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Vitamin D and all-cause mortality among adults in USA: findings from the National Health and Nutrition Examination Survey Linked Mortality Study

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Background Whether concentrations of vitamin D are related to mortality remains unresolved. Our objective was to examine the relationship between serum concentrations of 25-hydroxyvitamin D and all-cause mortality in a national sample of US adults.

Methods We used data from the National Health and Nutrition Examination Survey Mortality Study from 2001 to 2004 with mortality compiled through 2006. Mortality status was established through a match to the National Death Index.

Results Of the 7531 participants, 347 died. Median follow-up was 3.8 years. The mean unadjusted concentrations of vitamin D were 54.1 nmol/l (21.7 ng/ml) among participants who died and 60.7 nmol/l (24.3 ng/ml) among participants who survived ($P = 0.002$). After adjustment for socio-demographic factors, the hazard ratios (HR) for all-cause mortality were 1.65 [95% confidence interval (CI): 95% CI: 1.13–2.40] for participants with a concentration <50 nmol/l (<20 ng/ml) and 1.02 (95% CI: 0.74–1.41) for participants with a concentration of 50 to <75 nmol/l (20 to <30 ng/ml) compared with participants who had a concentration of ⩾75 nmol/l (⩾30 ng/ml). After more extensive adjustment, the HRs were 1.28 (95% CI: 0.86–1.90) and 0.91 (95% CI: 0.63–1.33), respectively. The fully adjusted HR per 10 nmol/l of vitamin D was 0.93 (95% CI: 0.86–1.01). The HRs did not vary by gender ($P = 0.80$) or among the three major racial or ethnic groups ($P = 0.46$).

Conclusions Concentrations of vitamin D were weakly and inversely related to all-cause mortality in this sample of US adults.

Keywords Cohort studies, health surveys, mortality, vitamin D

Introduction

Historically, vitamin D is recognized for its critical role in maintaining calcium homoeostasis and bone health. Over time, the extraskeletal effects of vitamin D also emerged.[1,2] Vitamin D is now thought to affect cell proliferation and differentiation,[3–6] the immune system[7] and renin/angiotensin system.[8,9] Along with this new appreciation of the physiological effects of

vitamin D, evidence has also been accumulating suggesting that vitamin D affects the risk for morbidity and mortality from a growing list of chronic conditions including cardiovascular disease, cancer and diabetes.[10]

Major contributors to vitamin D status include exposure to sunshine, diet and the use of supplements.[11] Because of societal changes, many people do not receive enough sunshine to produce adequate amounts of vitamin D to ensure optimal health. Thus, the prevalence of low concentration of vitamin D in many populations including USA is high.[12–14] Furthermore, there is evidence that low vitamin D status is worsening in USA.[14]

Because only a limited number of studies have examined the risks for all-cause mortality associated with low concentrations of vitamin D,[15–26] our objective was to examine the relationship between circulating concentrations of 25-hydroxyvitamin D and all-cause mortality in a representative sample of adults in USA.

Methods

We used data from the mortality follow-up of adults aged ⩾20 years who participated in the National Health and Nutrition Examination Survey (NHANES) from 2001 to 2004. During the baseline surveys, a national sample was recruited using a multistage, stratified sampling design. The survey was designed to produce results representative of the civilian, non-institutionalized US population. The participants were interviewed at home and were invited to attend a mobile examination centre, where they were asked to complete additional questionnaires, to undergo various examinations, and to provide a blood sample. The study received human subjects' approval, and participants were asked to sign an informed consent form. Details about the survey may be found elsewhere.[27]

Mortality for participants of the NHANES 2001–04 was ascertained through 31 December 2006 by linking participants' information to death certificate data contained in the National Death Index.[28] Participants who were not identified as having died were considered to be alive. A small number of participants ($N = 18$) were considered ineligible for the study because of insufficient data to conduct the matching.

Serum concentrations of 25-hydroxyvitamin D were measured using the Diasorin 25-OH-Vitamin D assay, a radioimmunoassay. The coefficient of variation ranged from 4.4% to 13.2%.

