

U-Shaped Association of Standardized Serum 25-Hydroxyvitamin D with Risk of Low Muscle Mass: A Population-Based Cross-Sectional Study

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Background: In the United States (U.S.) general population, the association between standardized serum 25-hydroxyvitamin D (25(OH)D) concentration and risk of low muscle mass (LMM) remains unclear. Our research aimed to determine whether or not there was a relationship between serum 25(OH)D concentration and risk of LMM.

Methods: We analyzed the cross-sectional data of the US population that participated in the National Health and Nutrition Examination Survey between 2011 and 2014. The relationship between serum 25(OH)D concentration and LMM risk was evaluated using restricted cubic spline (RCS) with multivariate logistic regression model and subgroup analysis.

Results: In all, we included 10,256 people in our analysis. The RCS plot demonstrated a U-shaped relationship between serum 25(OH)D concentration and risk of LMM (P for nonlinearity <0.05). At a Vitamin D concentration of 38.5 nmol/L, LMM risk was at its lowest. Based on analyses stratified by age, sex, hypertension, and diabetes mellitus (DM), serum 25(OH)D concentration and risk of LMM were U-curve correlated for those age 40 or older, male, with hypertension, or without DM. However, LMM risk was positively related to serum 25(OH)D concentration in those younger than age 40 or in women.

Conclusion: There is a U-shaped relationship between serum 25(OH)D concentration and the risk of LMM in the general U.S. population. Careful monitoring and appropriate Vitamin D supplementation might lessen the risk of LMM.

Keywords: cross-sectional study, low muscle mass, serum 25-hydroxyvitamin D concentration, National Health and Nutrition Examination Survey, United States

Introduction

Rosenberg first proposed the term “sarcopenia” to describe the loss of muscle mass associated with aging in 1989.¹ Sarcopenia is defined as a geriatric syndrome characterized by progressive and widespread loss of muscle mass and function, with adverse risks of decreased quality of life and increased mortality.² The average prevalence among the elderly in the community was 12.8% worldwide.³ It is estimated to have a greater global disease burden than major depression and chronic respiratory illnesses combined.⁴

Studies have shown that sarcopenia is closely related to malnutrition.⁵ Casati and his team found that certain serum nutritional markers, including hemoglobin (Hb), albumin, selenium, magnesium, and Vitamin D, are also associated with sarcopenia.⁶ Among them, Vitamin D is an essential fat-soluble vitamin involved in the regulation of calcium and phosphorus, promoting bone mineralization and bone remodeling, and is closely related to bone metabolism.⁷ This clinical biomarker for Vitamin D status is serum 25-hydroxyvitamin D (25(OH)D).⁸ Vitamin D levels affect muscle cell contractility, proliferation, and differentiation, which are linked to skeletal muscle health.⁹ Vitamin D insufficiency results in muscle deficits, and Vitamin D supplementation has beneficial effects. Further, identification of the Vitamin D receptor in

skeletal muscle provides evidence for its direct effect on sarcopenia.¹⁰ Muscle strength is affected by vitamin D deficiency, which may contribute to the onset of sarcopenia.¹¹ The maintenance of sufficient serum 25(OH)D may prevent unfavorable changes in muscle mass in both young and middle-aged Korean adults.¹² Ko et al found that the levels of 25(OH)D in men might be correlated positively with skeletal muscle mass.¹³ Kim and his team revealed that regardless of obesity, subjects with sarcopenia had significantly lower vitamin D levels than those without sarcopenia. Additionally, in the older Korean population, they also found a strong inverse association between 25(OH)D level and sarcopenia.¹⁴ Meanwhile, Park et al also found that among Korean women aged 50 years or older, serum 25(OH)D levels were a negative moderator of sarcopenia.¹⁵ Additionally, in postmenopausal Korean women, sarcopenia was associated with both insulin resistance and 25-hydroxyvitamin D levels, regardless of obesity status.¹⁶ However, the link between serum 25(OH)D and the risk of low muscle mass (LMM) have not been studied in recent years in the general United States (US) population. The National Center for Health Statistics (NCHS) conducts a population-based study called the National Health and Nutrition Examination Survey (NHANES) to monitor the health and nutritional status of civilians and non-medical personnel. Data collection and analysis is carried out using a multi-stage, probabilistic cluster design rather than a simple random sample based on the US population.¹⁷ Therefore, in this study, we aimed to determine whether serum 25(OH)D concentration has an influence on LMM in the general US population using NHANES data from 2011–2014.

