Prospective Study of Serum 25-Hydroxyvitamin D Level, Cardiovascular Disease Mortality, and All-Cause Mortality in Older U.S. Adults

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OBJECTIVES: To evaluate the association between serum 25-hydroxyvitamin D (25(OH)D) levels and mortality in a representative U.S. sample of older adults.

DESIGN: Prospective cohort from the Third National Health and Nutrition Examination Survey (NHANES III) and linked mortality files.

SETTING: Noninstitutionalized U.S. civilian population.

PARTICIPANTS: Three thousand four hundred eight NHANES III participants aged 65 and older enrolled from 1988 to 1994 and followed for mortality through 2000.

MEASUREMENTS: Primary exposure was serum 25(OH)D level at enrollment. Primary and secondary outcomes were all-cause and cardiovascular disease (CVD) mortality, respectively.

RESULTS: During the median 7.3 years of follow-up, there were 1,493 (44%) deaths, including 767 CVD-related deaths. Median 25(OH)D level was 66 nmol/L. Adjusting for demographics, season, and cardiovascular risk factors, baseline 25(OH)D levels were inversely associated with all-cause mortality risk (adjusted hazard ratio (HR) = 0.95, 95% confidence interval (CI) = 0.92–0.98, per 10 nmol/L 25(OH)D). Compared with subjects with 25(OH)D levels of 100 nmol/L or higher, the adjusted HR for subjects with levels less than 25.0 nmol/L was 1.83 (95% CI = 1.14–2.94) and for levels of 25.0 to 49.9 nmol/L was 1.47 (95% CI = 1.09–1.97). The association appeared stronger for CVD mortality (adjusted HR = 2.36, 95% CI = 1.17–4.75, for subjects with 25(OH)D levels <25.0 nmol/L vs those ≥100.0 nmol/L) than for non-CVD mortality (adjusted HR = 1.42, 95% CI = 0.73–2.79, for subjects with 25(OH)D levels <25.0 nmol/L vs those ≥100.0 nmol/L).

CONCLUSION: In noninstitutionalized older adults, a group at high risk for all-cause mortality, serum 25(OH)D levels had an independent, inverse association with CVD and all-cause mortality. Randomized controlled trials of vitamin D supplementation in older adults are warranted to determine whether this association is causal and reversible.


Key words: vitamin D; mortality; cardiovascular disease; epidemiology; geriatrics

Although many healthcare professionals previously believed that the major health problems from vitamin D were limited to rickets, osteoporosis, and osteomalacia, there has been intense interest in the role of vitamin D in a variety of nonskeletal medical conditions during the past decade.† Vitamin D insufficiency has been associated with higher incidences of many medical conditions that affect mortality risk, including hypertension,‡,§ diabetes mellitus,¶,¶‡ cardiovascular disease (CVD),¶¶–¶¶¶ cancer,¶¶§–¶¶¶¶ and infection.¶¶¶–¶¶¶¶ Vitamin D supplementation appears to mitigate incidence of, and adverse outcomes from, these various diseases.¶¶¶¶–¶¶¶¶

Accordingly, recent evidence suggests that vitamin D may play a role in mortality risk.¶¶†,¶¶‡,¶¶¶‡ Low serum levels of 25-hydroxyvitamin D (25(OH)D), the major circulating form of vitamin D, have been associated with all-cause mortality in individuals with end-stage renal disease¶¶¶ and coronary artery disease¶¶¶ and even in the general population.¶¶¶ Further evidence suggests that vitamin D supplementation may lower mortality.¶¶¶–¶¶¶¶ Although older adults are at high risk for lower 25(OH)D levels¶¶‡ and mortality,¶¶¶¶ the association between vitamin D insufficiency and mortality risk has not been specifically evaluated in older adults.

Older adults are at high risk for vitamin D insufficiency because of a reduction of 7-dehydrocholesterol, the
precursor for vitamin D in the skin,\textsuperscript{1} and lower ultraviolet (UV) B light exposure from lower outdoor activity.\textsuperscript{31} Furthermore, the incidence of vitamin D insufficiency in older adults is increasing,\textsuperscript{32} and currently recommended supplementation doses appear inadequate to support the higher 25(OH)D levels associated with improved general health outcomes.\textsuperscript{33,34} Thus, although serum 25(OH)D predicts all-cause mortality for U.S. adults aged 20 and older,\textsuperscript{23} this study sought to evaluate the association between serum 25(OH)D levels and mortality in a sample of adults aged 65 and older representative of the U.S. population, including specific evaluation of mortality from CVD.

**METHODS**

**Study Design and Participants**

From October 1988 to October 1994, the National Center for Health Statistics conducted the Third National Health and Nutrition Examination Survey (NHANES III), followed by the mortality assessment from enrollment through December 31, 2000. A secondary analysis of this nationally representative, prospective observational cohort of the noninstitutionalized U.S. civilian population, limited to older adults (aged \( \geq 65 \)) was performed. A waiver from the institutional review boards was received as an exempt study.

