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## Lung function, 25-hydroxyvitamin D concentrations and mortality in US adults

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### Abstract

**OBJECTIVE**—To explore the associations between serum concentrations of vitamin D (25(OH)D) and all-cause mortality among US adults defined by lung function (LF) status, particularly among adults with obstructive LF (OLF).

**METHODS**—Data from 10 795 adults aged 20–79 years (685 with restrictive LF (RLF) and 1309 with OLF) who participated in the Third National Health and Nutrition Examination Survey (1988–1994), had a spirometric examination, and were followed through 2006 were included.

**RESULTS**—During 14.2 years of follow-up, 1792 participants died. Mean adjusted concentrations of 25(OH)D were 75.0 nmol/l (s.e. 0.7) for adults with normal LF (NLF), 70.4 nmol/l (s.e. 1.8) for adults with RLF, 75.5 nmol/l (s.e. 1.5) for adults with mild obstruction and 71.0 nmol/l (s.e. 1.9) among adults with moderate or worse obstruction ( $P = 0.030$ ). After adjustment for sociodemographic factors, lifestyle factors, clinical variables and prevalent chronic conditions, a concentration of <25 nmol/l compared with 75 nmol/l was associated with mortality only among adults with NLF (hazard ratio (HR) 1.76; 95% confidence interval (CI) 1.03, 3.00). Among participants with OLF, adjusted HRs were 0.65 (95% CI 0.29, 1.48), 1.21 (95% CI 0.89, 1.66) and 0.97 (95% CI 0.78, 1.19) among those with concentrations <25, 25–<50 and 50–<75 nmol/l, respectively.

**CONCLUSIONS**—Baseline concentrations of 25(OH)D did not significantly predict mortality among US adults with impaired LF.

### INTRODUCTION

Chronic obstructive pulmonary disease is a major source of morbidity and mortality in the United States.<sup>1</sup> In 2011, 6.3% of adults reported having chronic obstructive pulmonary disease.<sup>2</sup> In 2010, 10.3 million outpatient visits for chronic obstructive pulmonary disease were made, 1.5 million visits to emergency department were made, and almost 700 000 hospital discharges were recorded.<sup>1</sup> In 2008, chronic lower respiratory disease became the third leading cause of death.<sup>3</sup> Because adults with chronic obstructive pulmonary disease are

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#### CONFLICT OF INTEREST

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at increased risk for mortality from all-causes and cardiovascular disease,<sup>4-7</sup> identifying potential approaches to lessen mortality among adults with chronic obstructive pulmonary disease is of clinical and public health relevance.

Trials of supplementation with vitamin D have yielded mixed evidence of its effects on all-cause mortality and incidence and mortality from cardiovascular disease.<sup>8-15</sup> A recent review of systematic reviews and meta-analyses concluded that the relationships between concentrations of vitamin D, supplementation with vitamin D, and a range of health outcomes remain largely clouded in uncertainty.<sup>16</sup> Nevertheless, adequate vitamin D status may lessen the risk for developing respiratory infections, a finding that may be especially relevant to people with chronic obstructive pulmonary disease among whom exacerbations, often due to respiratory infections, adversely affect their clinical course as manifested by increased morbidity and mortality.<sup>17-24</sup> Vitamin D has anti-inflammatory, anti-infectious and immunomodulating properties that are potentially highly relevant in the setting of chronic obstructive pulmonary disease, a disease commonly triggered by environmental exposures and infectious agents and characterized by inflammation, oxidative stress and exacerbations due to respiratory infections.<sup>25</sup>

These considerations suggested that circulating concentrations of vitamin D could be inversely related to all-cause mortality among adults with evidence of obstructive airways disease on pulmonary function testing. However, this domain of research remains largely unexplored although recently several studies have failed to show that concentrations of 25(OH)D predicted mortality in patients with chronic obstructive pulmonary disease.<sup>26-28</sup> Thus, the objective of this study was to examine the prospective association between circulating concentrations of vitamin D (25 (OH)D) and all-cause mortality in a national sample of adults with obstructive lung function (LF). Secondary objectives included examining the prospective association between circulating concentrations of 25(OH)D and all-cause mortality among adults with restrictive LF (RLF) and among all participants.

