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Serum 25-Hydroxyvitamin D Values and Risk of All-Cause and Cause-Specific Mortality: A Population-Based Cohort Study

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Abstract

Objective: To determine the relationship between 25-hydroxyvitamin D (25[OH]D) values and all-cause and cause-specific mortality.

Patients and Methods: We identified all serum 25(OH)D measurements in adults residing in Olmsted County, Minnesota, between January 1, 2005, and December 31, 2011, through the Rochester Epidemiology Project. All-cause mortality was the primary outcome. Patients were followed up until their last clinical visit as an Olmsted County resident, December 31, 2014, or death. Multivariate analyses were adjusted for age, sex, race/ethnicity, month of measurement, and Charlson comorbidity index score.

Results: A total of 11,022 individuals had a 25(OH)D measurement between January 1, 2005, and December 31, 2011, with a mean ± SD value of 30.0±12.9 ng/mL. Mean age was 54.3±17.2 years, and most were female (77.1%) and white (87.6%). There were 723 deaths after a median follow-up of 4.8 years (interquartile range, 3.4-6.2 years). Unadjusted all-cause mortality hazard ratios (HRs) and 95% CIs for 25(OH)D values of less than 12, 12 to 19, and more than 50 ng/mL were 2.6 (95% CI, 2.0-3.2), 1.3 (95% CI, 1.0-1.6), and 1.0 (95% CI, 0.72-1.5), respectively, compared with the reference value of 20 to 50 ng/mL. In a multivariate model, the interaction between the effect of 25(OH)D and race/ethnicity on mortality was significant ($P<.001$). In white patients, adjusted HRs for 25(OH)D values of less than 12, 12 to 19, 20 to 50, and greater than 50 ng/mL were 2.5 (95% CI, 2.2-2.9), 1.4 (95% CI, 1.2-1.6), 1.0 (referent), and 1.0 (95% CI, 0.81-1.3), respectively. In patients of other race/ethnicity, adjusted HRs were 1.9 (95% CI, 1.5-2.3), 1.7 (95% CI, 1.1-2.6), 1.5 (95% CI, 1.0-2.0), and 2.1 (95% CI, 0.77-5.5).

Conclusion: White patients with 25(OH)D values of less than 20 ng/mL had greater all-cause mortality than those with values of 20 to 50 ng/mL, and white patients had greater mortality associated with low 25(OH)D values than patients of other race/ethnicity. Values of 25(OH)D greater than 50 ng/mL were not associated with all-cause mortality.

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Vitamin D deficiency is a globally prevalent condition that is associated with multiple adverse health outcomes including mortality.[1-3] An inverse relationship between serum 25-hydroxyvitamin D (25[OH]D), the accepted measure of vitamin D status, and all-cause mortality has been reported for 25(OH)D values up to 20 to 36 ng/mL (to convert to nmol/L, multiply by 2.496).[4-9] Higher cardiovascular, cancer, and respiratory mortality have been associated with low vitamin D status.[7,10]

More recent debate has surfaced regarding the effect of high 25(OH)D levels on mortality. A handful of studies have reported a reverse J-shaped association between serum 25(OH)D and mortality with increased risk of all-cause mortality[4,11,12] and cardiovascular disease mortality[4] at 25(OH)D values greater than 50 to 60 ng/mL. We previously described an increasing incidence of 25(OH)D values greater than 50 ng/mL, which raises potential concern for the long-term impact of this change.[13] Taking a cautious approach to the literature, the Institute of Medicine committee formulating Dietary Reference Intakes for vitamin D recommended a tolerable upper intake level of 4000 IU, corresponding to a serum 25(OH)D concentration of approximately 50 ng/mL.[14] The committee noted that individual vitamin D requirements

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are variable, but they identified serum 25(OH)D values below 20 ng/mL as increasing the risk of vitamin D deficiency.

Most previous studies of vitamin D and mortality have been limited by low numbers of patients with high serum 25(OH)D values, lack of racial diversity, or lack of information on cause-specific mortality or were not population-based. Our objective was to conduct a population-based study in the United States of the relationship between vitamin D status and all-cause and cause-specific mortality. We hypothesized that we would observe a reverse J-shaped association between 25(OH)D concentrations and mortality.