Full details of survey methodology, including sampling, interview, examination, laboratory measurements, mortality linkage, ethics approval, and informed consent, are described elsewhere.\textsuperscript{35} Briefly, the survey used a complex, stratified, multistage probability sample design. NHANES III oversampled certain subgroups of people, including low-income persons, adolescents, older adults, African Americans, and Mexican Americans. Because physical and laboratory examinations occurred in mobile examination centers, inclement weather was a challenge during data collection. To avoid this challenge and improve response, the NHANES preferentially scheduled data collection in the lower latitudes (farther south) during winter months and higher latitudes (farther north) in the summer months.\textsuperscript{36}

NHANES III collected household interview data, including demographic characteristics and data on health and nutrition, for 33,994 (85.6\%) of 39,695 invited participants, of whom 5,262 were aged 65 and older. The majority (4,094, 77.8\%) subsequently received physical and laboratory examination in a mobile examination center or at a home visit. Participants without reported serum 25(OH)D measurements (216 missing) and valid mortality data (7 missing) were excluded. Poverty-income ratio (ratio of a family’s income to the poverty threshold of a family of the same size) was used to assess socioeconomic status; 463 participants without data for this important covariate were excluded. Thus, 3,408 participants, who represent 24 million older U.S. adults, were included in the final analysis. Serum 25(OH)D levels were similar for excluded and analyzed participants (data not shown).

**Definition of Study Variables**

From the household interview data, information on self-reported age, sex, race or ethnicity, and socioeconomic status, as measured according to the poverty-income ratio was analyzed. Smoking history (current smoking and pack-years), current asthma, and chronic obstructive pulmonary disease (emphysema or chronic bronchitis) diagnosis from self-reported history were included. Physical activity was measured in total metabolic equivalent tasks (METs) and calculated as the sum of leisure-time physical activities reported during the prior month (as measured for each activity by the product of intensity rating, in METS, and frequency of activity during the month). Factors that are known to be associated with serum 25(OH)D,\textsuperscript{31} but without a clear direct relationship to mortality, such as milk intake and vitamin D supplementation, were not included in the models because of collinearity.

From the examination data, body mass index was calculated as weight in kilograms divided by the square height in meters. Hypertension was defined as self-reported physician-diagnosed hypertension, average systolic blood pressure greater than 140 mmHg at baseline, or average diastolic blood pressure greater than 90 mmHg at baseline. One to three blood pressure measurements were made at the baseline data collection. Diabetes mellitus was defined as self-reported physician-diagnosed diabetes mellitus (except gestational diabetes only), fasting (\( \geq 8 \) hours) blood glucose of 126 mg/dL or greater at baseline, or nonfasting blood glucose of 200 mg/dL or greater at baseline. Hyperlipidemia was defined as self-reported physician-diagnosed high cholesterol, non-high-density lipoprotein cholesterol of 160 mg/dL or greater, or triglycerides of 200 mg/dL or greater.

Blood samples collected during the examination were centrifuged, aliquoted, and frozen to \(-70^\circ\)C on site and shipped on dry ice to central laboratories, where they were stored at \(-70^\circ\)C until analysis. The National Center for Environmental Health (Atlanta, GA) measured serum 25(OH)D levels using a radioimmunoassay kit after extraction with acetonitrile (DiaSorin, Stillwater, MN). The date of the examination and laboratory data collection was used to most accurately adjust for the effect of season on serum 25(OH)D levels. Estimated glomerular filtration rate was calculated using the abbreviated Modification in Diet in Renal Disease (MDRD) equation. Serum creatinine measurements were calibrated to the MDRD standard by subtracting 0.23 mg/dL from NHANES III values, as previously described.\textsuperscript{37}

**Vital Status and Cause of Death**

Mortality outcomes were collected by matching National Death Index screen or death certificate data from the time of enrollment until December 31, 2000. Participants were classified as “dead” or, for all participants without a probabilistic match, “presumed alive.” The underlying cause of death was coded using the International Classification of Diseases, Ninth Revision (ICD-9) until 1998 and ICD-10 in 1999 and 2000. The National Center for Health Statistics subsequently recoded all deaths before 1999 to ICD-10 codes for comparability. CVD mortality was defined as ICD-10 codes I00-I99 and non-CVD mortality as all other causes of death.

The primary outcome for the cohort was all-cause mortality during the follow-up period, and the secondary
outcome was CVD mortality. It was attempted to analyze cancer and infection-related mortality, but the number of observations was too small for meaningful analysis; thus, non-CVD mortality was used as a second category for cause of death.

**Statistical Analysis**

Statistical analyses were performed using Stata 9.0 (StataCorp., College Station, TX). Using survey commands, the recommended subsample weights for the interview plus examination data were applied to account for unequal probabilities of selection and to accurately represent estimates for the U.S. population. All results are presented as weighted values. Variance was calculated based on NHANES-provided masked variance units, using the Taylor Series linearization method. All P-values were two-tailed, with P < 0.05 considered statistically significant.