Materials and Methods

Study Population

The NHANES database is a large, ongoing cross-sectional survey designed to be nationally representative (<https://www.cdc.gov/nchs/nhanes/>).^{18,19} Two two-year cycles (2011–2014) from the NHANES database were used in this analysis. Among the 19,134 participants in the total sample, we excluded participants for whom data on vitamin D levels ($n = 2954$) and information about LMM ($n = 5924$) were not available in the NHANES database. Finally, this research included a total of 10,256 individuals. The NCHS study ethics review board approved all NHANES protocols, and participants or their proxies provided informed consent prior to participation.²⁰

Serum 25(OH)D Concentration

A blood sample was collected during the examination, centrifuged, divided, and frozen to -70°C on site, then shipped on dry ice to a central laboratory, where it was stored at -70°C until analysis. A radioimmunoassay kit (DiaSorin, Stillwater, MN) after acetonitrile-based extraction was used by the National Center for Environmental Health (Atlanta, GA) to measure serum 25(OH)D levels. For six two-year cycles (2007–2018), the United States Centers for Disease Control and Prevention laboratory used the LC-MS/MS method to analyze serum 25(OH)D metabolites, and the combined total serum 25(OH)D (nmol/L) was calculated by adding 25(OH)D2 and 25(OH)D3, excluding epi-25-hydroxyvitamin D3. The detailed information and procedure are described on the NHANES website <https://wwwn.cdc.gov/nchs/nhanes/vitamind/analyticalnote.aspx>.

LMM Ascertainment

Using the QDR-4500 Hologic Scanner (Bedford, MA), dual-energy x-ray absorptiometry (DEXA) was used to evaluate body composition (muscle mass and body fat). Except for false teeth and hearing aids, everything metal was removed before testing. Appendicular lean mass (ALM) was defined as the sum of the fat-free masses of all four extremities (arms and legs). For this study, Foundation for the National Institutes of Health criteria were used for ALM-defined LMM ($<19.75\text{kg}$ in males, $<15.02\text{ kg}$ in females) and ALM adjusted for body mass index (BMI) ($<0.789\text{ kg}$ for males, $<0.512\text{ kg}$ for females).^{21–23}

Covariates

The following covariates were included: demographic data (age, sex, race/ethnicity, family poverty income ratio (PIR), education level, and marital status), complication data (hypertension, and diabetes mellitus (DM)), history of smoking and drinking, body measurement data (body mass index (BMI), waist circumference), blood pressure data (systolic blood

pressure (SBP), diastolic blood pressure (DBP)), dietary data (mean energy intake, dietary Vitamin D intake), and laboratory test data (hemoglobin (Hb), fast glucose (FBG), glycosylated hemoglobin (HbA1C), high-density lipoprotein-cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG), blood urea nitrogen (BUN), serum uric acid (sUA), serum creatinine (Scr), and estimated glomerular filtration rate (eGFR)). The dietary intake of Vitamin D and mean energy were assessed during an in-person 24-h dietary recall using the automated multiple-pass method.²⁴ The following demographic data were collected by interview questionnaires: age, sex, race or ethnicity, education level, marital status, smoking and drinking status, and mean energy intake. Additionally, biospecimens were collected, processed, and stored in the mobile examination center until shipping to a laboratory for analysis. The following biomarkers were collected: data on Hb, FBG, HbA1C, HDL-C, TC, TG, BUN, sUA, Scr, and eGFR. The detailed information on the variables in this study can be found at www.cdc.gov/nchs/nhanes/.

Statistical Analysis

All analyses were performed using package R (version 4.2.0, <http://www.R-project.org>) and SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). The serum 25(OH)D concentration was divided into quartiles (Q1, 9.37–43.2 nmol/L; Q2, 43.3–57.9 nmol/L; Q3, 58.0–72.9 nmol/L; and Q4, 73.0–250.0 nmol/L), and the lowest quartile served as the reference group (Q1). All estimates were calculated accounting for NHANES sample weights. Continuous variables are expressed as means (standard deviations, SDs), and categorical variables are presented as numbers (%). To calculate differences between groups, we used weighted linear regression models (continuous variables) and weighted chi-square tests (categorical variables). Three models were constructed, as follows: Model 1 was adjusted for age and sex; model 2 was adjusted for model 1 variables plus race/ethnicity, education level, marital status, family PIR, the complication of hypertension, DM, smoking, and drink status; model 3 was adjusted for model 2 variables plus waist circumference, SBP, DBP, mean energy intake, dietary Vitamin D intake, Hb, FBG, HbA1C, HDL-C, TC, TG, BUN, sUA, Scr, and eGFR, as the final model. A restricted cubic spline (RCS) is also used to fit the nonlinear relationship between the independent variable (iron metabolism) and the dependent variable (blood pressure). A spline curve is essentially a piecewise polynomial function that is limited by some control points, called “nodes”. Nodes are placed in multiple positions within the data range. The type of polynomial and the number and position of nodes determine the type of spline curve. In addition, the RCS model requires a minimum of three knots. A *P*-value of 0.05 was regarded as statistically significant.