PATIENTS AND METHODS

Olmsted County and the Rochester Epidemiology Project

Data from the Rochester Epidemiology Project (REP) were used to retrieve the cohort and outcomes data. The REP database is a rare example of a population-based medical records linkage system that includes over 50 years of health care utilization and diagnostic and laboratory data from virtually all medical care providers within Olmsted County, Minnesota, covering 98% of all health care services provided for Olmsted County residents.[15,16] The county is served by 2 large integrated health systems, Mayo Clinic and Olmsted Medical Center, including primary through tertiary services and outpatient and hospital care.[17] More than 95% of the Olmsted County population has granted the medical records research authorization required by Minnesota law, thus allowing their records to be used for research.[18,19]

Olmsted County, Minnesota, is located in the Upper Midwest of the United States (44° north latitude) and has limited sun exposure for residents in winter months. The population of Olmsted County increased from 135,897 to 148,700 between 2002 and 2011. In the 2000 and 2010 censuses, the proportions of Olmsted County residents classified as white, black, Asian, and Hispanic were 90% and 86%, 2.7% and 4.8%, 4.3% and 5.5%, and 2.4% and 4.2%, respectively. The proportions of males were 49% and 48% and of individuals aged 65 years and older, 11% and 13%, respectively. Compared with the entire US 2010 population, the county is less ethnically diverse (72% vs 86% white), more educated (85% vs 94% high school graduates), and wealthier ($51,914 vs $64,090 median household income). However, characteristics of the population are very similar to the overall population of the Upper Midwest.[19]

Patient Selection and Outcomes

We identified all initial serum 25(OH)D measurements (index 25(OH)D measurement) in persons aged 18 years and older residing in Olmsted County between January 1, 2005, and December 31, 2011, using the resources of the REP. Patients were followed up until their last clinical visit in Olmsted County as an Olmsted County resident, December 31, 2014, or death, whichever came first. We required that survival be conditional on surviving the first 30 days following the first ever 25(OH)D measurement because of concerns about sampling bias; our fear was that some patients may have had 25(OH)D measured because they were already so ill that their immediate life expectancy was low.

We collected data on age at medical visit, sex, race/ethnicity, and Charlson comorbidity index score. Cause-specific mortality was assessed according to 4 *International Classification of Diseases, Tenth Revision* (*ICD-10*) subsets: circulatory system diseases (includes cardiovascular, cerebrovascular, and other vascular causes), I00-I99; respiratory diseases (includes respiratory infections and chronic respiratory diseases), J00-J98; all malignant cancers, C00-C97; and all other causes.

Laboratory Methods

All 25(OH)D tests ordered in Olmsted County were measured at Mayo Medical Laboratories during the study interval, with results and date of blood draw recorded. The method of 25(OH)D measurement was isotope-dilution liquid chromatography—tandem mass spectrometry with an interassay coefficient of variation of 3.7% to 11% (Ravinder Singh, PhD, written communication, August 22, 2014).

Statistical Analyses

Serum 25(OH)D was examined as a continuous variable and as a categorical variable

TABLE 1. Baseline Characteristics of the Study Population[a,b,c]