For the primary analysis, serum 25(OH)D levels were stratified into five groups (<25.0 nmol/L, 25.0–49.9 nmol/L, 50.0–74.9 nmol/L, 75.0–99.9 nmol/L, and ≥100.0 nmol/L), which were chosen a priori based on previously reported 25(OH)D thresholds for improving general health. It is likely that consistency of thresholds in the literature, rather than using percentiles (which vary from study to study), facilitates integration of multiple studies in the literature, although a secondary analysis of 25(OH)D deciles has also been included to evaluate linearity of observed associations.

Proportions and means with 95% confidence intervals (CIs) were calculated for the selected covariates, according to 25(OH)D strata. Univariate associations were determined between characteristics and 25(OH)D levels using the Pearson chi-square test for categorical variables and analysis of variance for continuous variables. The association between each covariate and mortality outcomes was evaluated using simple (unadjusted) Cox proportional hazards analysis.

The primary analysis focused on the association between baseline serum 25(OH)D level and all-cause, CVD, and non-CVD mortality during follow-up using multivariable Cox proportional hazards models. Three different multivariable models were used, specified a priori, to test for the independent effect of serum 25(OH)D levels on mortality. The first model adjusted for age, sex, and race or ethnicity (all important in adjustment of mortality rates) and season (important in adjustment of 25(OH)D levels). Building on the first model, the second model added other potential confounders: poverty: income ratio, region, body mass index, physical activity, smoking status, cigarette pack years, asthma, chronic obstructive pulmonary disease, and renal function. This model was considered to be fully adjusted for subsequent analyses. The third model added potential intermediates to help explain the observed associations, including hypertension, diabetes mellitus, hyperlipidemia, history of myocardial infarction, history of stroke, and history of cancer (nonskin). Finally, effect modification by covariates on the associations between 25(OH)D and mortality were formally tested for by adding interaction terms to the adjusted models.

**RESULTS**

Characteristics of the weighted NHANES III sample, stratified according to baseline 25(OH)D level, are summarized in Table 1. The median 25(OH)D level was 66.0 nmol/L. Women, non-Hispanic blacks, and Mexican Americans had lower 25(OH)D levels. Lower socioeconomic status, winter season, Midwest region, lower physical activity, hypertension, diabetes mellitus, and history of stroke were also associated with lower 25(OH)D levels.

During the median 7.3 years of follow-up, there were 1,493 (43.8%) deaths among the 3,408 participants, of which 767 (51.4%) were related to CVD. The remaining 726 non-CVD deaths could not be further stratified according to other causes (e.g., cancer, infection) for valid analysis because of the small number of individual observations. The association between baseline characteristics and all-cause, CVD, and non-CVD mortality are presented in Table 2. Baseline 25(OH)D level, older age, diabetes mellitus, history of myocardial infarction, and history of stroke were most strongly associated with CVD and all-cause mortality (all P < 0.05).

In the multivariable models (Table 3), baseline serum 25(OH)D level maintained an independent association with all-cause mortality, even after controlling for potential confounders and intermediate variables. Additionally, the Kaplan-Meier curves (Figure 1A) demonstrates an immediate and sustained divergence of mortality risk between 25(OH)D strata. Stratification of the mortality outcome suggested that the association was stronger for CVD than for non-CVD mortality (Figure 1B, C).

There appeared to be a dose-response association with the largest risk in the lowest 25(OH)D stratum (<25.0 nmol/L). Additionally, analysis according to deciles suggests that the association between 25(OH)D and mortality is linear in the range from 0 to 120 nmol/L (Figure 2), and baseline 25(OH)D levels analyzed as a continuous and linear variable had a strong inverse association with mortality risk (hazard ratio (HR) = 0.95, 95% CI = 0.92–0.98 for every 10-nmol/L increase in 25(OH)D). The association between 25(OH)D and all-cause mortality was stronger in participants with diabetes mellitus at baseline than in those without (HRs = 0.86 and 0.96, respectively; P for interaction = 0.2). There was no other statistically significant interaction between covariates and the associations between 25(OH)D and all-cause or CVD mortality (data not shown).

**DISCUSSION**

This study demonstrated a significant inverse association between baseline serum 25(OH)D level and mortality risk in older adults. The association was strong (two time greater odds of mortality for 25(OH)D level < 25.0 nmol/L) and appeared linear within the range of the data and independent of demographic factors and other common CVD and mortality risk factors. Additional strengths of the study include the generalizability of this large, diverse, nationally representative sample, the robust measurement of covariates, and the quality of the mortality follow-up data.