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of the research participants. The characteristics of the participants were subclassified based on serum 25(OH)D quartiles (Q1, 9.37–43.2 nmol/L; Q2, 43.3–57.9 nmol/L; Q3, 58.0–72.9 nmol/L;

Table 1 Characteristics of the Study Population Based on Serum 25(OH)D Quartiles

Serum 25(OH)D	Total (n=10,256)	Q1 (n=2572)	Q2 (n=2570)	Q3 (n=2553)	Q4 (n=2561)	P-value
Age, years	33.903 ± 0.308	33.738 ± 0.362	32.337 ± 0.521	32.374 ± 0.385	36.085 ± 0.481	< 0.001
Sex, %						< 0.001
Male	5085 (49.6%)	1192 (11.6%)	1341 (13.1%)	1325 (12.9%)	1227 (12.0%)	< 0.001
Female	5171 (50.4%)	1380 (13.5%)	1229 (12.0%)	1228 (12.0%)	1334 (13.0%)	
Race/ethnicity, %						
Mexican American	1618 (15.8%)	400 (3.9%)	537 (5.2%)	461 (4.5%)	220 (2.1%)	
Other Hispanic	991 (9.7%)	179 (1.7%)	324 (3.2%)	294 (2.9%)	194 (1.9%)	
Non-Hispanic Black	2459 (24.0%)	1190 (11.6%)	603 (5.9%)	414 (4.0%)	252 (2.5%)	
Non-Hispanic White	3460 (33.7%)	326 (3.2%)	633 (6.2%)	979 (9.5%)	1522 (14.8%)	< 0.001
Other race	1728 (16.8%)	477 (4.7%)	473 (4.6%)	405 (3.9%)	373 (3.6%)	

(Continued)

Table I (Continued).

Serum 25(OH)D	Total (n=10,256)	Q1 (n=2572)	Q2 (n=2570)	Q3 (n=2553)	Q4 (n=2561)	P-value
Family PIR	2.761 ± 0.079	2.240 ± 0.073	2.486 ± 0.079	2.767 ± 0.090	3.195 ± 0.081	< 0.001
Education level, %						
Less than high school	4387 (42.8%)	1014 (9.9%)	1229 (12.0%)	1220 (11.9%)	924 (9.0%)	
High school	1667 (16.3%)	493 (4.8%)	422 (4.1%)	367 (3.6%)	385 (3.8%)	
More than high school	4202 (41.0%)	1065 (10.4%)	919 (9.0%)	966 (9.4%)	1252 (12.2%)	< 0.001
Marital status, %						
Having a partner	4956 (48.3%)	1079 (10.5%)	1179 (11.5%)	1340 (52.5%)	1358 (13.2%)	
No partner	1004 (9.8%)	267 (2.6%)	234 (2.3%)	218 (2.1%)	285 (2.8%)	
Unmarried	4296 (41.9%)	1226 (12.0%)	1157 (11.3%)	995 (9.7%)	918 (9.0%)	< 0.001
Hypertension, %						
No	8290 (80.8%)	1997 (19.5%)	2131 (82.9%)	2137 (20.8%)	2025 (19.7%)	
Yes	1966 (19.2%)	575 (5.6%)	439 (4.3%)	416 (4.1%)	536 (5.2%)	< 0.001
DM, %						
No	9512 (92.7%)	2337 (22.8%)	2394 (23.3%)	2396 (23.4%)	2385 (23.3%)	
Yes	744 (7.3%)	234 (2.3%)	176 (1.7%)	157 (1.5%)	176 (1.7%)	< 0.001
Smoker, %						
No	6643 (64.8%)	1685 (16.4%)	1733 (16.9%)	1635 (15.9%)	1590 (15.5%)	
Former	1267 (12.4%)	250 (2.4%)	290 (2.8%)	340 (3.3%)	387 (3.8%)	
Now	2346 (22.9%)	637 (6.2%)	547 (5.3%)	578 (5.6%)	584 (5.7%)	0.004
Alcohol user, %						
Never	2129 (20.8%)	599 (5.8%)	582 (5.7%)	530 (5.2%)	418 (4.1%)	
Former	905 (8.8%)	209 (2.0%)	206 (2.0%)	227 (2.2%)	263 (2.6%)	
Mild	2643 (25.8%)	648 (6.3%)	639 (6.2%)	642 (6.3%)	714 (27.9%)	
Moderate	1722 (16.8%)	417 (4.1%)	403 (3.9%)	447 (4.4%)	455 (4.4%)	
Heavy	2857 (27.9%)	699 (6.8%)	740 (7.2%)	707 (6.9%)	711 (6.9%)	
BMI, kg/m ²	27.542 ± 0.152	29.788 ± 0.240	28.367 ± 0.254	27.166 ± 0.182	26.158 ± 0.186	< 0.001
Waist circumference, cm	93.896 ± 0.359	98.657 ± 0.605	95.859 ± 0.618	92.918 ± 0.479	90.965 ± 0.523	< 0.001
SBP, mmHg	115.534 ± 0.316	118.824 ± 0.635	116.119 ± 0.512	114.567 ± 0.412	114.202 ± 0.409	< 0.001
DBP, mmHg	68.706 ± 0.342	69.688 ± 0.550	68.509 ± 0.511	68.284 ± 0.513	68.636 ± 0.410	0.235
FBG, mg/mL	99.67 ± 0.36	103.16 ± 0.88	101.85 ± 0.82	98.16 ± 0.57	97.64 ± 0.39	< 0.001
HbA1c, %	5.45 ± 0.01	5.60 ± 0.03	5.49 ± 0.02	5.39 ± 0.02	5.39 ± 0.02	< 0.001
Mean energy intake, kcal	2157.25 ± 10.00	2131.55 ± 25.06	2137.87 ± 25.95	2161.51 ± 16.83	2179.28 ± 18.90	0.539
Vitamin D intake, mcg	4.78 ± 0.06	3.68 ± 0.08	4.56 ± 0.10	5.21 ± 0.16	5.17 ± 0.08	< 0.001
Hb, g/dL	14.14 ± 0.04	13.88 ± 0.07	14.21 ± 0.06	14.20 ± 0.05	14.18 ± 0.05	< 0.001
BUN, mg/dL	11.69 ± 0.07	10.43 ± 0.12	11.56 ± 0.11	11.72 ± 0.12	12.40 ± 0.12	< 0.001
sUA, mg/dL	5.24 ± 0.02	5.32 ± 0.04	5.33 ± 0.04	5.24 ± 0.03	5.14 ± 0.04	0.006
Scr, mg/dL	0.83 ± 0.00	0.81 ± 0.01	0.82 ± 0.01	0.82 ± 0.01	0.86 ± 0.01	< 0.001
eGFR, mL/min/1.73m ²	109.29 ± 0.41	114.64 ± 0.57	113.13 ± 0.65	111.15 ± 0.63	102.80 ± 0.70	< 0.001
HDL-C, mg/dL	52.23 ± 0.30	50.50 ± 0.40	50.20 ± 0.40	51.32 ± 0.38	55.05 ± 0.48	< 0.001
TC, mg/dL	185.03 ± 0.77	184.02 ± 1.23	183.14 ± 1.15	183.27 ± 1.11	188.03 ± 0.99	< 0.001
TG, mg/dL	117.05 ± 1.71	123.85 ± 3.11	119.16 ± 2.40	117.02 ± 2.68	112.28 ± 2.66	0.021
Low muscle mass, %						0.027
No	9715 (94.7%)	2477 (24.2%)	2420 (23.6%)	2373 (23.1%)	2445 (23.8%)	
Yes	541 (5.3%)	95 (0.9%)	150 (5.8%)	180 (1.8%)	116 (1.1%)	