Characteristic	Total (N=11,022)	Serum 25(OH)D categories (ng/mL) <12 (n=643)	12-19 (n=1605)	20-50 (n=8210)	>50 (n=564)	*P* value
25(OH)D (ng/mL)	30.0±12.9	8.5	15.9	32.4	60.9	
Age (y)	54.3±17.2	51.4±18.0	51.8±17.0	54.9±17.1	55.8±18.0	.10[d]
Age groups (y)						
18-49	4244 (38.5)	311 (48.4)	725 (45.2)	3014 (36.7)	194 (34.4)	
50-64	3784 (34.3)	195 (30.3)	546 (34.0)	2851 (34.7)	192 (34.0)	
≥65	2994 (27.2)	137 (21.3)	334 (20.8)	2345 (28.6)	178 (31.6)	
Sex						<.001
Women	8496 (77.1)	463 (72.0)	1176 (73.3)	6357 (77.4)	500 (88.7)	
Men	2526 (22.9)	180 (28.0)	429 (26.7)	1853 (22.6)	64 (11.3)	
Race/ethnicity						<.001
White	9653 (87.6)	420 (65.3)	1209 (75.3)	7482 (91.1)	542 (96.1)	
Other	1369 (12.4)	223 (34.7)	396 (24.7)	728 (8.9)	22 (3.9)	
Season						<.001
Winter (December-February)	2751 (25.0)	225 (35.0)	483 (30.1)	1934 (23.6)	109 (19.3)	
Spring (March-May)	2863 (26.0)	209 (32.5)	510 (31.8)	1992 (24.3)	152 (27.0)	
Summer (June-August)	2525 (22.9)	92 (14.3)	247 (15.4)	2032 (24.8)	154 (27.3)	
Fall (September-November)	2883 (26.2)	117 (18.2)	365 (22.7)	2252 (27.4)	149 (26.4)	
Charlson index	3.37±3.4	3.75±4.1	3.23±3.5	3.36±3.4	3.54±3.2	.06[e]

[a]25(OH)D = 25-hydroxyvitamin D.
[b]Data are presented as mean ±SD or No. (percentage). Percentages may not equal 100 because of rounding.
[c]SI conversion units: To convert 25(OH)D values to nmol/L, multiply by 2.496.
[d]Pearson correlation.
[e]Spearman correlation.

using predetermined ranges of interest: 25(OH)D values of less than 12, 12 to 19, 20 to 50 (reference category), and greater than 50 ng/mL. The Kaplan-Meier estimator (product limit method) was used to calculate the probability of survival for each of the 4 categories of 25(OH)D. Cox proportional hazards regression was used to assess the relationship of 25(OH)D and all-cause mortality, univariately and in a multivariate model. Multivariate analysis was adjusted for age, sex, race/ethnicity, month of 25(OH)D measurement, and Charlson comorbidity index score at the time of 25(OH)D measurement. All 2-way interactions between main effects were examined. Ties in event and censoring times were handled using the Efron method. The functional form of continuous variables was assessed using martingale residuals, and the proportional hazards assumption was assessed via plots of the Schoenfeld residuals.[20] Additionally, after examining a penalized spline fit to the martingale residuals, an outcome-based cut point analysis[21] with a log-rank–based test[22] was used to look for the best initial 25(OH)D value separating 25(OH)D values into the most homogeneous groups with respect to survival. After looking at all-cause mortality, we performed similar analyses looking at the cause-specific deaths: cancer-related deaths, circulatory-related deaths, respiratory-related deaths, and other deaths (determined on the basis of the diagnosis listed first on the death certificate; circulatory *ICD-10*, I00-I99; respiratory *ICD-10*, J00-J98; cancer *ICD-10*, C00-C97; other, all remaining deaths).

RESULTS

A total of 13,599 individuals had a 25(OH)D measurement between January 1, 2005, and December 31, 2011. After excluding those with a death or censored within 30 days following first ever 25(OH)D measurement, we were left with a sample size of 11,022 patients (Table 1). The mean ± SD age was 54.3±17.2 years with a predominance of women (8496 [77.1%]) and whites (9653 [87.6%]). The mean 25(OH)D value was 30.0±12.9 ng/mL. Of the total cohort, the proportions of patients with 25(OH)D values

TABLE 2. Associations Between Serum 25(OH)D Values and All-Cause Mortality, With Univariate Hazard Ratios for Serum 25(OH)D, as Categorized, From Cox Proportional Hazards Modeling of Time to Death[a,b,c]