These results are consistent with several recent reports that link vitamin D insufficiency with CVD, and all-cause mortality risk. The data add to
the existing literature in that the cohort already was at high risk for mortality, with an overall mortality rate of 44% during the median 7.3 years of follow-up. For instance, this rate was higher than recently reported (14% over median 8.7 years of follow-up\textsuperscript{23} and 23% over median 7.7 years of follow-up\textsuperscript{14}). A nested case-control study of hemodialysis patients, a group that is also at higher risk for mortality, with an overall mortality rate of 44%, found that lower baseline 25(OH)D levels were associated with higher 90-day mortality.\textsuperscript{24} Given the aging population, and that even a small reduction in mortality could have a substantial effect on public health, the potential importance of these findings is large. Additionally, a stronger association was found between vitamin D and all-cause mortality in older adults with diabetes mellitus than in those without.

These results differ from those reported previously\textsuperscript{25} in their more-general look at the NHANES III data for adults aged 20 and older. This age-specific difference may be related to higher prevalence of diabetes mellitus, vitamin D insufficiency, or mortality in the older cohort in the current study and requires further study.

The association between vitamin D and mortality was particularly robust in participants with baseline 25(OH)D levels less than 25.0 nmol/L and 25.0 to 49.9 nmol/L. Although these subgroups represented 26% of the current cohort, epidemiological data suggests that vitamin D insufficiency, or mortality in the older cohort in the current study and requires further study.

Table 1. Description of Baseline Characteristics According to Serum 25-Hydroxyvitamin D Levels in 3,408 Participants of the Third National Health and Nutrition Examination Survey Aged ≥65