Covariates included age, gender, race or ethnicity (white, African American, Mexican American, other Hispanic, mixed race), educational status (<high school, high school graduate and >high school), smoking status, alcohol consumption, leisure-time physical activity, dietary supplement use during the past month (yes/no), systolic blood pressure, concentrations of high-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol, concentrations of haemoglobin A1c (HbA1c), concentrations of C-reactive protein, concentrations of serum calcium, urinary albumin–creatinine ratio, waist circumference, 6-month time period when an examination was performed (1 May through 31 October and 1 November through 30 April) and physician-diagnosed cardiovascular disease, cancer and diagnosed diabetes (yes, no). Current smokers were defined as participants who had smoked ⩾100 cigarettes during their lifetime and were still smoking. Former smokers were defined as participants who had smoked ⩾100 cigarettes during their lifetime but had stopped. Participants who had smoked <100 cigarettes during their lifetime were classified as never having smoked. The intake of alcohol (gram/day) was obtained from a single 24-h dietary recall. To estimate leisure-time physical activity, we summed the product of monthly time spent in each activity multiplied by the metabolic equivalent (MET) value for that activity yielding a MET-hours index. One MET is the energy expenditure of ∼3.5 ml oxygen/kg body weight/min or 1 kcal/kg body weight/h. The use of vitamins, minerals and supplements was derived from the question 'Have you used or taken any vitamins, minerals or other dietary supplements in the past month?' Up to four blood pressure measurements were attempted from each participant. We used the average of the last two measurements for participants who had three measurements, the second one for participants with only two measurements and the one for participants who had one measurement. Concentrations of serum cholesterol and high-density lipoprotein cholesterol were measured enzymatically on a Hitachi 704 (Boehringer Mannheim Diagnostics, Indianapolis, IN, USA) using commercial reagents. Concentrations of C-reactive protein were measured by using latex-enhanced nephelometry (N High Sensitivity CRP assay) on a Nephelometer II Analyzer System (BN II) (Dade Behring Deerfield, IL, USA). Concentrations of HbA1c were measured with boronate affinity high-performance liquid chromatography using Primus CLC330 and Primus CLC385 instruments (Primus Corporation, Kansas City, MO, USA). Concentrations of serum calcium were measured by using colorometry after reacting with *o*-cresolphthalein complexone in the presence of 8-hydroxyquinoline (Beckman Synchron LX20, Beckman Coulter Brea, CA, USA). Albumin was measured by using a solid-phase fluorescent immunoassay with a digital Sequoia-Turner model 450 Fluorometer (Sequoia-Turner Corp., Mountain View, CA, USA), and creatinine was measured by using a Jaffé rate reaction on a Beckman Synchron CX3 clinical analyzer (Beckman Instruments, Brea, CA, USA). The waist circumference was measured at the high point of the iliac crest at minimal respiration to the nearest 0.1 cm. Participants who responded

affirmatively to the question 'Have you ever been told by a doctor or health professional you have diabetes or sugar diabetes?' were considered to have diagnosed diabetes. Those who answered that they had not been told so or that they had borderline diabetes were not considered to have diagnosed diabetes. Participants were considered to have cardiovascular disease if they had ever been told by a doctor or other health professional that they had congestive heart failure, coronary heart disease, angina, heart attack or stroke. Participants were considered to have cancer if they had ever been told by a doctor or other health professional that they had cancer or a malignancy.

Differences in means and percentages were tested with *t*-tests and chi-squared tests, respectively. We used proportional hazard regression analysis to examine the independent association between concentrations of vitamin D and mortality. We examined vitamin D as a continuous variable as well as a categorical variable <50 nmol/l (<20 ng/ml = deficiency), 50 to <75 nmol/l (20 to <30 ng/ml = insufficiency) and $\geqslant 75$ nmol/l ($\geqslant 30$ ng/ml = sufficiency). To account for the complex survey design, analyses were conducted with SUDAAN and sampling weights were used.

Results

Of the 11 595 participants who were eligible for the mortality study, 10 877 attended the mobile examination centre. After excluding pregnant women, 10 270 participants were left. Further exclusions for missing data reduced the sample to 7531 participants of whom 347 died (92 malignant neoplasms, 120 major cardiovascular disease and 135 other causes). The 7531 participants included 3867 men, 4089 whites, 1359 African Americans, 1554 Mexican Americans and 529 of another race or ethnicity. The median follow-up was 3.8 years.

In the analytic sample, the mean concentration of vitamin D was 60.6 nmol/l (24.3 ng/ml) [25th percentile: 43.3 nmol/l (17.4 ng/ml), 50th percentile: 57.9 nmol/l (23.2 ng/ml), 75th percentile: 73.2 nmol/l (29.3 ng/ml)]. The mean concentrations of vitamin D were 54.1 nmol/l (21.7 ng/ml) among participants who died and 60.7 nmol/l (24.3 ng/ml) among participants who survived ($P = 0.002$). Furthermore, 31.5% of participants had a concentration <50 nmol/l (<20 ng/ml), 42.5% had a concentration 50 to <75 nmol/l (20 to <30 ng/ml) and 26.0% had a concentration $\geqslant 75$ nmol/l ($\geqslant 30$ ng/ml).

