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Association between serum vitamin D levels and cardiorespiratory fitness in the adult population of the USA

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Abstract

Aims: The small number of studies that have investigated the relationship between serum vitamin D levels and cardiorespiratory fitness (CRF) have reported conflicting results. We investigated the association between vitamin D levels and CRF in a representative sample of the US population using data from the National Health and Nutrition Survey (2001–2004).

Methods: We included participants between the ages of 20 and 49 years and excluded those with vitamin D levels at the 5% extremes of the distribution. We used survey-weighted linear regression without and with adjustment for age, sex, race, body mass index, hypertension, diabetes, smoking, C-reactive protein, hemoglobin, and glomerular filtration rate to examine the relationship between the maximal oxygen consumption (VO_2 max) (as a surrogate for CRF) and vitamin D levels.

Results: Of the 1995 participants, 45.2% were women, 49.1% were white, 13% had hypertension, and 4% had diabetes. The mean $\pm$ SD age was 33 ± 8.6 years, with a mean $\pm$ SD vitamin D level of 58 ± 5.3 nmol/L and a mean $\pm$ SD VO_2 max of 40 ± 9.7 ml/kg/min. Participants in the highest quartile of vitamin D levels had a significantly higher CRF than participants in the lowest quartile (difference 4.3, 95% confidence interval (CI) 3.0–5.5; $P < 0.001$). After adjustment for potential confounders, the difference between the highest and lowest vitamin D quartiles remained significant (difference 2.9, 95% CI 1.6–4.1; $P < 0.001$). In unadjusted and adjusted linear regression, each 10 nmol/L increase in vitamin D level was associated with a significant increase in VO_2 max ($\beta = 0.78$ ml/kg/min, 95% CI 0.55–1.01; $P < 0.001$; $\beta = 0.51$ ml/kg/min, 95% CI 0.23–0.79; $P = 0.001$, respectively).

Conclusions: We found an independent and robust association between serum vitamin D levels and CRF, but our results need to be validated with clinical trials examining the effect of vitamin D supplementation on CRF.

Keywords
Cardiorespiratory fitness, vitamin D, VO_2 max

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Introduction

Low serum vitamin D levels have been associated with a high risk of hypertension, poor outcomes in patients with heart failure, and increased all-cause and cardiovascular mortality.[1,2] Receptors for vitamin D are found in at least 30 different types of cell, including skeletal muscle cells.[3,4] Therefore vitamin D may have several effects in addition to its role in bone homeostasis.[4,5] The American Heart Association recommended in 2016 that cardiorespiratory fitness (CRF) should be measured in routine clinical practice for high-risk patients because there is unequivocal evidence that CRF significantly improves cardiovascular risk prediction.[6] CRF refers to the ability of the circulatory and respiratory systems to supply oxygen to skeletal muscles during sustained physical activity. It is best measured as the maximal oxygen consumption (VO_2 max) during exercise.[6] It is well established that a higher CRF is associated with better outcomes in

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all-cause and cardiovascular mortality.[6–8] Some studies have investigated the association between vitamin D and CRF, but the reported results are contradictory. These studies had several limitations. Some enrolled only adolescents and others were not representative of the general population in other ways.[9–13] The objective of our study was therefore to investigate the association between serum vitamin D levels and CRF in a representative sample of the US population using the National Health and Nutrition Examination Survey (NHANES) database.

Methods

We used data from the NHANES database, which is an ongoing, multistage probability sample, cross-sectional survey designed to assess the health and nutritional status of the civilian, noninstitutionalized population of the USA.[14] The data include demographic, medical, dental, and physiological measurements, in addition to laboratory tests (Table 1). Both vitamin D and CRF data were collected from NHANES participants between 2001 and 2004 and data from these years were used for this study. CRF data were also available for patients between the ages of 20 and 49 years. Participants were excluded from CRF testing based on certain medical conditions, such as an irregular heart rate, the use of beta blockers and antiarrhythmic medication, and weight >159 kilograms due to limitations of the equipment. We excluded participants with markedly high or low serum vitamin D levels (5% from both extremes) from the analysis to avoid bias by indication. The study participants self-reported age, sex, and race. Body mass index (BMI) was calculated by dividing the body weight in kilograms by the squared height in meters. Blood pressure was recorded up to four times and participants were classified as hypertensive if they had a diagnosis of hypertension, their mean systolic blood pressure was $\geq$140 mmHg and their mean diastolic blood pressure was $\geq$90 mmHg, or if they were currently receiving antihypertensive drugs. Diabetes mellitus was defined as a personal history of diabetes, the use of insulin or oral antidiabetic drugs, or hemoglobin A1C >7%.