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N = 3,408</th>
<th>&lt;25.0 n = 115</th>
<th>25.0–49.9 n = 904</th>
<th>50.0–74.9 n = 1,296</th>
<th>75.0–99.9 n = 775</th>
<th>≥100.0 n = 318</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>73 ± 0.2</td>
<td>76 ± 0.8</td>
<td>74 ± 0.4</td>
<td>74 ± 0.3</td>
<td>73 ± 0.3</td>
<td>72 ± 0.4</td>
<td>.001</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>56 (1.1)</td>
<td>84 (3.1)</td>
<td>71 (1.9)</td>
<td>56 (1.8)</td>
<td>45 (1.8)</td>
<td>40 (2.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
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<tr>
<td>Non-Hispanic white</td>
<td>87 (1.1)</td>
<td>67 (4.5)</td>
<td>77 (2.7)</td>
<td>89 (1.2)</td>
<td>90 (1.2)</td>
<td>95 (1.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>7 (1)</td>
<td>27 (4.7)</td>
<td>15 (1.8)</td>
<td>6 (0.7)</td>
<td>4 (0.6)</td>
<td>1 (nc)</td>
<td></td>
</tr>
<tr>
<td>Mexican American</td>
<td>2 (0.2)</td>
<td>4 (nc)</td>
<td>3 (0.4)</td>
<td>2 (0.2)</td>
<td>1 (0.3)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (0.6)</td>
<td>2 (nc)</td>
<td>5 (nc)</td>
<td>3 (0.8)</td>
<td>4 (nc)</td>
<td>3 (nc)</td>
<td></td>
</tr>
<tr>
<td>Poverty/income ratio, mean ± SD</td>
<td>3 ± 0.1</td>
<td>2 ± 0.3</td>
<td>3 ± 0.1</td>
<td>3 ± 0.1</td>
<td>3 ± 0.2</td>
<td>3 ± 0.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Season, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Winter (December to February)</td>
<td>13 (2.6)</td>
<td>24 (8.3)</td>
<td>15 (3.5)</td>
<td>11 (2.3)</td>
<td>13 (3.1)</td>
<td>10 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Spring (March to May)</td>
<td>23 (4.8)</td>
<td>30 (6.3)</td>
<td>25 (5.0)</td>
<td>22 (5.1)</td>
<td>21 (4.9)</td>
<td>22 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Summer (June to August)</td>
<td>34 (5.6)</td>
<td>23 (7.1)</td>
<td>31 (5.7)</td>
<td>36 (5.7)</td>
<td>34 (6.0)</td>
<td>35 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Fall (September to November)</td>
<td>30 (6.1)</td>
<td>24 (8.0)</td>
<td>28 (5.9)</td>
<td>30 (5.9)</td>
<td>32 (7.1)</td>
<td>32 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Region, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>Northeast</td>
<td>21 (2.1)</td>
<td>20 (4.8)</td>
<td>21 (2.5)</td>
<td>22 (2.3)</td>
<td>19 (2.7)</td>
<td>19 (3.9)</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>26 (2.9)</td>
<td>14 (3.0)</td>
<td>21 (3.0)</td>
<td>28 (3.2)</td>
<td>27 (3.1)</td>
<td>30 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>30 (3.4)</td>
<td>42 (7.7)</td>
<td>30 (4.0)</td>
<td>28 (3.5)</td>
<td>34 (4.2)</td>
<td>29 (4.5)</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>22 (4.8)</td>
<td>24 (4.9)</td>
<td>27 (6.4)</td>
<td>22 (4.7)</td>
<td>19 (4.1)</td>
<td>22 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m², mean ± SD</td>
<td>27 ± 0.1</td>
<td>26 ± 1.0</td>
<td>27 ± 0.3</td>
<td>27 ± 0.2</td>
<td>26 ± 0.2</td>
<td>26 ± 0.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical activity, metabolic equivalents, mean ± SD</td>
<td>97 ± 3.7</td>
<td>23 ± 6.3</td>
<td>71 ± 6.1</td>
<td>87 ± 4.1</td>
<td>120 ± 7.9</td>
<td>149 ± 12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.14</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>45 (1.1)</td>
<td>49 (6.4)</td>
<td>45 (3.3)</td>
<td>47 (1.7)</td>
<td>43 (2.5)</td>
<td>42 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>13 (0.9)</td>
<td>23 (6.6)</td>
<td>15 (1.9)</td>
<td>12 (1.4)</td>
<td>11 (1.3)</td>
<td>12 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>42 (1.4)</td>
<td>28 (5.6)</td>
<td>40 (3.6)</td>
<td>40 (1.9)</td>
<td>46 (2.3)</td>
<td>46 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Cigarette amount, pack years, mean ± SD</td>
<td>20 ± 0.8</td>
<td>21 ± 5.2</td>
<td>19 ± 1.7</td>
<td>20 ± 1.2</td>
<td>20 ± 1.5</td>
<td>23 ± 2.2</td>
<td>.28</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mL/min per 1.73 m², mean ± SD</td>
<td>73 ± 0.5</td>
<td>74 ± 3.9</td>
<td>72 ± 1.0</td>
<td>74 ± 0.7</td>
<td>72 ± 0.9</td>
<td>71 ± 1.2</td>
<td>.38</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>66 (1.1)</td>
<td>80 (4.6)</td>
<td>70 (1.6)</td>
<td>66 (1.4)</td>
<td>63 (2.3)</td>
<td>62 (3.9)</td>
<td>.02</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>15 (1.0)</td>
<td>28 (7.1)</td>
<td>22 (2.1)</td>
<td>15 (1.4)</td>
<td>11 (1.4)</td>
<td>9 (1.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>67 (1.6)</td>
<td>60 (6.5)</td>
<td>66 (3.4)</td>
<td>67 (1.9)</td>
<td>69 (2.1)</td>
<td>68 (3.5)</td>
<td>.65</td>
</tr>
<tr>
<td>History of myocardial infarction, n (%)</td>
<td>12 (1.0)</td>
<td>15 (nc)</td>
<td>12 (1.6)</td>
<td>12 (1.6)</td>
<td>14 (1.4)</td>
<td>10 (2.1)</td>
<td>.59</td>
</tr>
<tr>
<td>History of stroke, n (%)</td>
<td>7 (0.6)</td>
<td>16 (nc)</td>
<td>9 (1.4)</td>
<td>6 (0.9)</td>
<td>7 (1.0)</td>
<td>6 (nc)</td>
<td>.02</td>
</tr>
<tr>
<td>History of cancer, n (%)</td>
<td>10 (0.7)</td>
<td>16 (nc)</td>
<td>9 (1.4)</td>
<td>9 (1.1)</td>
<td>12 (1.7)</td>
<td>8 (1.6)</td>
<td>.20</td>
</tr>
<tr>
<td>Asthma, n (%)</td>
<td>5 (0.4)</td>
<td>7 (nc)</td>
<td>4 (0.7)</td>
<td>5 (0.9)</td>
<td>5 (1.1)</td>
<td>4 (nc)</td>
<td>.58</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n (%)</td>
<td>13 (0.8)</td>
<td>14 (nc)</td>
<td>14 (2.0)</td>
<td>13 (1.2)</td>
<td>11 (1.7)</td>
<td>15 (2.6)</td>
<td>.80</td>
</tr>
</tbody>
</table>

SD = standard deviation; nc = not calculable because of fewer than 30 observations.
increased from 2% during 1988 to 1994 to 6% during 2001 to 2004. Similarly, the percentage of adults with levels of 25.0 to 49.9 nmol/L increased from 24% to 30%. Because exposure to UVB rays is the primary determinant of vitamin D status in humans, it is likely that decreases in outdoor physical activity and widespread campaigns for sunscreen use have contributed to the recently observed population increase in vitamin D insufficiency. Thus, it is