Numerous differences in the unadjusted means or percentages of covariates across the three categories of concentrations of vitamin D existed (Table 1).

Concentrations of vitamin D modelled as a continuous variable predicted all-cause mortality in models that were adjusted for socio-demographic factors as well as lifestyle factors (Table 2). Once a series of physiological factors were added, however, the regression coefficient lost statistical significance but did retain borderline significance in the final model that was also adjusted for several comorbidities. We did not find evidence that the risk estimates varied by gender ($P = 0.80$) or among the three major racial or ethnic groups ($P = 0.46$). In models that included concentrations of vitamin D categorized into three groups, participants who were deficient had an increased risk of mortality compared with participants who had sufficient concentrations. However, the inclusion of lifestyle behaviours and physiological variables attenuated the HRs to the extent that the 95% confidence interval (95% CI) included unity.

Discussion

Given the high prevalence of vitamin D deficiency and insufficiency in many populations and the existence of relative inexpensive and easy interventions to boost concentrations of vitamin D, supplementation with vitamin D to potentially reduce morbidity and mortality holds great appeal. Our results provide limited evidence that vitamin D is associated with reduced all-cause mortality. Only concentrations of vitamin D used as a continuous variable had some degree of predictive ability of all-cause mortality. Our analyses illustrate that adjustment for potential confounders can substantially affect the risk estimates and, therefore, the selection of potential confounders deserves careful consideration.

Several analyses of the NHANES III Mortality Study reported that low concentrations of vitamin D were associated with mortality from all causes and/or cardiovascular disease.[17,18,23] Whereas several other studies have described inverse relationships between concentrations of vitamin D and all-cause mortality,[19–22,24,26] some studies have not found concentrations of vitamin D to be an independent predictor of mortality from all causes or coronary heart disease.[15,16,25] A meta-analysis of prospective studies found that the highest quintile of concentrations of vitamin D was associated with an elevated risk of mortality from cardiovascular disease.[29] Reductions in mortality from cancer, and particularly from colorectal cancer, have also been reported in prospective studies.[30,31] An ecological analysis suggested that cancer mortality for 10 sites was inversely related to ultraviolet-B exposure.[32]

An expanding body of literature examines the relationships between concentrations of vitamin D and the incidence of many chronic and acute conditions. We will restrict our brief summary of the emerging literature to cardiovascular disease, cancer and respiratory infections. A meta-analysis of four prospective studies found that participants with the lowest category of concentrations of vitamin D had an elevated risk of cardiovascular disease incidence.[29] However, another meta-analysis was more cautious

Table 1 Unadjusted baseline characteristics by category of serum concentration of vitamin D among 7531 participants aged ⩾20 years, National Health and Nutrition Examination Survey Linked Mortality Study 2001–06

	Vitamin D concentration (nmol/l)						
	<50 ($N=2983$)		50 to <75 ($N=3049$)		⩾75 ($N=1489$)		
Characteristics	% or mean	SE	% or mean	SE	% or mean	SE	***P***
Men (%)	44.9	1.0	53.4	1.1	49.6	1.7	0.04
Whites (%)	52.8	2.9	78.9	2.0	91.1	1.4	<0.01
High school graduate or higher (%)	51.6	1.6	59.2	1.4	56.2	2.1	0.07
Current smoker (%)	28.5	1.2	22.9	1.0	24.9	1.6	0.06
Vitamin, mineral or supplement use (%)	40.0	1.1	57.7	1.4	63.0	1.4	<0.01
Urinary-albumin–creatinine ratio <30 g/g (%)	88.4	0.8	92.3	0.4	94.5	0.8	<0.01
Cardiovascular disease (%)	9.6	0.7	7.8	0.8	7.5	0.8	0.03
Cancer (%)	7.4	0.5	9.0	0.7	9.2	0.6	0.02
Diabetes (%)	9.4	0.6	6.3	0.5	4.7	0.8	<0.01
Age (years)	45.3	0.4	46.6	0.5	45.6	0.5	0.56
Alcohol intake (g/day)	10.7	0.8	13.1	0.9	14.2	1.5	0.02
Leisure-time physical activity (MET-h)	53.0	3.6	79.5	3.9	105.6	7.3	<0.01
Systolic blood pressure (mmHg)	124.5	0.4	122.5	0.4	120.0	0.7	<0.01
Non-high-density lipoprotein cholesterol (mmol/l)	3.92	0.03	3.88	0.02	3.78	0.04	0.01
High-density lipoprotein cholesterol (mmol/l)	1.31	0.01	1.35	0.01	1.45	0.01	<0.01
HbA1c (%)	5.6	<0.1	5.5	<0.1	5.4	<0.1	<0.01
C-reactive protein (mg/l)	5.1	0.3	3.6	0.1	3.5	0.2	<0.01
Serum calcium (mmol/l)	2.4	0.0	2.4	0.0	2.4	0.0	<0.01
Waist circumference (cm)	100.0	0.5	96.5	0.4	92.8	0.6	<0.01
Vitamin D (nmol/l)	35.3	0.3	60.9	0.2	90.5	0.8	<0.01