Notes: Q1, 9.37–50.5 nmol/L; Q2, 50.6–67.2 nmol/L; Q3, 67.3–85.8 nmol/L; Q4, 85.9–318.0 nmol/L.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fast glucose; HbA1c, glycosylated hemoglobin; Hb, hemoglobin; BUN, blood uric acid; sUA, serum uric acid; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein-cholesterol; TC, total cholesterol; TG, triglyceride.

and Q4, 73.0–250.0 nmol/L). The prevalence of LMM in this study population was 5.3%. There is no significant difference in DBP or mean energy intake among the Q1, Q2, Q3, and Q4 groups ($P > 0.05$). Other indicators were statistically significant among the four groups ($P < 0.05$). Compared with the Q1, Q3, and Q4 groups, Individuals in the Q2 group had the highest levels of Hb and sUA and the lowest levels of HDL-C and TC. Participants in the Q3 group had a lower proportion of hypertension and DM. In addition, the Q4 group had the highest levels of family PIR, BUN, Scr, HDL-C, and TC and the lowest levels of eGFR and TG.

Association Between Serum 25(OH)D and LMM

As shown by the restricted cubic spline (RCS) plot, serum 25(OH)D is associated with a U-shaped association with the prevalence of LMM (P for nonlinearity < 0.05 , Figure 1). When the serum 25(OH)D concentration reached 38.5 nmol/l, the risk of LMM was the lowest. Then, as serum 25(OH)D concentration increased, so does the risk of LMM. Table 2 shows the findings of multivariate logistic regression analysis for the relationship between serum 25(OH)D concentration and LMM risk. After adjusting for interfering factors, the odds ratios with 95% confidence intervals for LMM across rising quartiles were 1.264 (0.877, 1.823), 1.978 (1.368, 2.861), and 2.186 (1.142, 2.315) for serum 25(OH)D, compared to the reference group (Q1).