	Univariate model		Univariate model adjusted for 1 additional risk factor, serum 25(OH)D categories (ng/mL)				
Adjusting risk factor	HR (95% CI)	*P* value	20-50 HR[d] (95% CI) *P* value	<12 HR[d] (95% CI) *P* value	12-19 HR[d] (95% CI) *P* value	>50 HR[d] (95% CI) *P* value	*P* value
25(OH)D (ng/mL)							
20-50	1.0						
<12	2.56 (2.04-3.21)	<.001					
12-19	1.27 (1.04-1.55)	.02					
>50	1.03 (0.72-1.48)	.87					
Sex			ref	2.51 (2.00-3.15) <.001	1.24 (1.02-1.52) .03	1.12 (0.78-1.61) .55	
Female	1.0						
Male	1.88 (1.61-2.19)	<.001					
Age (per 10 y)	2.45 (2.31-2.60)	<.001	ref	3.08 (2.46-3.87) <.001	1.52 (1.24-1.86) <.001	0.93 (0.65-1.34) .70	
Race/ethnicity							.003[e]
White	1.0		ref	3.57 (2.81-4.54)	1.46 (1.18-1.81)	1.06 (0.73-1.54)	
Other	0.97 (0.77-1.24)	.82	1.41 (1.05-1.90)	0.79 (0.51-1.22)	0.80 (0.57-1.12)	1.23 (0.46-3.29)	
CCI (per unit)	1.29 (1.27-1.31)	<.001	ref	1.86 (1.48-2.35) <.001	1.31 (1.07-1.61) .008	1.06 (0.74-1.52) .76	
Season		.45[f]	ref	2.59 (2.25-2.98) <.001	1.38 (1.22-1.56) .01	0.93 (0.73-1.18) .91	
Winter (December-February)	1.0						
Spring (March-May)	1.16 (0.94-1.42)	.16					
Summer (June-August)	1.17 (0.94-1.45)	.15					
Fall (September-November)	1.12 (0.91-1.38)	.28					

[a]CCI = Charlson comorbidity index; HR = hazard ratio; 25(OH)D = 25-hydroxyvitamin D; ref = reference.

[b]SI conversion factors: To convert 25(OH)D values to nmol/L, multiply by 2.496.

[c]Time 0 is 30 days after index 25(OH)D measurement.

[d]From model containing 25(OH)D level and 1 adjusting risk factor (except for the model with race/ethnicity, which also includes the interaction between 25[OH]D level and race/ethnicity in the model).

[e]Interaction *P* value. Hazard ratios presented separately by race/ethnicity because of race/ethnicity—25(OH)D interaction.

[f]Joint test.

of less than 12, 12 to 19, 20 to 50, and greater than 50 ng/mL were 5.8% (643), 14.6% (1605), 74.5% (8210), and 5.1% (564), respectively. Among patients of other race/ethnicity, a greater proportion were in the lower 25(OH)D ranges than whites.

There were 723 deaths (123 cancer-related, 125 circulatory-related, 159 respiratory-related, and 316 other) after a median observed follow-up of 4.8 years (interquartile range, 3.4-6.2 years). Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org) includes the numbers of deaths according to 25(OH)D category, sex, and race/ethnicity. The overall survival was 93.6% (95% CI, 93.1%-94.2%) at 5 years after index 25(OH)D measurement. On univariate analysis, the risk of death was greater in males (hazard ratio [HR], 1.88; 95% CI, 1.61-2.19), in those who were older (HR per 10-year increase, 2.45; 95% CI, 2.31-2.60), and in those with a higher Charlson comorbidity index score (HR per unit, 1.29; 95% CI, 1.27-1.31) (Table 2). All-cause mortality unadjusted HRs for 25(OH)D values of less than 12, 12 to 20, and greater than 50 ng/mL were 2.56 (95% CI, 2.04-3.21), 1.27 (95% CI, 1.04-1.55), and 1.03 (95% CI, 0.72-1.48), respectively, compared with 25(OH)D values of 20 to 50 ng/mL. There was a significant interaction between 25(OH)D values and race/ethnicity on mortality (*P*=.003). For whites, 25(OH)D values of less than 12, 12 to 20, and greater than 50 ng/mL had HRs of 3.57 (95% CI, 2.81-4.54), 1.46

TABLE 3. Hazard Ratios From Multivariate Cox Proportional Hazards Modeling of Time to Death[a,b,c]