### Table 2. Unadjusted Risk of All-Cause, Cardiovascular, and Noncardiovascular Mortality During Median 7.3 Years of Follow-Up in 3,408 Participants of the Third National Health and Nutrition Examination Survey Aged ≥65 According to Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All-Cause (n = 1,493)</th>
<th>Cardiovascular (n = 767)</th>
<th>Noncardiovascular (n = 726)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum 25-hydroxyvitamin D, nmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25.0</td>
<td>2.50 (1.64–3.80)</td>
<td>3.08 (1.72–5.52)</td>
<td>2.02 (1.11–3.66)</td>
</tr>
<tr>
<td>25.0–49.9</td>
<td>1.51 (1.14–2.00)</td>
<td>1.62 (1.08–2.42)</td>
<td>1.42 (0.98–2.07)</td>
</tr>
<tr>
<td>50.0–74.9</td>
<td>1.24 (0.95–1.62)</td>
<td>1.37 (0.92–2.03)</td>
<td>1.13 (0.79–1.61)</td>
</tr>
<tr>
<td>75.0–99.9</td>
<td>1.24 (0.93–1.65)</td>
<td>1.36 (0.89–2.07)</td>
<td>1.13 (0.78–1.65)</td>
</tr>
<tr>
<td>≥100.0</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Age, per year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.09 (1.08–1.10)</td>
<td>1.11 (1.09–1.13)</td>
<td>1.08 (1.06–1.09)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.72 (0.62–0.83)</td>
<td>0.70 (0.57–0.86)</td>
<td>0.73 (0.60–0.90)</td>
</tr>
<tr>
<td>Race or ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>1.17 (1.00–1.37)</td>
<td>1.10 (0.88–1.37)</td>
<td>1.24 (0.99–1.54)</td>
</tr>
<tr>
<td>Mexican American</td>
<td>0.83 (0.68–1.02)</td>
<td>0.78 (0.60–1.02)</td>
<td>0.89 (0.67–1.17)</td>
</tr>
<tr>
<td>Other</td>
<td>0.64 (0.39–1.05)</td>
<td>0.61 (0.30–1.22)</td>
<td>0.68 (0.35–1.31)</td>
</tr>
<tr>
<td>Poverty:income ratio, per unit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.86 (0.82–0.91)</td>
<td>0.88 (0.81–0.94)</td>
<td>0.85 (0.79–0.90)</td>
<td></td>
</tr>
<tr>
<td>Season of enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winter (December to February)</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Spring (March to May)</td>
<td>0.92 (0.72–1.18)</td>
<td>1.20 (0.85–1.71)</td>
<td>0.73 (0.52–1.02)</td>
</tr>
<tr>
<td>Summer (June to August)</td>
<td>0.90 (0.71–1.14)</td>
<td>1.13 (0.82–1.57)</td>
<td>0.74 (0.54–1.02)</td>
</tr>
<tr>
<td>Fall (September to November)</td>
<td>0.94 (0.75–1.18)</td>
<td>1.16 (0.84–1.60)</td>
<td>0.79 (0.58–1.08)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>South</td>
<td>1.12 (0.88–1.41)</td>
<td>0.98 (0.72–1.34)</td>
<td>1.27 (0.92–1.77)</td>
</tr>
<tr>
<td>Midwest</td>
<td>1.17 (0.95–1.45)</td>
<td>0.99 (0.75–1.31)</td>
<td>1.39 (1.03–1.89)</td>
</tr>
<tr>
<td>West</td>
<td>1.09 (0.85–1.41)</td>
<td>1.10 (0.78–1.55)</td>
<td>1.08 (0.75–1.56)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20.0</td>
<td>1.72 (1.27–2.33)</td>
<td>1.60 (1.08–2.39)</td>
<td>1.82 (1.22–2.73)</td>
</tr>
<tr>
<td>20.0–24.9</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>0.91 (0.77–1.08)</td>
<td>1.00 (0.79–1.27)</td>
<td>0.83 (0.65–1.05)</td>
</tr>
<tr>
<td>≥30.0</td>
<td>0.68 (0.55–0.84)</td>
<td>0.75 (0.55–1.02)</td>
<td>0.62 (0.46–0.83)</td>
</tr>
<tr>
<td>Physical activity per 10 metabolic equivalents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.98 (0.97–0.99)</td>
<td>0.99 (0.98–1.00)</td>
<td>0.98 (0.97–0.99)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.58 (1.27–1.96)</td>
<td>1.05 (0.77–1.45)</td>
<td>2.27 (1.71–3.03)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1.30 (1.11–1.53)</td>
<td>1.08 (0.86–1.34)</td>
<td>1.59 (1.27–1.99)</td>
</tr>
<tr>
<td>Cigarettes per 10 pack-years</td>
<td>1.05 (1.03–1.07)</td>
<td>1.03 (1.01–1.06)</td>
<td>1.07 (1.04–1.09)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate per 10 mL/min per 1.73 m²</td>
<td>0.85 (0.81–0.89)</td>
<td>0.80 (0.74–0.85)</td>
<td>0.91 (0.85–0.97)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.16 (0.99–1.37)</td>
<td>1.35 (1.07–1.71)</td>
<td>1.01 (0.81–1.26)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.68 (1.39–2.03)</td>
<td>1.86 (1.46–2.38)</td>
<td>1.51 (1.16–1.96)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.85 (0.73–0.99)</td>
<td>0.96 (0.78–1.19)</td>
<td>0.76 (0.61–0.94)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>2.09 (1.72–2.54)</td>
<td>3.03 (2.39–3.85)</td>
<td>1.29 (0.93–1.78)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>2.19 (1.78–2.69)</td>
<td>2.56 (1.94–3.37)</td>
<td>1.83 (1.31–2.57)</td>
</tr>
<tr>
<td>History of cancer</td>
<td>1.31 (1.04–1.65)</td>
<td>1.18 (0.85–1.64)</td>
<td>1.44 (1.06–1.96)</td>
</tr>
<tr>
<td>Asthma</td>
<td>1.36 (0.97–1.90)</td>
<td>1.07 (0.63–1.81)</td>
<td>1.73 (1.10–2.47)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1.52 (1.22–1.88)</td>
<td>1.31 (0.97–1.77)</td>
<td>1.73 (1.30–2.30)</td>
</tr>
</tbody>
</table>