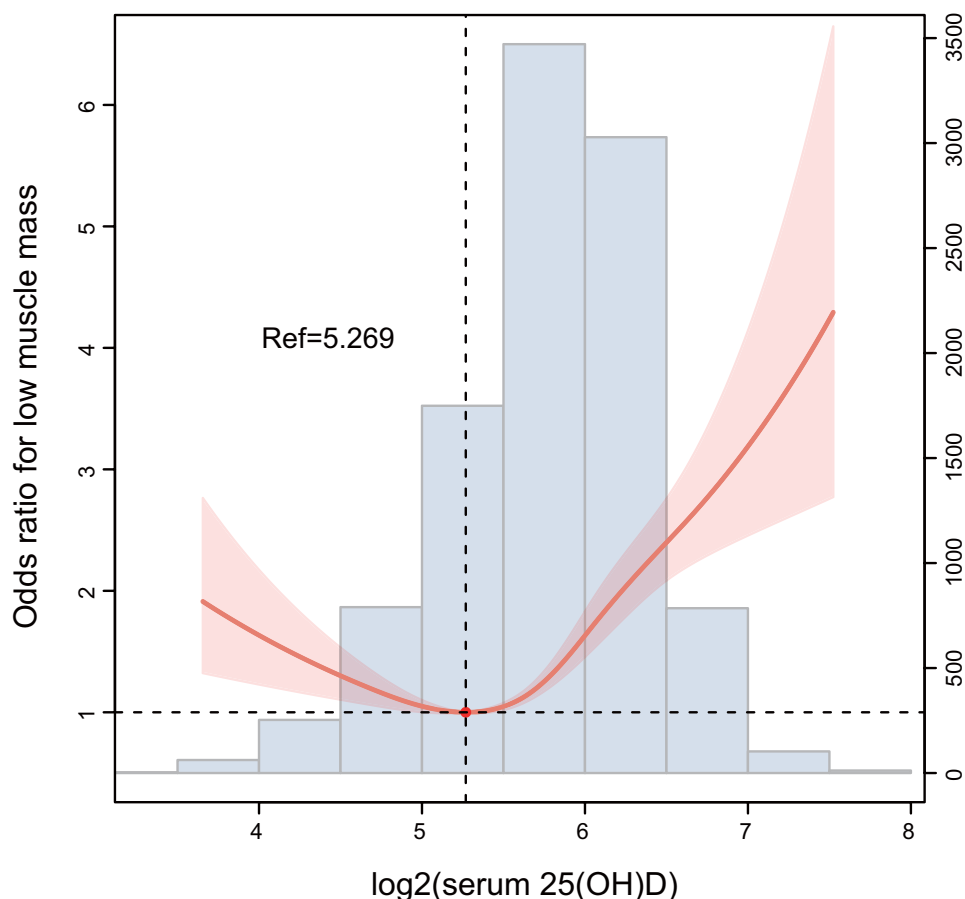


Figure 1 The RCS plot of the association between serum 25(OH)D and the risk of low muscle mass. The levels of 25(OH)D were log₂ transformed. Analyses were adjusted for age, sex, race/ethnicity, education level, marital status, family poverty income ratio, the complication of hypertension, and DM, body mass index, waist circumference, mean energy intake, dietary vitamin D intake, hemoglobin, fast glucose, glycosylated hemoglobin, high-density lipoprotein-cholesterol, total cholesterol, triglyceride, blood urea nitrogen, serum uric acid, serum creatinine, and estimated glomerular filtration rate. Solid and dashed lines represent the log-transformed odds ratios and the corresponding 95% confidence intervals.

Abbreviations: RCS, restricted cubic spline; Serum 25(OH)D, serum 25-hydroxyvitamin D.

Table 2 Adjusted Odds Ratios for Associations Between Serum 25(OH)D and the Risk of Low Muscle Mass

Serum 25(OH)D	Model 1	Model 2	Model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Q1	Ref.	Ref.	Ref.
Q2	1.032 (0.768, 1.389)	0.902 (0.644, 1.263)	1.264 (0.877, 1.823)
Q3	1.125 (0.852, 1.487)	1.028 (0.762, 1.386)	1.978 (1.368, 2.861)***
Q4	1.357 (1.033, 1.783)	1.258 (0.933, 1.697)	2.186 (1.142, 2.315)***
P for trend	0.517	0.923	<0.001

Notes: Q1: 9.37–43.2 nmol/L; Q2: 43.3–57.9 nmol/L; Q3: 58.0–72.9 nmol/L; and Q4: 73.0–250.0 nmol/L; *** $P < 0.001$; Model 1: age and sex. Model 2: model 1 variables plus race/ethnicity, education level, marital status, family poverty income ratio, the complication of hypertension, and diabetes mellitus, smoke status, and drink status. Model 3 was adjusted for model 2 variables plus body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, mean energy intake, dietary Vitamin D intake, hemoglobin, fast glucose, glycosylated hemoglobin, high-density lipoprotein-cholesterol, total cholesterol, triglyceride, blood urea nitrogen, serum uric acid, serum creatinine, and estimated glomerular filtration rate.

Abbreviations: Serum 25(OH)D, serum 25-hydroxyvitamin D; OR, odd ratio; CI, confidence interval.

Subgroup Analyses

Subgroup analyses, stratified by age, sex, hypertension, and DM were performed to estimate the association between serum 25(OH)D and LMM risk. The result of stratified subgroup analysis demonstrated the U-shaped relationship between serum 25(OH)D and risk of LMM existed in participants who were 40 years of age or older, male, with or without hypertension, and with or without DM. However, there was a linear and positive relationship between serum 25(OH)D concentration LMM risk among individuals who were < 40 years, and female (Table 3, and Figure 2). In addition, there were significant interactions for associations between age, sex, hypertension, as well as DM and serum 25(OH)D concentration (P for interaction <0.05).

