moreover, Hsia et al[44] proposed several hypotheses, such as the insufficient dose of vitamin D, poor adherence of the subjects, and the ineffectiveness of vitamin D for cardiovascular disease. Considering the positive correlation between vitamin D intake and serum 25(OH)D,[47] the differing results from the prospective and retrospective studies should be further discussed.

TABLE 2 Association of 25(OH)D With Estimated 10-Year Risk of Atherosclerotic Cardiovascular Disease by Using Regression Models

	Nonadjusted Model		Minimally Adjusted Model		Fully Adjusted Model	
Items	***B* Coefficient**	***P***	***B* Coefficient**	***P***	***B* Coefficient**	***P***
25(OH)D (per 10 nmol/L)	−0.127	<.001	−0.229	<.001	−0.172	<.001
Categories						
Severe deficiency	Reference		Reference		Reference	
Moderate deficiency	−0.606	.238	−0.351	.503	−0.449	.362
Insufficient deficiency	−0.908	.092	−1.173	.026	−0.957	.046
Sufficient	−1.204	.027	−1.846	.002	−1.475	.003

Vitamin D levels of 4 groups: severe deficiency, [0, 25] nmol/L; moderate deficiency, [25, 50] nmol/L; insufficient deficiency, [50, 75] nmol/L; sufficient, [75, 318] nmol/L.

The minimally adjusted model was adjusted for gender, age, and race; the fully-adjusted model was adjusted for gender, age, race, estimated glomerular filtration rate, blood calcium, blood phosphorus, albumin, body mass index, sodium intake, diabetes history, and total cholesterol

TABLE 3 Subgroup Analysis of the Association Between Serum 25(OH)D and the Estimated 10-Year Risk of Atherosclerotic Cardiovascular Disease

	B Coefficient	*P*	*P* for Interaction
Gender			.578
Male	−0.217	.002	
Female	−0.141	.008	
Age, y			.058
<60	−0.228	<.001	
≥60	−0.038	.529	
Hypertension			.091
Yes	−0.111	.048	
No	−0.237	<.001	
Diabetes			.705
Yes	−0.211	.114	
No	−0.171	<.001	
BMI, kg/m^2			.353
<30	−0.177	.001	
≥30	−0.148	.010	

The associations were adjusted for gender, age, race, estimated glomerular filtration rate, blood calcium, blood phosphorus, albumin, BMI, sodium intake, diabetes history, and total cholesterol. Importantly, the specific variable was not adjusted when analyzing each subgroup.
Abbreviation: BMI, body mass index.

Atherosclerotic cardiovascular disease remains the major cause of mortality and morbidity worldwide, which can be avoided by prevention of traditional cardiovascular risk factors.[6,48,49] Therefore, estimating the absolute risk of future ASCVD is important for decision making on lifestyle changes or pharmacotherapy. Recently, the American College of Cardiology/American Heart Association guideline concerning primary prevention of cardiovascular disease recommended that Pooled Cohort Equations be routinely used to assess the 10-year risk of ASCVD for adults from 40 to 75 years old; the estimated risks of less than 5%, 5% to less than 7.5%, 7.5% to less than 20%, and 20% or greater are respectively defined as low risk, borderline risk, intermediate risk, and high risk.[6,50]

Limitations

This study has some limitations. First, in our study, we only analyzed the relationship between serum 25(OH)D and a 10-year risk of ASCVD for those aged 40 to 79 years. Determining the ASCVD risk of those younger or older is challenging due to the limitation of Pooled Cohort Equations. Second, we analyzed a nationally representative US sample. However, it remains unclear whether our conclusion could directly expand to other populations for lifestyle and genetic variation between different ethnicities/races. Third, although we have considered multiple covariates, we cannot completely overcome all residual and unknown confounders. Fourth, it is hard to determine the causality because this was a cross-sectional study. Further research should be proposed to confirm whether vitamin D deficiency would lead to the elevated risk of developing ASCVD.

What's New and Important

- Lower levels of vitamin are associated with higher ASCVD risk.

Conclusion

This study demonstrated the significant negative association between vitamin D levels and the 10-year risk of ASCVD. Yet, further studies are required to investigate whether vitamin D supplements could reduce the risk of ASCVD.

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