## MATERIALS AND METHODS

This study used public use data from the Third National Health and Nutrition Examination Survey (NHANES III) Linked Mortality Study (baseline examination from 1988 through 1994; follow-up through 2006).<sup>29</sup> A stratified multistage probability sample was used to select a sample that was representative of the civilian non-institutionalized population in the United States. After agreeing to participate in the survey, participants were interviewed in their homes. Those who accepted an invitation to have an examination completed additional questionnaires, underwent a series of examinations, and provided blood and urine specimens in the mobile examination center. The interview and examination response rates were 86 and 78%, respectively. NHANES III received Institutional Review Board Approval.

Deaths were identified through a probabilistic match of participants' information with National Death Index death certificate records. Participants whose attempted match did not lead to the identification of a death were considered to be alive.

A pulmonary function test was administered to adults, and no post-bronchodilator testing was performed. A detailed description of the procedures used to conduct spirometry can be found elsewhere.<sup>30</sup> Borrowing from the GOLD (Global Initiative for Chronic Obstructive Lung Disease classification), four categories of LF were established: normal LF (NLF), RLF (forced expiratory volume in one second (FEV<sub>1</sub>)/forced vital capacity (FVC)  $\geq 0.70$  and FVC  $\geq 80\%$  predicted), mild obstructive LF (OLF) (FEV<sub>1</sub>/FVC  $< 0.70$  and FEV<sub>1</sub>  $\geq 80\%$ ), moderate OLF (FEV<sub>1</sub>/FVC  $< 0.70$  and FEV<sub>1</sub> 50 to  $< 80\%$  predicted) and severe OLF (FEV<sub>1</sub>/FVC  $< 0.70$  and FEV<sub>1</sub>  $< 50\%$  predicted). To increase sample size, participants with moderate or severe OLF were combined for some descriptive analyses of concentrations of 25(OH)D, and participants with any OLF were combined for analyses involving estimation of risk for mortality.

Serum concentrations of 25-hydroxyvitamin D or 25(OH)D were measured using a radioimmunoassay method (DiaSorin, Stillwater, MN, USA).<sup>16</sup> Details about the methods including quality control procedures and results can be found elsewhere.<sup>31</sup> For some analyses, 25(OH)D was classified into four categories  $< 25$ , 25– $< 50$ , 50– $< 75$  and  $\geq 75$  nmol/l.<sup>32</sup> In addition, concentrations of 25(OH)D were categorized into three categories  $< 30$ , 30– $< 50$  and  $\geq 50$  nmol/l.<sup>33</sup>

Covariates included age, gender, self-reported race or ethnicity (white, African American and other), educational level, smoking status, alcohol use, leisure-time physical activity, use of vitamin or mineral supplements, systolic blood pressure, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, body mass index, C-reactive protein, urinary albumin-creatinine ratio, health status, diabetes and histories of myocardial infarction and stroke.

Three categories of smoking status were established: current smokers (participants who had smoked  $\geq 100$  cigarettes during their lifetime and were still smoking), former smokers (participants who had smoked  $\geq 100$  cigarettes during their lifetime but had stopped) and never having smoked (participants who had smoked  $< 100$  cigarettes during their lifetime were classified as having never smoked). The frequency of alcohol consumption was estimated from answers to questions about the number of times per month a participant had consumed beer, wine, or spirits. Four levels of physical activity were defined: vigorous activity (participating three or more times per week in an activity with a metabolic equivalent level of  $\geq 6$  for participants who were 60 years or older and  $\geq 7$  metabolic equivalents for participants who were younger than 60 years), moderate activity (participating five or more times per week in activities of which no more than two could be considered vigorous activities), light activity (participation that was not vigorous or moderate), and sedentary (engaging in no leisure-time physical activity). The use of vitamins or minerals was assessed with the question ‘Have you taken any vitamins or minerals in the past month?’

The average of the second and third systolic blood pressure measurement was used in the analyses. Measured weight and height was used to calculate body mass index (weight in kilograms divided by height in meters squared). Following the precipitation of other lipoproteins with a heparin-manganese chloride mixture, concentrations of high-density

lipoprotein cholesterol were measured on a Hitachi 704 Analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN, USA). Concentrations of non-high-density lipoprotein cholesterol were calculated by subtracting the concentration of high-density lipoprotein cholesterol from that of total cholesterol. Serum C-reactive protein was measured by using latex-enhanced nephelometry on a Behring Nephelometer Analyzer System (BNA) (Behring Diagnostics Inc., Somerville, NJ, USA). Urinary albumin was measured on a Sequoia-Turner Fluoremeter (Sequoia-Turner Corp., Mountain View, CA, USA) with a fluorescent immunoassay. Urinary creatinine was measured on a Beckman Synchron AS/ASTRA clinical analyzer (Beckman Instruments Inc., Brea, CA, USA).