Hemoglobin A1C was measured using an A1c 2.2 Plus or A1c G7 HPLC Glycohemoglobin Analyzer.

Table 1. Characteristics of the study population by vitamin D quartiles.

Variable	Q1 ($N=453$)	Q2 ($N=479$)	Q3 ($N=538$)	Q4 ($N=525$)	P[a]
Age (years)	32.6 ± 8.4	32.8 ± 8.7	33.6 ± 8.6	33.7 ± 8.7	0.07
Age (in categories)					0.017
Young (20–35 years)	424 (93.6)	437 (91.2)	482 (89.5)	461 (87.8)	
Middle-aged (35–49 years)	29 (6.4)	42 (8.8)	56 (10.4)	64 (12.2)	
Female sex	232 (51.2)	201 (42)	223 (41.4)	246 (46.9)	0.006
White	78 (17.2)	189 (39.7)	310 (57.6)	402 (76.6)	<0.001
Vitamin D level (nmol/L)	35 ± 5.4	50.9 ± 3.7	64.2 ± 4.1	83 ± 8	<0.001
VO_2 max (mL/kg/min)	37.7 ± 9.35	40.2 ± 9.5	40.9 ± 9.45	41.4 ± 10	<0.001
Body mass index (kg/m^2)	29.1 ± 6.7	27.6 ± 5.7	26.9 ± 5.2	25.9 ± 4.9	<0.001
Smoking					0.03
Current smoker	132 (29.3)	130 (27.1)	152 (28.2)	150 (28.6)	
Ever-smoker	50 (11.1)	70 (14.6)	95 (17.7)	97 (18.5)	
Non-smoker	269 (59.6)	279 (58.2)	291 (54.1)	278 (52.9)	
C-reactive protein (mg/dL)[b]	0.18 (0.41)	0.14 (0.28)	0.13 (0.25)	0.13 (0.33)	0.005
GFR (mL/min)	110.7 ± 17.3	108.9 ± 16.2	106.1 ± 15.8	101 ± 15.7	<0.001
Hypertension	47 (10.4)	49 (10.2)	43 (8)	24 (4.6)	0.002
Diabetes	12 (2.6)	14 (2.9)	9 (1.7)	4 (0.8)	0.05
Hemoglobin (g/dL)	14.1 ± 1.6	14.6 ± 1.5	14.8 ± 1.4	14.7 ± 1.4	<0.001
Total cholesterol (mg/dL)	188.9 ± 39.5	196.2 ± 40.8	192.5 ± 40.4	192.6 ± 38.4	0.04

Data are presented as mean ± SD or *n* (%) values.

GFR: glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration test; VO_2 max: estimated maximum volume of oxygen uptake.

[a]*P* for categorical variables was calculated using Pearson's χ^2 test; *P* for continuous variables was calculated using analysis of variance (ANOVA) and *P* for C-reactive protein was calculated with the Kruskal–Wallis rank test.

[b]Median (interquartile range).

Hemoglobin was measured using a single-beam photometer for hemoglobinometry. Serum C-reactive protein was quantified by latex-enhanced nephelometry using a Behring Nephelometer II Analyzer. Serum creatinine was measured using Jaffe kinetic alkaline picrate method and the recommended adjustments were made to the measurements. The glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI equation). Participants were categorized as smokers if they were currently smoking, ever-smokers if they had smoked >100 cigarettes in their lifetime but were not currently smoking, and non-smokers if they had never smoked or smoked ≤100 cigarettes in lifetime.