Variable		Adjusted HR (95% CI)	*P* value
Age (y)[d]			<.001
50		1.0	
60		1.48 (1.39-1.57)	
70		2.47 (2.24-2.73)	
Sex			<.001
Female		1.0	
Male		1.52 (1.38-1.68)	
Charlson comorbidity index score (per unit)		1.16 (1.15-1.17)	<.001
Season			.24[e]
Winter (December-February)		1.0	
Spring (March-May)		1.01 (0.88-1.15)	.94
Summer (June-August)		1.12 (0.98-1.28)	.11
Fall (September-November)		1.10 (0.96-1.25)	.18
Vitamin D race/ethnicity[f]	White	Other	<.001[f,g]
25(OH)D 20-50 ng/mL	1.0	1.86 (1.50-2.31)	
25(OH)D <12 ng/mL	2.52 (2.17-2.91)	1.69 (1.10-2.62)	
25(OH)D 12-19 ng/mL	1.43 (1.25-1.63)	1.46 (1.04-2.04)	
25(OH)D >50 ng/mL	1.04 (0.81-1.33)	2.06 (0.77-5.51)	

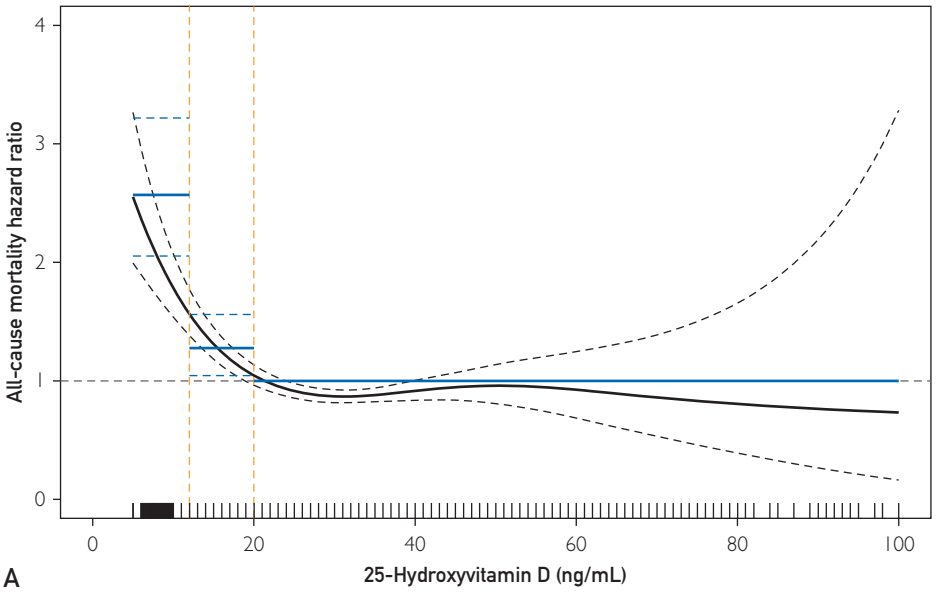
[a]HR = hazard ratio; 25(OH)D = 25-hydroxyvitamin D.
[b]SI conversion factors: To convert 25(OH)D values to nmol/L, multiply by 2.496.
[c]Time 0 is 30 days after index 25(OH)D measurement.
[d]Age is modeled as a quadratic function; the HRs are compared to a 50-year-old.
[e]Joint test.
[f]Indicates that there was a significant interaction between 25(OH)D and race/ethnicity.
[g]Interaction *P* value.

(95% CI, 1.18-1.81), and 1.06 (95% CI, 0.73-1.54), respectively, compared with the reference category of whites with 25(OH)D values of 20 to 50 ng/mL. For patients of other race/ethnicity, the respective HRs were 0.79 (95% CI, 0.51-1.22), 0.80 (95% CI, 0.57-1.12), and 1.23 (95% CI, 0.46-3.29), compared with the same reference category (Table 2). There were no significant interactions of sex and age with 25(OH)D values and mortality.