Bold values denote $P < .05$.  

increased from 2% during 1988 to 1994 to 6% during 2001 to 2004. Similarly, the percentage of adults with levels of 25.0 to 49.9 nmol/L increased from 24% to 30%. Because exposure to UVB rays is the primary determinant of vitamin D status in humans, it is likely that decreases in outdoor physical activity and widespread campaigns for sunscreen use have contributed to the recently observed population increase in vitamin D insufficiency. Thus, it is
likely that more than one-third of older adults now have 25(OH)D levels of less than 50.0 nmol/L, which is associated with higher risk for mortality, and few have levels of 100.0 nmol/L or greater, which is associated with the lowest risk for mortality.

CVD mortality, the leading cause of death in the United States, appeared to be the primary cause of the greater risk for all-cause mortality. Early epidemiological studies suggested associations between CVD and markers of lower vitamin D status, including winter season, higher latitudes, lower altitudes, older age, and darker skin pigmentation. Several mechanisms for the protective effect of vitamin D against CVD have been proposed, including beneficial changes in cardiac function, blood pressure, arterial function, and inflammatory processes. For example, vitamin D may suppress the renin-angiotensin system and matrix metalloproteinases, which are important in blood pressure control and arterial wall compliance, respectively. Additionally, other epidemiological studies have found associations between lower serum 25(OH)D levels and other cardiovascular risk factors, including diabetes mellitus and metabolic syndrome. Although it is likely that CVD is the major component of the inverse association between vitamin D and mortality, it has been suggested that vitamin D may also have a beneficial effect on cancer and infection which are also important contributors to all-cause mortality, although the current study was underpowered to individually assess these cause-specific mortality outcomes.

The present study raises additional concerns about current recommendations for vitamin D supplementation (200–600 IU/d), which are inadequate for most older U.S. adults to achieve serum 25(OH)D levels greater than 75.0 to 100.0 nmol/L, the levels that are associated with optimal general health and lower mortality. For instance, 400 IU or 800 IU per day would raise 25(OH)D levels by only approximately 11 or 22 nmol/L, respectively, which would be inadequate for many older adults based on the current analysis. The only clinical trial of vitamin D in the general U.S. population, the Women’s Health Study, failed to detect any effect of vitamin D and calcium supplementation on CVD mortality and morbidity, although that study used a low-dose vitamin D supplementation (400 IU/d) and had several methodological concerns. A recent meta-analysis of 18 randomized controlled trials on bone health found that vitamin D supplementation of 400 to 800 IU per day reduced all-cause mortality by 7% (95% CI = 1–13%), mostly due to CVD and infection-related mortality. Higher dose supplementation (e.g., 3000 IU/d), which may be given safely in monthly dosing, is more likely to raise serum 25(OH)D levels above 100.0 nmol/L in older U.S. adults and thus may have more-impressive effects on CVD and all-cause mortality.

There are several potential limitations to this study. Serum was collected at only one point in time and preferentially collected in northern states in the summer and southern states in the winter, although age and season were controlled for, which limits the potential for biased

Table 3. Risk of All-Cause and Cause-Specific Mortality According to Serum 25-Hydroxyvitamin D Level in 3,408 Older Adult Participants of the Third National Health and Nutrition Examination Survey