Discussion

Sarcopenia is a geriatric syndrome characterized by gradual and systemic muscular weakness, a decrease in muscle mass, and a drop in function. Loss of muscular strength and mobility issues are the primary symptoms, which diminish patients' quality of life and increase their risk of falls, fractures, metabolic illnesses, and other morbidity as well as

Table 3 Subgroups Analysis for the Associations of Serum 25(OH)D with the Risk of Low Muscle Mass

Serum 25(OH)D	Q1 OR (95% CI)	Q2 OR (95% CI)	Q3 OR (95% CI)	Q4 OR (95% CI)	P for Trend	P for Interaction
Age						0.002
< 40	1.00	2.219 (1.275, 3.861)**	3.174 (1.809, 5.569)***	3.779 (1.993, 7.166)***	<0.001	
≥ 40	1.00	0.479 (0.241, 0.954)*	0.684 (0.343, 1.365)	0.718 (0.354, 1.453)	0.397	
Sex						0.090
Male	1.00	1.286 (0.817, 2.025)	2.142 (1.352, 3.392)**	2.437 (1.461, 4.063)***	<0.001	
Female	1.00	1.002 (0.492, 2.044)	1.095 (0.509, 2.356)	0.765 (0.296, 1.978)	0.743	
Hypertension						0.082
No	1.00	1.267 (0.792, 2.027)	1.792 (1.112, 2.887)*	2.159 (1.256, 3.713)**	0.002	
Yes	1.00	0.861 (0.404, 1.834)	0.889 (0.391, 2.024)	0.814 (0.352, 1.882)	0.657	
DM						0.010
No	1.00	1.410 (0.937, 2.122)	2.165 (1.432, 3.273)***	2.453 (1.537, 3.915)***	<0.001	
Yes	1.00	0.999 (0.315, 3.167)	1.080 (0.293, 3.988)	0.989 (0.288, 3.401)	0.985	

Notes: Q1: 9.37–43.2 nmol/L; Q2: 43.3–57.9 nmol/L; Q3: 58.0–72.9 nmol/L; and Q4: 73.0–250.0 nmol/L; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; Analysis was adjusted for age, sex, race/ethnicity, education level, marital status, family poverty income ratio, the complication of hypertension, and DM, smoke status, and drink status, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, mean energy intake, dietary Vitamin D intake, hemoglobin, fast glucose, glycosylated hemoglobin, high-density lipoprotein-cholesterol, total cholesterol, triglyceride, blood urea nitrogen, serum uric acid, serum creatinine, and estimated glomerular filtration rate.

Abbreviations: Serum 25(OH)D, serum 25-hydroxyvitamin D; DM, diabetes mellitus; OR, odd ratio; CI, confidence interval.