The final model for all-cause mortality included age (quadratic), sex, Charlson comorbidity index score, index month, race/ethnicity, vitamin D categories, and the interaction between race/ethnicity and serum 25(OH)D (Table 3). As in the univariate analysis, we observed a greater risk of death in males, in those who were older, and in those with a higher Charlson index score. For low 25(OH)D levels, whites were at a much higher risk of death than patients of other race/ethnicity (Figure; Supplemental Figure [available online at http://www.mayoclinicproceedings.org]). In whites, 25(OH)D values of less than 20 ng/mL were associated with increased all-cause mortality, but this association did not exist for patients of other race/ethnicity. For the entire cohort, 25(OH)D values of greater than 50 ng/mL were not associated with increased mortality.

The cut-point analysis of the relationship of overall survival with 25(OH)D values identified nodes at approximately 12 and 20 ng/mL, which were consistent with our predetermined 25(OH)D categories. We estimated a 25(OH)D value of 20 to 25 ng/mL as the lower bound of the range without a significant association between 25(OH)D and mortality. Cut-point analysis did not reveal higher values of 25(OH)D that would suggest an association with high values of 25(OH)D and mortality (ie, the risk of death was similar across 25[OH]D values for those with 25[OH]D values greater than 20-25 ng/mL) (Figure).

The final models for cause-specific mortality included age, sex, Charlson comorbidity index score, index month, race/ethnicity, and 25(OH)D categories (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org). The risk of cancer-related death was greater in those who were older and in those with a higher Charlson score. Low 25(OH)D values were associated with a significantly greater risk of



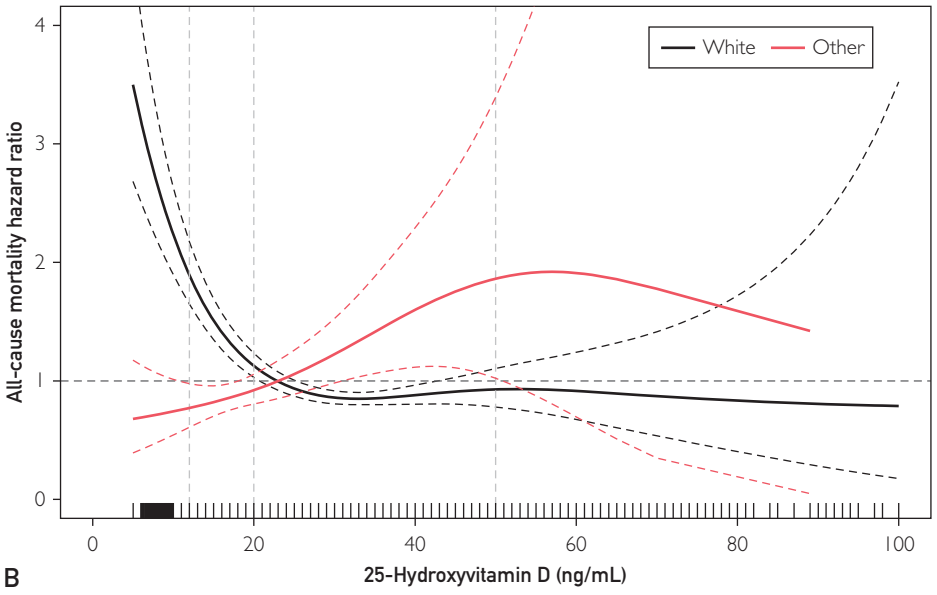


FIGURE. Spline plots displaying unadjusted hazard ratios for all-cause mortality with serum 25-hydroxyvitamin D values as a continuous variable. Dotted lines indicate 95% CIs. A, All patients. Hazard ratios with 95% CIs are shown for categorical 25-hydroxyvitamin D ranges based on cut-point analysis (<12 ng/mL, 12-19 ng/mL, and >19 ng/mL). B, Separated by race/ethnicity.