Vitamin D levels were measured using the Diasorin 25-hydroxyvitamin D assay. This procedure consists of two steps: (a) the extraction of 25-hydroxyvitamin D metabolites from serum with acetonitrile and (b) a radioimmunoassay. CRF, represented as VO_2 max, was measured using submaximal exercise test protocols. The goal was to reach 75% of the age-predicted maximum heart rate. Each protocol included a warm-up, exercise, and cool down stages. The final outcome was reported using the estimated VO_2 max.

Analyses were performed using Stata/IC version 14.0 (Stata Corp LP, College Station, TX, USA) using survey-specific commands. We used Student's *t*-test or the χ^2 statistic to examine the differences between the groups and the Pearson correlation coefficient to examine the relationship between continuous variables. Selected variables were log-transformed to meet the assumptions of residual normality. We performed analyses with vitamin D as the continuous variable and in quartiles to reduce the potential effect of the vitamin D distribution on the results. The mean change in VO_2 max was reported as β coefficients with 95% confidence intervals (CIs) for each nmol/L change in vitamin D concentration (when vitamin D was used as a continuous variable) or for the difference from the lowest vitamin D quartile. Linear regression models were adjusted for age, sex, race, BMI, hypertension, diabetes mellitus, smoking, C-reactive protein, total cholesterol, hemoglobin, and renal function as estimated by the GFR. $P < 0.05$ was considered statistically significant.

Results

Of the 1995 participants, 902 (45.2%) were women and 979 (49.1%) were white. The mean ± SD age was 33.2 ± 8.7 years, the mean serum vitamin D level was 59.3 ± 18.3 nmol/L, the mean ± SD BMI was 27.2 ± 5.7 kg/m^2, the mean ± SD total cholesterol level was 192.6 ± 39.8 mg/dL, and the mean ± SD VO_2 max was 40.1 ± 9.7 mL/kg/min. The VO_2 max was significantly higher in men than in women (43.6 vs. 35.9; $P < 0.001$), in younger than in middle-aged participants (40.4 vs. 38.1; $P = 0.002$), in white than in non-white participants (40.8 vs. 39.5; $P = 0.003$), in participants with normal blood pressure than in those with hypertension (40.4 vs. 37.6; $P < 0.001$), and in current smokers than in non-smokers (41.6 vs. 39.4; $P < 0.001$). The difference between participants without and with diabetes was not statistically significant (37.4 vs. 40.2; $P = 0.07$). There was an inverse correlation between VO_2 max and age ($r = -0.12$; $P < 0.001$), serum cholesterol ($r = -0.10$; $P < 0.001$), serum C-reactive protein ($r = -0.10$; $P < 0.001$), and BMI ($r = -0.20$; $P < 0.001$). VO_2 max had a positive and significant correlation with vitamin D levels ($r = 0.10$; $P < 0.001$) and hemoglobin ($r = 0.31$; $P < 0.001$). The correlation between VO_2 max and the estimated GFR was not statistically significant ($r = -0.01$; $P = 0.89$). Participants in the highest quartile for vitamin D levels had a significantly higher VO_2 max than participants in the lowest quartile (41.4 vs. 37.7; $P < 0.001$). There was a significant positive correlation between vitamin D and VO_2 max across all participants ($r = 0.13$; $P < 0.001$).

In the unadjusted linear regression analysis, each 10 nmol/L increase in vitamin D level was associated with a statistically significant 0.78 mL/kg/min increase in VO_2 max ($\beta = 0.78$; 95% CI 0.55–1.01; $P < 0.001$). This association remained statistically significant after adjustment for covariates ($\beta = 0.51$; 95% CI 0.23–0.79; $P = 0.001$). The relationship between vitamin D and VO_2 max remained significant when vitamin D was included in the regression models as quartiles (Figure 1). Participants in the highest quartiles had a significantly higher VO_2 max than participants in the lowest quartile (difference between the highest and lowest quartiles 4.3 mL/kg/min; 95% CI 3.0–5.5; $P < 0.001$) and this difference remained significant after adjusting for potential confounding variables (2.9 mL/kg/min; 95% CI 1.6–4.2; $P < 0.001$).