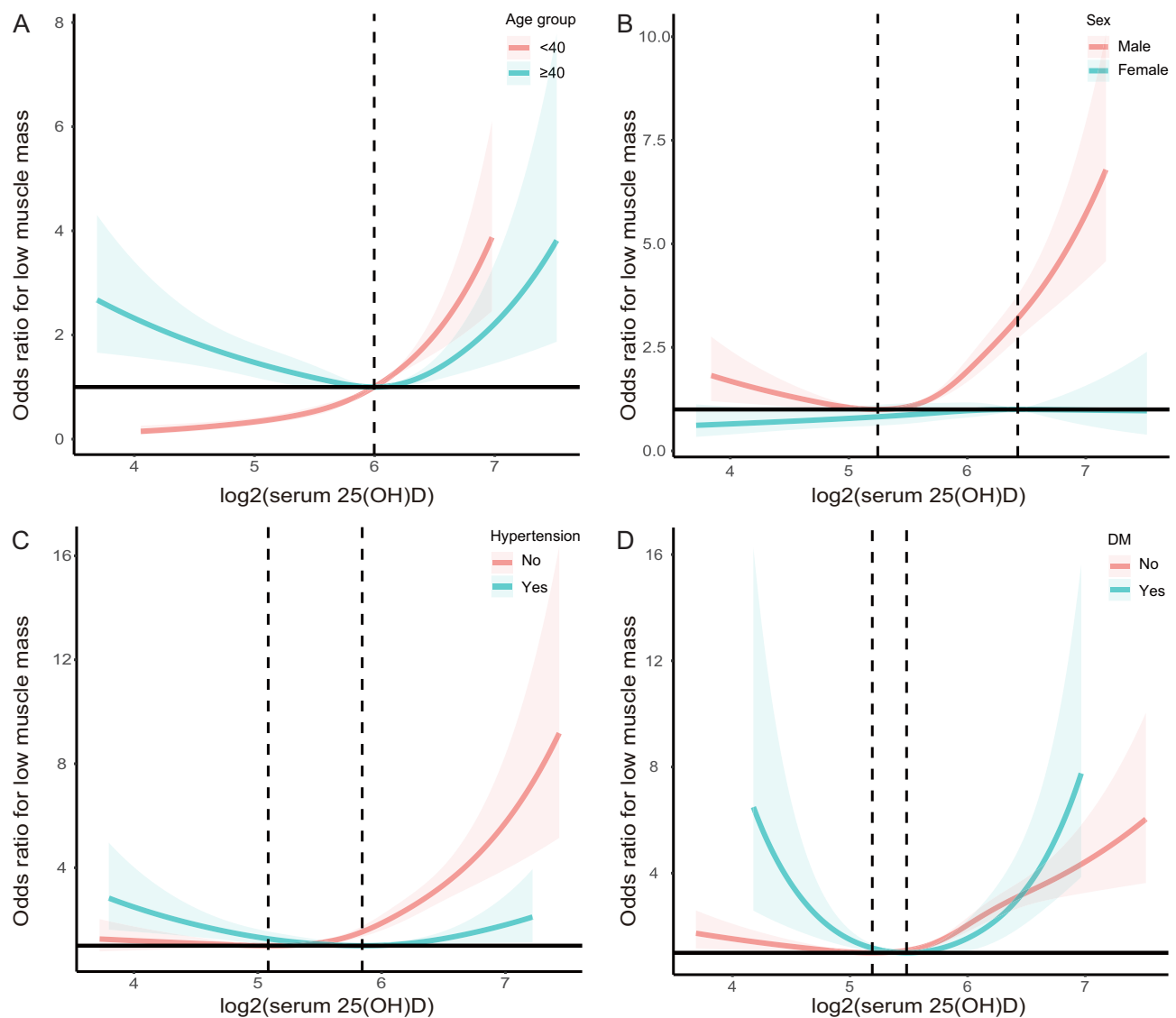


Figure 2 Subgroup analysis for the associations of serum 25(OH)D and the risk of low muscle mass based on (A) age, (B) sex, (C) hypertension, and (D) DM. The levels of 25(OH)D were log₂ transformed. Analyses were adjusted for age, sex, race/ethnicity, education level, marital status, family poverty income ratio, the complication of hypertension, and DM, body mass index, waist circumference, mean energy intake, dietary vitamin D intake, hemoglobin, fast glucose, glycosylated hemoglobin, high-density lipoprotein-cholesterol, total cholesterol, triglyceride, blood urea nitrogen, serum uric acid, serum creatinine, and estimated glomerular filtration rate. Solid and dashed lines represent the log-transformed odds ratios and the corresponding 95% confidence intervals.

Abbreviation: DM, diabetes mellitus.

mortality.^{25,26} This research investigated the relationship between serum 25(OH)D and LMM risk. The study demonstrated a U-shaped relationship between serum 25(OH)D and the prevalence of LMM. Moreover, the risk of LMM was lowest when the serum 25(OH)D levels reached 38.5 nmol/L in the U. S. population.

The pathophysiological foundation of sarcopenia is an increase in pro-inflammatory cytokines in the blood, which is caused by pro-inflammatory immunogenic stimulation.^{27,28} Numerous studies have shown that inflammatory cytokines may activate many signaling pathways, resulting in an increase in protein catabolism and a reduction in anabolic metabolism. In addition, they may inhibit protein synthesis by lowering the levels of growth hormone and insulin-like growth factor-1, leading to skeletal muscle atrophy and ultimately sarcopenia.²⁹ Additionally, previous studies have shown that inflammatory factors are negatively correlated with muscle strength and mass.³⁰ Multiple in vitro investigations have shown that Vitamin D can inhibit the release of pro-inflammatory cytokines in adipose tissue, thereby reducing its chronic inflammatory response.^{31,32} Amer et al found that serum 25(OH)D levels less than 52.42 nmol/L were

negatively correlated with C-reactive protein (CRP) levels. However, serum vitamin D levels ≥ 52.42 nmol/L were positively correlated with CRP levels.³³ Zittermann et al found that interleukin-6, tumor necrosis factor, and high-sensitivity CRP levels decreased when vitamin D levels were significantly elevated in both the vitamin D and placebo groups.³⁴ Previous research has shown that the anticipated response to vitamin D treatment is related to lower baseline vitamin D concentrations. The anticipated biological dosage response of vitamin D supplementation to inflammatory cytokines would vary depending on vitamin D levels at baseline.³⁵ Aolin et al found that vitamin D supplementation inhibited the decline of muscle mass, muscle fiber and grip strength in gastritis muscle by reducing the expression of MuRF1, MAFbx and FOXO3a proteins.³⁶ In addition, a systematic analysis shows some intervention effects of vitamin D in elderly patients with sarcopenia, but whether vitamin D supplementation has beneficial effects in patients with sarcopenia, such as inhibiting muscle atrophy and increasing muscle strength, is still controversial, in part due to the complex mechanism of the effect of vitamin D on muscle tissue.³⁷ Studies have shown that Vitamin D supplementation could prevent and treat sarcopenia in older adults based on evidence from biological, experimental, and epidemiological studies.³⁸ A 2009 intervention study enrolled 70-year-old community-dwelling men and women with vitamin D serum levels less than 78 nmol/l who supplemented with calcium and vitamin D daily (compared with calcium supplementation alone). Comparing the oral supplementation group to the placebo group after 12 months, the oral supplementation group demonstrated an increase in muscle strength and physical performance along with a decrease in fall rates of 27% and 39%, respectively.³⁹ Moreover, in 2017, an observational cohort study also reported that vitamin D supplementation (20 μ g a day) for 6 months in post-menopausal women with a diagnosis of osteoporosis and/or vitamin D deficiency (<30 ng/mL) was significantly correlated to an increase of appendicular muscle strength (hand grip strength and knee extension strength) and physical performance (SPPB and 4-m gait speed) with a parallel reduction in the risk of falls.⁴⁰ As mentioned above, the risk of LMM was lowest when the serum 25(OH)D levels reached 38.5 nmol/L. When serum 25(OH)D levels increased (<50 – ≥ 50 nmol/L) or were persistently adequate (50 nmol/L) between baseline and follow-up visit, young and middle-aged Korean adults were less likely to develop incident low muscle mass than those with persistently low 25(OH)D levels.¹² Additionally, among Korean women, lowering serum 25-OH-D by 10 ng/mL increased the risk of sarcopenia by 1.46-fold.¹⁵ With this in mind, it seems plausible to show a U-shaped association between serum 25(OH)D concentration and LMM risk in the American population, given the findings presented above.