<table>
<thead>
<tr>
<th>Cause of Mortality</th>
<th>Model 1 (n = 3,408)</th>
<th>Model 2 (n = 3,303)</th>
<th>Model 3 (n = 3,265)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause (n = 1,483)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25.0 nmol/L</td>
<td>2.28 (1.44–3.59)</td>
<td>2.19 (1.34–3.55)</td>
<td>1.83 (1.14–2.94)</td>
</tr>
<tr>
<td>25.0–49.9 nmol/L</td>
<td>1.63 (1.24–2.15)</td>
<td>1.61 (1.21–2.16)</td>
<td>1.47 (1.09–1.97)</td>
</tr>
<tr>
<td>50.0–74.9 nmol/L</td>
<td>1.23 (0.95–1.60)</td>
<td>1.26 (0.96–1.66)</td>
<td>1.21 (0.92–1.59)</td>
</tr>
<tr>
<td>75.0–99.9 nmol/L</td>
<td>1.19 (0.91–1.57)</td>
<td>1.24 (0.93–1.64)</td>
<td>1.15 (0.86–1.53)</td>
</tr>
<tr>
<td>≥100.0 nmol/L</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Cardiovascular related (n = 767)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25.0 nmol/L</td>
<td>2.81 (1.48–5.32)</td>
<td>2.97 (1.53–5.78)</td>
<td>2.36 (1.17–4.75)</td>
</tr>
<tr>
<td>25.0–49.9 nmol/L</td>
<td>1.74 (1.16–2.63)</td>
<td>1.76 (1.16–2.68)</td>
<td>1.54 (1.01–2.34)</td>
</tr>
<tr>
<td>50.0–74.9 nmol/L</td>
<td>1.34 (0.91–1.99)</td>
<td>1.37 (0.92–2.04)</td>
<td>1.26 (0.85–1.88)</td>
</tr>
<tr>
<td>75.0–99.9 nmol/L</td>
<td>1.30 (0.86–1.96)</td>
<td>1.34 (0.88–2.02)</td>
<td>1.20 (0.79–1.81)</td>
</tr>
<tr>
<td>100.0 nmol/L</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Noncardiovascular (n = 726)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25.0 nmol/L</td>
<td>1.83 (0.97–3.45)</td>
<td>1.62 (0.82–3.18)</td>
<td>1.42 (0.73–2.79)</td>
</tr>
<tr>
<td>25.0–49.9 nmol/L</td>
<td>1.53 (1.04–2.24)</td>
<td>1.49 (0.99–2.24)</td>
<td>1.42 (0.94–2.13)</td>
</tr>
<tr>
<td>50.0–74.9 nmol/L</td>
<td>1.13 (0.80–1.60)</td>
<td>1.17 (0.81–1.71)</td>
<td>1.16 (0.79–1.68)</td>
</tr>
<tr>
<td>75.0–99.9 nmol/L</td>
<td>1.10 (0.76–1.59)</td>
<td>1.17 (0.79–1.72)</td>
<td>1.11 (0.75–1.63)</td>
</tr>
<tr>
<td>100.0 nmol/L</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
</tbody>
</table>

Model 1: age, sex, race/ethnicity, and season.
Model 2 (+ confounders): Model 1 plus poverty-income ratio, region, body mass index, physical activity, smoking status, cigarette pack years, asthma, chronic obstructive pulmonary disease, and renal function.
Model 3 (+ intermediates): Model 2 plus hypertension, diabetes mellitus, hyperlipidemia, history of myocardial infarction, history of stroke, and history of cancer (nonskin).
Bold values denote P < .05.
results. This prospective cohort was an observational study; thus, the causality of the association between vitamin D and mortality requires further study. The study attempted to address this shortcoming by controlling for known confounders, but unmeasured confounding could exist. For instance, although common conditions associated with CVD and mortality were adjusted for, lower 25(OH)D levels may be a nonspecific marker of poor general health, and thus, vitamin D insufficiency may identify individuals who are less likely to go outdoors and produce vitamin D from sunlight exposure. Large randomized controlled trials of vitamin D supplementation are required to enhance causal inference. Finally, it was not possible to evaluate individual non-CVD mortality causes of mortality (e.g., cancer, infection) because of limited statistical power.

In summary, in noninstitutionalized older adults, a group at high risk for mortality, baseline serum 25(OH)D levels had an independent, inverse association with CVD and all-cause mortality. Individuals with baseline 25(OH)D levels less than 50.0 nmol/L appear to be at highest risk for mortality, but levels of 100.0 nmol/L or greater may be necessary for better survival. Current dosage recommendations for vitamin D supplementation appear to be inadequate in most older adults to support these higher 25(OH)D levels that are associated with optimal general health and reduced mortality. Randomized controlled trials of higher-dose vitamin D supplementation in older adults are warranted to determine whether this association is causal and reversible.

ACKNOWLEDGMENTS
Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.
Dr. Ginde was supported by the University of Colorado Denver Hartford/Fajnhagen Center of Excellence in Geriatrics and National Institutes of Health (NIH) Grant KL2 RR025779. Dr. Scragg was supported by the Health Research Council of New Zealand. Dr. Schwartz was supported by NIH Grants R01 AG019339 and R01 AG028746. Dr. Camargo was supported by the Massachusetts General Hospital Center for D-receptor Activation Research and NIH Grant R01 HL84401.

**Author Contributions:** Dr. Ginde had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Ginde, Camargo. Acquisition of data: Ginde. Analysis and interpretation of data: Ginde, Scragg, Schwartz, Camargo. Preparation of the manuscript: Ginde. Critical revision of the manuscript for important intellectual content: Ginde, Scragg, Schwartz, Camargo. Statistical analysis: Ginde.

**Sponsor's Role:** The sponsors had no role in the design, methods, analysis, or preparation of the manuscript.

**REFERENCES**