Discussion

We found a significant positive association between vitamin D levels and VO_2 max, a measure of CRF, in a young and middle-aged population reflective of the general US population. This association was independent of the potential confounders age, sex, race, BMI, hypertension, diabetes, smoking, CRP, total cholesterol, hemoglobin, and GFR. Our results were robust to assumptions regarding the vitamin D distribution and were similar when vitamin D was included in regression models in quartiles.

Several lines of evidence support the biological plausibility of a potential role of vitamin D in CRF. About 3% of all genes are directly or indirectly affected

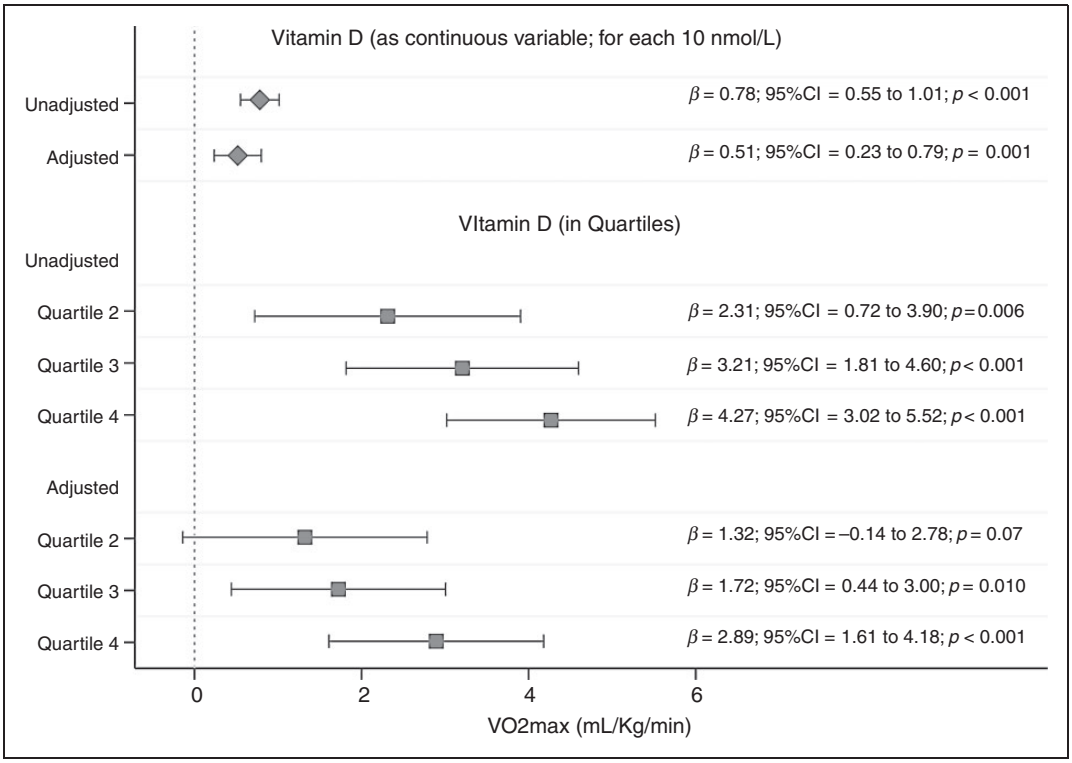

Figure 1. Results of adjusted and unadjusted survey weight-adjusted linear regression analysis showing relationship between vitamin D and cardiorespiratory fitness as measured by maximal oxygen consumption (VO_2 max). The first quartile is a reference and hence is not shown.