Health status was assessed with the question 'Would you say your health in general is excellent, very good, good, fair or poor?'. Diabetes was defined as a positive response to the question 'Have you ever been told by a doctor that you have diabetes or sugar diabetes?' or a concentration of HbA1c  $\geq 6.5\%$ . Positive responses to the questions 'Has a doctor ever told you that you had a heart attack?'; and 'Has a doctor ever told you that you had a stroke?' were used to identify participants with histories of myocardial infarction or stroke, respectively.

The analyses were limited to men and non-pregnant women aged 20–79 years who had a spirometric examination in the mobile examination center and reproducible FEV1 and FVC results. Participants with self-reported asthma were excluded ('Has a doctor ever told you that you had asthma?'). Mortality rates per 1000 person-years of survival time were calculated. Age adjustment was done to the projected year 2000 US population for adults aged 20–79 years using the direct method. Least-square adjusted mean concentrations of 25(OH)D by categories of LF status were calculated, and *P*-values for differences in concentrations were estimated from linear regression results. Proportional hazards analysis was used to estimate hazard ratios (HRs) for mortality according to categories of 25(OH)D concentrations for the entire sample and for groups stratified by LF status. Analyses were conducted in SAS and SUDAAN, the latter to account for the complex sampling design of the surveys.

## RESULTS

Of the 15 331 participants aged 20–79 years, 10 were ineligible because information needed to determine their follow-up status was not available. Eliminating pregnant women reduced the sample size to 15 033. Limiting the sample to participants with acceptable spirometric maneuvers left 13 134 participants, a number that was further reduced to 12 235 after excluding participants with self-reported asthma. Additional reductions due to participants with missing information for other study variables resulted in an analytic sample of 10 795 participants.

The analytic sample included 5263 men, 5532 women, 4348 whites, 2908 African Americans, 3112 Mexican Americans and 427 of another race or ethnicity. Overall, 79.9% (s.e. 0.6) had NLF, 6.5% (s.e. 0.4) had RLF and 13.6% (s.e. 0.6) had OLF. The mean concentration of 25(OH)D was 74.5 nmol/l, and the median concentration was 71.6 nmol/l.

The mean and median lengths of follow-up were 14.2 and 14.5 years, respectively. In all, 1792 participants died (1012 of 8801 adults with normal pulmonary function, 208 of 685 adults with an RLF and 572 of 1309 adults with any OLF).

Numerous differences of means and percentages of study variables were present between survivors and decedents (Table 1). However, the age-adjusted means of concentrations of 25(OH)D did not differ significantly. In addition, numerous differences in study variables among the three groups of respiratory function status were present.

### **25(OH)D concentrations and pulmonary function status**

Adjusted mean concentrations of 25(OH)D in participants with RLF were significantly lower than that of persons with normal function ( $P = 0.016$ ) (Table 2). However adjusted mean concentrations among those with moderate–severe ( $P = 0.043$ ) but not mild ( $P = 0.736$ ) OLF differed significantly from mean concentrations of participants with normal pulmonary function. The age-adjusted percentages of 25(OH)D deficiency (<50 nmol/l) for the four groups were 20.7% (s.e. 1.1) for participants with normal pulmonary function, 32.1% (s.e. 2.8) for participants with RLF, 16.6% (s.e. 2.8) for participants with mild OLF and 20.8% (s.e. 3.3) for participants with moderate–severe OLF. The percentage of 25(OH)D deficiency among participants with RLF was significantly higher compared with each of the three other categories (all  $P < 0.050$ ). Using a threshold for 25(OH)D deficiency of <30 nmol/l, 3.2% (s.e. 0.3) of participants with normal LF, 6.0% (s.e. 1.4) of participants with restrictive LF, 4.6% (s.e. 1.5) of participants with mild OLF and 3.0% (s.e. 0.8) of participants with moderate or worse OLF were considered as deficient. No significant differences among these estimates were observed.

### **25(OH)D concentrations and mortality among all participants**

In models adjusted for sociodemographic variables, concentrations of 25(OH)D as a 4-level variable were significantly associated with all-cause mortality (Table 3). In the fully adjusted model, however, concentrations of 25(OH)D lost statistical significance ( $P$ -adjusted Wald  $F$  test = 0.179). In models using 25(OH)D as a 3-level variable, 25(OH)D was significantly associated with mortality in all models (Table 4). Concentrations of 25(OH)D modeled as a continuous variable were not significantly associated with mortality ( $P$ -adjusted Wald  $F$  = 0.268), but the squared term for concentrations of 25(OH)D was significant ( $P$ -adjusted Wald  $F$  = 0.011) suggesting a non-linear association (Supplementary Table 1).