cancer-related death compared with the reference category of 20 to 50 ng/mL (HR for <12 ng/mL, 2.56 [95% CI, 1.45-4.53], *P*=.001; HR for 12-19 ng/mL, 1.69 [95% CI, 1.06-2.70], *P*=.03). The risk of circulatory-related death was greater in those who were older, males, and race/ethnicity other than white and in those with a higher Charlson score. Very low 25(OH)D values of less than 12 ng/mL were associated with a significantly greater risk of circulatory-related death compared with the reference category of 20 to 50 ng/mL (HR, 2.48; 95% CI, 1.53-4.02; *P*<.001). The risk of respiratory-related death was greater in those who were older, males, and

with higher Charlson score. Those with 25(OH)D values greater than 50 ng/mL were at marginally greater risk of respiratory-related death compared with the reference category (HR, 1.95; 95% CI, 1.004-3.78; P=.05). The risk of other causes of death was greater in those who were older, males, and with higher Charlson score. Very low 25(OH)D values of less than 12 ng/mL were associated with a significantly greater risk of other causes of death compared with the reference category of 20 to 50 ng/mL (HR, 2.72; 95% CI, 1.91-3.89; P<.001).

DISCUSSION

We found a strong association between 25(OH)D concentrations of less than 20 ng/mL and all-cause mortality. There was a significant interaction by race/ethnicity, with no association for patients of other race/ethnicity even at very low 25(OH)D values (<12 ng/mL). Values of 25(OH)D greater than 50 ng/mL were not associated with greater all-cause mortality.

We confirmed the association between low 25(OH)D levels and higher all-cause mortality that has been found in previous studies, including several meta-analyses.[5-7,10,23] Previous studies have reported inverse relationships between serum 25(OH)D concentrations as high as 20 to 36 ng/mL and mortality.[4,5,23] We also found that the association between all-cause mortality and 25(OH)D values of at least 20 to 25 ng/mL was no longer statistically significant, which was in agreement with our a priori cutoff of 20 ng/mL.

Lower 25(OH)D values may not cause increasing mortality but may be associated with illness and a prognostic marker for mortality.[24] However, the effects of vitamin D and its metabolites on inflammation, cellular proliferation, genetic regulation, calcium homeostasis, and immune modulation could have a salutary effect in a variety of diseases that contribute to mortality.[10,25] Low 25(OH)D values have an adverse effect on mortality independent of parathyroid hormone levels,[26] and high parathyroid hormone concentrations are associated with increased mortality independent of 25(OH)D values.[27] It is not clear that changing the 25(OH)D concentration would alter the mortality risk. Randomized trials have found a modest mortality benefit with vitamin D supplementation, although most of the included studies were not designed to evaluate mortality as a primary outcome, and most participants were white.[28]

Values of 25(OH)D greater than 50 ng/mL were not associated with higher all-cause mortality. Although most previous studies found no increase in all-cause mortality associated with 25(OH)D values higher than 50 ng/mL,[6,23,25] a few found an increased risk with 25(OH)D concentrations greater than 50 to 60 ng/mL.[4,11,12] However, vitamin D assay standardization appears to abolish the apparent increased mortality risk associated with high 25(OH)D concentrations because the radioimmunoassay used in the National Health and Nutrition Examination Survey (NHANES) III tends to inflate values of 25(OH)D greater than 40 ng/mL.[29] Most individuals with 25(OH)D values higher than 50 ng/mL are taking vitamin D to achieve these levels. Some of these patients are possibly being treated with vitamin D because they have had or are at risk for vitamin D deficiency.[30] Individuals with a disease associated with vitamin D deficiency (eg, osteoporosis) may take vitamin D even in the absence of documented vitamin D deficiency. Thus, the reported increase in all-cause mortality is likely confounded by the indication for vitamin D intake. Given the rapid increase in the incidence of 25(OH)D values greater than 50 ng/mL in the population,[13] our finding is reassuring that all-cause mortality was not increased in this group.