when it reported that only five of the nine prospective studies found inverse relationships between concentrations of vitamin D and incident cardiovascular disease.[33] Furthermore, the results from four trials did not yield conclusive evidence about a beneficial effect of supplementation with vitamin D on cardiovascular outcomes.[33] A series of meta-analyses based on prospective observational studies has concluded that concentrations of vitamin D are inversely related to breast cancer[34] and colorectal cancer[35–37] but not prostate cancer.[38] A promising randomized trial found that supplementation with 1500 mg/day of calcium and 1100 IU/day of vitamin D_3 reduced cancer incidence by ~60%.[39] Clinical trials suggest that supplementation with vitamin D may reduce incident influenza, recurrent pneumonia and upper respiratory tract infections in children and young adults,[40–42] and a prospective study suggests that concentrations of vitamin D were inversely associated with the incidence of upper respiratory tract infections in adults.[43]

Supplementation studies provide mixed evidence concerning a beneficial effect of vitamin D on disease prevention or reduction in mortality. A meta-analysis of 18 randomized controlled trials found that supplementation with vitamin D in amounts ranging from 300 to 2000 IU and a mean of 528 IU reduced mortality by 7% [risk ratio (RR) = 0.93, 95% CI: 0.97–0.99].[44] Our estimate that a change in the serum concentration of vitamin D of 10 nmol/l equates to an approximate change of 6–7% in mortality is consistent with the estimated reduction in mortality from the meta-analysis assuming that an increase in the intake of vitamin D by 1000 IU/day increases the serum concentration of vitamin D by 15–25 nmol/l.[45] In two trials, however, vitamin D supplementation produced a 10% reduction in cardiovascular outcomes (RR = 0.90, 95% CI: 0.77–1.05).[46]

Because of the aforementioned health consequences of hypovitaminosis D, the high prevalence of vitamin D deficiency and insufficiency in USA is troublesome. Data from NHANES III showed that—depending on gender, race or ethnicity and age—from 8% to 76% of the participants had a concentration <49.9 nmol/l (<20 ng/ml).[12] Deficiency was particularly prominent among African American women. More recent national data suggested that the mean serum

Table 2 HRs (95% CI) for concentrations of vitamin D and all-cause mortality among 7531 participants aged ⩾20 years, National Health and Nutrition Examination Survey Linked Mortality Study 2001–06

	Vitamin D (nmol/l)						
Model	<50	50 to <75	⩾75	Quartile 1 (7 to <45)	Quartile 2 (45 to <60)	Quartile 3 (60 to <75)	Quartile 4 (⩾75)	Continuous (per 10 nmol/l)
No. deaths/total[a]	163/2983	127/3049	57/1499	127/2362	93/1962	70/1708	57/1499	347/7531
Model 1	1.66 (1.16–2.37)	1.03 (0.74–1.43)	1.00	1.74 (1.18–2.58)	1.24 (0.83–1.86)	0.93 (0.66–1.33)	1.00	0.89 (0.82–0.96)
Model 2	1.65 (1.13–2.40)	1.02 (0.74–1.41)	1.00	1.74 (1.15–2.64)	1.25 (0.84–1.85)	0.92 (0.65–1.29)	1.00	0.89 (0.81–0.97)
Model 3	1.46 (0.97–2.19)	0.99 (0.71–1.37)	1.00	1.57 (1.01–2.44)	1.20 (0.80–1.80)	0.90 (0.63–1.27)	1.00	0.91 (0.84–<1.00)
Model 4	1.26 (0.85–1.88)	0.93 (0.65–1.31)	1.00	1.39 (0.89–2.17)	1.13 (0.76–1.69)	0.85 (0.59–1.23)	1.00	0.94 (0.86–1.01)
Model 5	1.28 (0.86–1.90)	0.91 (0.63–1.33)	1.00	1.39 (0.90–2.14)	1.12 (0.77–1.64)	0.83 (0.56–1.22)	1.00	0.93 (0.86–1.01)