By using subgroup analysis, we found that serum 25(OH)D concentration and risk of LMM were U-curve correlated for those 40 or older, male, with hypertension, with or without DM. However, there was a linear and positive relationship between serum 25(OH)D concentration and LMM risk among individuals who were <40 years old and female. Sarcopenia and serum 25(OH)D deficiency among elderly people have been associated with epidemiological studies.⁴¹ The aging of organs and tissues, arteriosclerosis, changes in heart function, and the connective tissue surrounding blood vessels will affect the microcirculation as the age of patients increases. Serum 25(OH)D may decrease pro-inflammatory factor activity and ameliorate sarcopenia. In terms of gender, the incidence rate in women was 16% compared to 11% in men, which may be related to the fact that women live longer and have higher disability rates.⁴² Simultaneously, there are considerable gender disparities in immune response homeostasis and the risk of age-related illnesses. Decreased estrogen levels impact the skeletal musculoskeletal system, which is also one of the causes of the high prevalence of sarcopenia among women.⁴³

The levels of vitamin D are closely related to autoimmune diseases, including rheumatoid arthritis, spondylarthritis, systemic sclerosis, inflammatory bowel disease, and autoimmune diabetes, and play an important role in the pathophysiology and treatment of these conditions.^{44,45} There was an average increase in parathyroid hormone (PTH) concentration for any plasma 25(OH) vitamin D range among patients with autoimmune rheumatic diseases (ARD), which suggests that vitamin D metabolism is impaired.⁴⁶ In addition, the results of a prospective, population-based study revealed that older men and women with lower 25(OH)D concentrations and higher PTH levels are more likely to suffer from sarcopenia.⁴⁷ A history of ARD is not associated with a lower serum 25(OH)vitamin D concentration or influences its increments after vitamin D supplementation. Among rheumatic patients, hypovitaminosis D is very common, especially among women and the elderly. Moreover, supplementation with vitamin D at 750–1000 IU daily is insufficient to normalize 25(OH)vitamin D values, so higher dose regimens should be considered.⁴⁸

Sarcopenia is a global age-related disease affected by chronic inflammation, physical activity, nutritional status, hormones, and other factors. The specific pathogenesis of sarcopenia remains unclear. Therefore, more basic and clinical studies are needed to further explore the pathogenesis and intervention of sarcopenia in the future. Through the study, we found that appropriate vitamin D supplementation can reduce the incidence of sarcopenia. The strength of the current research was to include a representative sampling design and a rigorous and standard protocol for data collection, which made our results of a U-shaped relationship between serum 25(OH)D concentration and risk of LMM more reliable. In addition, leveraging the extensive set of covariates and large sample size in the NHANES, we could have performed multiple subgroup analyses in accordance with participants' characteristics. Of note, our study had some limitations. First, all of the patients we utilized for analysis came from the NHANES public database, which spanned the years 2011 to 2014. Participants from other nations should be further employed to corroborate our findings, particularly the inflection point (38.5 nmol/L). Second, as a retrospective study, bias cannot be avoided in some relevant results. Third, when investigating the relationship between 25(OH)D and LMM in this population, the results could be biased. In young people, sarcopenia may be related to some acute disease, while in older adults, it is due to aging. Finally, the underlying mechanism of Serum 25(OH)D and the prevalence of LMM must also be studied.

Conclusion

In conclusion, there was a U-shaped relationship between serum 25(OH)D and the risk of LMM. In our study, an inflection point for serum 25(OH)D was observed, and the prevalence of LMM was lowest when the serum 25(OH)D level was 38.5 nmol/L. Appropriate vitamin D supplementation can reduce the prevalence of LMM.

Data Sharing Statement

The NHANES data are publicly available on the internet for data users and researchers (<https://www.cdc.gov/nchs/nhanes/>).

Ethics Approval and Informed Consent

The NHANES 2011–2014 was approved by the NCHS Research Ethics Review Board (Continuation of Protocol #2011–2014), and each participant signed the written informed consent. In addition, the study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the First Affiliated Hospital of Anhui Medical University. Due to the retrospective and public nature of the study data, the review board waived the requirement for written informed consent.

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Disclosure

The authors report no conflicts of interest in this work.

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