### **25(OH)D and mortality by pulmonary function status**

Among participants with normal pulmonary function, a significant association between 25(OH)D and mortality was noted for the first two models (Table 3). In the fully adjusted model, an elevated and significant HR was noted for participants with a concentration of 25(OH)D <25 nmol/l compared with those with a concentration of 75 nmol/l only among those with NLF (adjusted HR (aHR) = 1.76; 95% confidence interval (CI): 1.03, 3.00) although the  $P$ -value for the global test for the 25(OH)D terms was 0.226. When the analyses were repeated using three categories, participants with a concentration of <30 nmol/l had an elevated HR compared with those with a concentration of 50 nmol/l

(adjusted HR = 1.63, 95% CI 1.03, 2.58) (Table 4). Among participants with either OLF or RLF, there was no evidence to suggest that a concentration of 25(OH)D <50 or <30 nmol/L was significantly associated with mortality (Tables 3 and 4). No interaction between pulmonary function status and concentrations of 25(OH)D as the 4-category variable ( $P$  interaction = 0.464) or as the 3-category variable ( $P$  interaction = 0.756) was noted. Results for models in which 25(OH)D was modeled as a continuous variable are presented in Supplementary Table 1.

## DISCUSSION

In this cohort, baseline mean concentrations of 25(OH)D were significantly lower among participants with RLF and moderate or worse OLF than among participants with NLF or mild OLF. Furthermore, concentrations of 25(OH)D <25 nmol/l compared with 75 nmol/l among adults with an NLF, but not those with impaired LF, were significantly associated with mortality. Because limited information about possible health benefits of adequate vitamin D status in adults with OLF is available, the results of the present study add to a meager evidence base in an area of growing interest.

Several previous analyses of the relationship between concentrations of 25(OH)D and mortality using NHANES III data have been conducted.<sup>34–36</sup> In an analysis of 13 331 adults aged 20 years with mortality through the year 2000, those in the lowest quartile of 25(OH)D were at slightly increased risk of death (aHR 1.26, 95% CI: 1.08–1.46).<sup>34</sup> These results were adjusted for age, sex, race, season, hypertension, history of CVD, diabetes mellitus, smoking, body mass index, high-density lipoprotein cholesterol, total cholesterol, the use of cholesterol-lowering medications, estimated glomerular filtration rate categories, serum albumin level, log urinary albumin-to-creatinine ratio, C-reactive protein, physical activity level, vitamin supplementation and low socioeconomic status. A subsequent analysis limited to 3408 adults aged 65 years reported a significant inverse association between 25(OH)D and all-cause mortality (aHR 0.95 per 10 nmol/l, 95% CI: 0.92–0.98). The follow-up was also conducted through the year 2000.<sup>35</sup> More recently, another analysis of 13 131 participants aged 35–74 years with mortality followed through 2006 found an elevated risk for mortality among participants with concentrations of <20 ng/ml compared with those with a concentration of 30 ng/ml (aHR 1.40, 95% CI: 1.17–1.68).<sup>36</sup> The model was adjusted for age, gender, race or ethnicity, marital status, education, smoking status, alcohol intake, physical activity, body mass index and diabetes. The results of the present study among adults with NLF are broadly consistent with the latter publication.

Although reasons to suspect that adequate vitamin D concentrations could be particularly beneficial in adults with chronic obstructive pulmonary disease or OLF, no evidence in the present study was observed suggesting that adequate concentrations of 25(OH)D had a beneficial effect on the mortality experience of adults with OLF. In fact, the magnitude of the HR in this group was smaller than the HR for adults with normal pulmonary function although there was no statistical evidence that the associations differed among the three groups of pulmonary function. These results are consistent with findings from three other observational studies with durations of follow-up ranging from 2 to 10 years that failed to find significant associations between concentrations of 25(OH)D and mortality.<sup>26–28</sup> Also, a

clinical trial among patients with chronic obstructive pulmonary disease did not show that vitamin D supplementation lowered 1-year mortality.<sup>37</sup> Furthermore, concentrations of 25(OH)D have not been shown to be significantly associated with exacerbations.<sup>27,37–39</sup>