Model 1 is adjusted for age and 6-month examination period.
Model 2 is adjusted for age, gender, race or ethnicity, educational status and 6-month examination period.
Model 3 is adjusted for age, gender, race or ethnicity, educational status, smoking status, alcohol intake, leisure-time physical activity, vitamin or mineral or supplement use and 6-month examination period.
Model 4 is adjusted for age, gender, race or ethnicity, educational status, smoking status, alcohol intake, leisure-time physical activity, vitamin or mineral or supplement use, systolic blood pressure, non-high-density lipoprotein cholesterol, high-density lipoprotein cholesterol, HbA1c, C-reactive protein, albuminuria, serum calcium, waist circumference and 6-month examination period.
Model 5 is adjusted for age, gender, race or ethnicity, educational status, smoking status, alcohol intake, leisure-time physical activity, vitamin or mineral or supplement use, systolic blood pressure, non-high-density lipoprotein cholesterol, high-density lipoprotein cholesterol, HbA1c, C-reactive protein, albuminuria, serum calcium, waist circumference, histories of cardiovascular disease, cancer and diabetes, and 6-month examination period.
[a]Unweighted numbers.

concentrations of vitamin D in the US population had declined.[14] Increased body mass index, decreased consumption of milk and increased sun protection appeared to correlate with the decrease in vitamin D.

In USA, the recommended daily allowance for vitamin D in 2010 ranges from 600 to 800 IU/day.[47] During 2005–06, the percentage of adults surpassing the adequate intake ranged from <3% to 45% of male adults and from <3% to 32% of female adults.[48] However, various experts have proposed that increased intakes of vitamin D are necessary to maximize health.[49–52] Although optimal circulating concentrations of vitamin D remain under discussion, people with a great deal of sun exposure have concentrations in the range of ∼120–175 nmol/l.[53] To achieve such concentrations through the oral route requires amounts of vitamin D generally above current recommendations.[54–59]

Although the prospective design and the representative sample of US adults are positive attributes of our study, several limitations should be considered as well. First, the follow-up of our study with a mean of ∼4 years was relatively short. Thus, a limited number of deaths accrued. Nevertheless, our study included a higher number of deaths than several other studies. For outcomes such as cancer that generally have long incubation times, studies of limited duration may be especially problematical. Because blood concentrations of vitamin D reflect behaviours that include exposure to sunshine as well as intakes from diet and supplements, blood concentrations of vitamin D may be a risk marker rather than a risk factor for mortality. Adequate concentrations of vitamin D may reflect a pattern of behaviour to minimize threats to one's health that may include taking supplements with vitamin D. Although we controlled for numerous potential confounders, we may not have included all relevant ones and, therefore, residual confounding remains a distinct possibility. We were unable to include concentrations of parathyroid hormone in our analyses because this hormone was not assessed during the calendar years included in our study. In addition, we were unable to fully adjust for seasonality and geographical location because these data were not available. Only a single measurement of vitamin D was available. Had more such measurements been available, the vitamin D status of each participant and the relationships between concentrations of vitamin D and mortality could have been assessed with increased accuracy. Finally, laboratory drift may have affected the measurements of vitamin D in our sample.[60] However, an analysis that compared various statistics based on the original data from 2000 to 2004 and on a truncated set of data found only small differences.[61]

In conclusion, our study provides limited support for an inverse relationship between concentrations of vitamin D and all-cause mortality. Future monitoring of this cohort will provide additional opportunities to

link vitamin D status to mortality with larger numbers of events and longer duration of follow-up. Because some evidence has shown a benefit of adequate vitamin D status on morbidity and mortality, the high prevalence of vitamin D deficiency and insufficiency and the availability of an inexpensive and readily accessible remedy, it is imperative to clarify the relationships between vitamin D status and morbidity and mortality. The potential impact of adequate vitamin D status is illustrated by a study that suggested that, by supplementing adults in the United States with 1000 IU/day, economic costs from vitamin D-associated conditions could be reduced by ~$16 to $25 billion.[62]

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Conflict of interest: None declared.

KEY MESSAGES

- Observational studies yield inconclusive evidence about the relationship between circulating concentrations of vitamin D and all-cause mortality.
- In a national sample of adults aged $\geqslant 20$ years from USA, adults with a concentration of vitamin D < 50 nmol/l had a moderately increased risk for all-cause mortality compared with adults with a concentration of vitamin D $\geqslant 75$ nmol/l after adjustment for demographic variables (adjusted HR = 1.65, 95% CI: 1.13–2.40).
- After more extensive adjustment with lifestyle factors and physiological, biochemical and anthropometric variables, the HR was substantially attenuated (adjusted HR = 1.26, 95% CI: 0.85–1.88).
- The role of possible confounding in the relationship between concentrations of vitamin D and health outcomes such as all-cause mortality requires careful consideration.

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