by vitamin D levels and vitamin D receptors are expressed in a large variety of cells, including myocytes.[5,15] Vitamin D may affect myocytes by increasing muscle protein synthesis and calcium and phosphorus transport in energy production.[16,17] In addition, vitamin D may increase the relative number of one type of fast-twitch muscle fibers (IIa) and decrease another type of fast-twitch muscle fibers (IIb), suggesting that vitamin D may improve aerobic fitness.[18] In addition to its effect on muscles, animal studies suggest that vitamin D may have a role in heart structure and function.[5,15,19] Mitochondria from chick cardiomyocytes produced less energy when vitamin D levels were low.[16] In another study, vitamin D deficiency in rodents was associated with decreased myocardial contractility and cardiac output and increased heart rate, changes commonly seen in failing hearts.[20] Vitamin D deficiency has been reported to be associated with decreased myofibrillar area and the increased deposition of myocardial collagen in the extracellular space.[21]

CRF refers to the ability of mitochondria in the body to utilize atmospheric oxygen and reflects the efficiency of the heart, lung, and muscle cells to extract oxygen. CRF involves multiple organs and is considered to be a reflection of total body health. VO_2 max is considered to be a good measure of CRF because it shows the body's ability to utilize oxygen at the tissue level. Multiple studies have shown that low CRF is a strong and independent risk factor for stroke, lung cancer, diabetes, cardiovascular, and all-cause mortality.[22–25] A meta-analysis of 33 studies confirmed that a higher CRF is associated with a lower mortality rate and that the largest mortality benefit was in the least fit group, followed by the second least fit group.[24]

CRF may decrease the mortality rate through several mechanisms, including a lower risk of thrombotic events, better insulin sensitivity, improved lipid and lipoprotein profiles, and lower levels of inflammation.[23,26,27] Several cross-sectional and cohort studies have shown the beneficial effects of vitamin D on the cardiovascular and skeletal systems and CRF.[28–30] The Framingham offspring study showed a lower risk of a first cardiovascular event in participants with higher levels (>38 nmol/l) of vitamin D relative to participants who were deficient in vitamin D (<25 nmol/l).[30] Some studies have shown that low temperatures (a surrogate for sun exposure) have adverse effects on cardiovascular risk factors.[31–33] Sartini et al.[33] showed that a lower temperature was associated with lower vitamin D levels, which might contribute to the excess of cardiovascular events during the winter months. Other studies found that the prevalence of self-reported coronary

artery disease and heart failure was lower in participants with higher vitamin D levels than in those with vitamin D deficiency.[34] Several small studies have examined an association between vitamin D and CRF. In a small group of young healthy women, Mowry et al.[10] found that higher vitamin D levels were associated with higher VO_2 max. Two additional studies found a dose–response relationship between vitamin D and CRF, where increasing vitamin D levels were associated with a corresponding increase in CRF.[12,13] By contrast, another study that enrolled 145 participants did not find an association between 6-month vitamin D supplementation and CRF.[35]

Our findings have important clinical, research, and public health implications. Because of the association between vitamin D and CRF, identifying suboptimum levels of vitamin D should prompt an investigation of CRF. An important research question is identifying the optimum levels of vitamin D needed for cardiovascular health. Further research needs to be conducted into the biological pathways responsible for this observed association. Randomized clinical trials to examine the effect of vitamin D supplementation on CRF over a longer period of time are warranted. The public health benefits beyond bone health of the supplementation of food products with vitamin D need to be examined.

A major strength of our study was that the study sample was representative of the US population. We included participants with chronic diseases, such as diabetes, which makes our results generalizable to a larger target population. A major limitation of our study is its cross-sectional nature, means that we are unable to ascribe causality to the observed relationship. The target heart rate during CRF testing was 75% of the predicted heart rate and extrapolation of this relationship beyond 75% requires assumptions. The results were not adjusted for vitamin D intake or physical activity, both of which may have an effect on the observed association. The age of study population was limited to 49 years and hence these results may not be generalizable to older populations.

We found a strong independent association between vitamin D levels and CRF, which was robust to potential confounding variables. Future studies are needed to explore the underlying biological mechanisms of the observed association. Clinical trials of vitamin D supplementation are required to validate the relationship.

Author contribution

Amr Marawan and Rehan Qayyum contributed to the conception, design of the work, and the acquisition and analysis of data. Nargiza Kurbanova contributed to the design of work and the interpretation of the data. Amr Marawan drafted the paper. Rehan Qayyum and Nargiza Kurbanova critically revised the paper. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

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