A novel finding of our study was the significant interaction of race/ethnicity and serum 25(OH)D in the relationship with all-cause mortality. Despite a strong association between 25(OH)D concentrations of less than 20 ng/mL and all-cause mortality in whites, this relationship was absent in patients of other race/ethnicity, even at very low 25(OH)D values. Most previous studies involved predominantly white populations of European descent with minimal inclusion of other races/ethnicities. Of studies that adjusted for race/ethnicity,[8,11,26,31-34] an interaction between the effect of race/ethnicity and 25(OH)D on all-cause mortality was not described. All-cause mortality data from the NHANES-III included an oversampling of participants whose race/ethnicity was other than white, and in a subgroup analysis, investigators reported a nonsignificant interaction by race/ethnicity.[9]

In a 15-year follow-up of the same study, non-Hispanic whites had an increased all-cause mortality in all 25(OH)D categories of less than 30 ng/mL, whereas non-Hispanic blacks only had increased mortality with 25(OH)D values lower than 8 ng/mL when compared with a 25(OH)D reference category of 30 to 39 ng/mL.[11]

The biological and clinical implications of the race/ethnicity interaction in our study are unclear. Individuals who are not white generally have lower 25(OH)D concentrations than whites,[35,36] an effect that is accentuated by greater latitude from the equator.[37] However, the association of low 25(OH)D values with adverse outcomes in individuals of other race/ethnicity is only evident at very low 25(OH)D concentrations.[11,38] Despite their lower values of 25(OH)D, African Americans have a lower risk of osteoporosis, a situation called "the vitamin D paradox."[39] Unlike whites, low 25(OH)D values have not been associated with fracture risk in blacks.[40] Individuals of other race/ethnicity may have a different association between low 25(OH)D concentrations and other comorbidities.[41,42] Investigators using NHANES-III data found that 25(OH)D concentrations of less than 15 ng/mL were associated with higher fatal stroke compared with concentrations of 15 ng/mL or higher in whites but not in blacks after adjusting for multiple covariates.[43] Others using the NHANES-III data found that the excess cardiovascular mortality seen in blacks was completely eliminated after adjusting for 25(OH)D levels and income.[44]

The strengths of our study include a large community-based population and access to comprehensive data from primary through tertiary care for nearly the entire population. All measurements of 25(OH)D were performed in the same laboratory with isotope-dilution liquid chromatography—tandem mass spectrometry, which provides optimal accuracy of 25(OH)D values, and no standardization adjustment was necessary.

However, our study had limitations that are worth noting. We do not have a true population sample, and women are overrepresented. This issue may be related to more frequent measurement of 25(OH)D in women, who are at greater risk of osteoporosis than men. Study participants were those who presented for care and had 25(OH)D measured, so some selection bias is likely. Our population is less ethnically diverse than the US population, which may limit generalizability; in particular, among our population of patients of other race/ethnicity, only 75 individuals died (Supplemental Table 1). Compared with similar previous studies, most of which are from predominantly white populations of European descent, our cohort is actually more ethnically diverse. A larger number of patients of other race/ethnicity would have provided greater power to detect an increase in mortality among such patients associated with 25(OH)D values below 12 ng/mL. This factor is visually represented in the Figure by the line for the 95% CI rising above 1 for patients of other race/ethnicity. However, our finding of a difference in mortality between whites and others associated with low 25(OH)D values remains valid on the basis of the statistical significance of the interaction. We could not establish causality of the association of low 25(OH)D values with mortality because of the retrospective nature of the study. Furthermore, a single measurement of serum 25(OH)D may not represent long-term vitamin D status, but 25(OH)D values do appear to remain relatively stable over time.[45]

CONCLUSION

In this study, white patients with 25(OH)D values of less than 20 ng/mL had a greater all-cause mortality than those with 25(OH)D values of 20 to 50 ng/mL. White patients had greater mortality associated with low 25(OH)D values than patients of other race/ethnicity. Values of 25(OH)D greater than 50 ng/mL were not associated with an increased risk of all-cause mortality.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **HR** = hazard ratio; ***ICD-10*** = *International Classification of Diseases, Tenth Revision*; **NHANES** = National Health and Nutrition Examination Survey; **25(OH)D** = 25-hydroxyvitamin D; **REP** = Rochester Epidemiology Project

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