Researchers continue to investigate how vitamin D status may influence respiratory health. Several mechanisms have been proposed to explain potential links between vitamin D concentrations and chronic obstructive pulmonary disease and include effects of vitamin D on calcium homeostasis, host defense of the airways, extracellular matrix, and muscle strength.<sup>25,40,41</sup> Previous research has demonstrated a high prevalence of vitamin D deficiency among patients with chronic obstructive pulmonary disease as well as associations between concentrations of vitamin D and pulmonary function test parameters such as FEV1 and FVC. For example, a previous analysis of data from NHANES III showed that concentrations of 25(OH)D were directly associated with FEV1 and FVC.<sup>42</sup> However, the authors did not apply a GOLD-like classification to these data. Thus, the current study approached the question of a possible association between concentrations of 25(OH)D and pulmonary function from a different perspective. In a study of adults aged 59–73 years in the United Kingdom, serum concentrations of 25(OH)D were not significantly associated with FEV1, FVC and FEV1/FVC but were significantly associated with spirometrically defined chronic obstructive pulmonary disease.<sup>43</sup> Previous research has shown that with increasing severity of chronic obstructive pulmonary disease, vitamin D deficiency may increase.<sup>44</sup> Because of the small number of adults with severe OLF in the present study, an analysis of the association between concentrations of 25(OH)D and mortality in adults with more severe forms of OLF was not feasible.

Several limitations deserve consideration. First, sample sizes for the groups of participants with RLF and OLF were considerably smaller than the sample size for participants with normal pulmonary function. Despite these smaller sample sizes, the numbers of deaths were substantial and should have been adequate for showing a modest association. Second, no post-bronchodilator spirometry was performed and thus the sample of participants with OLF also contains some percentage of participants with asthma. The exclusion of participants with self-reported asthma should have reduced the possible effects on the analyses of such participants. Third, the debate about recommended spirometric criteria for detecting OLF in the elderly continues. Any misclassification of elderly participants with respect to their LF status could have conceivably affected the results. Fourth, only a single determination of concentrations of 25(OH)D was done, but most cohort studies examining health outcomes have been performed using a single measurement. Measurements of concentrations of 25(OH)D have shown good reproducibility over periods ranging up to 3 years.<sup>45–47</sup> Fifth, although this analysis adjusted for a large number of possible confounders, residual confounding remains a possibility.

In conclusion, this analysis of NHANES III data found no support for the hypothesis that adequate concentrations of 25(OH)D might favorably impact mortality among adults with impaired LF. Sample sizes of studies reporting on the association between concentrations of 25(OH)D and mortality in adults with OLF are limited, and hence additional studies are needed. Because vitamin D status has been linked to a host of adverse health outcomes,

characterizing the full spectrum of possible links between vitamin D status and morbidity and mortality among people with impaired LF warrants continued scientific pursuit.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Age-adjusted baseline means (standard errors) and percentages (standard errors) of study variables among adults aged 20–79 years, by mortality status and by pulmonary function status, National Health and Nutrition Examination Survey III (1988–1994)

Table 1

	Mortality status		P-value	Pulmonary function status			P-value normal vs obstructive	P-value normal vs restrictive	P-value restrictive vs obstructive
	Dead (N = 1792)	Alive (N = 9003)		Normal (N = 8801)	Restrictive impairment (N = 685)	Obstructive impairment (N = 1309)			
Age (years)	61.3 (0.6)	40.2 (0.3)	<0.001	40.3 (0.4)	48.2 (1.1)	56.7 (0.7)	<0.001	<0.001	<0.001
Sex (%)	59.4 (2.4)	47.8 (0.6)	<0.001	47.5 (0.7)	48.7 (3.0)	60.4 (2.4)	0.698	<0.001	0.004
White (%)	75.2 (2.8)	78.7 (1.3)	0.193	78.3 (1.2)	68.0 (3.3)	83.9 (1.8)	0.001	0.001	<0.001
Education (years)	11.5 (0.2)	12.7 (0.1)	<0.001	12.6 (0.1)	11.8 (0.2)	12.3 (0.2)	<0.001	0.089	0.072
Current smoker (%)	46.6 (2.8)	26.6 (0.8)	<0.001	24.9 (0.8)	31.5 (2.5)	50.1 (3.0)	0.013	<0.001	<0.001
Moderate-vigorous leisure-time physical activity (%)	37.0 (3.0)	41.5 (1.3)	0.106	41.3 (1.4)	31.6 (2.9)	47.5 (3.3)	0.001	0.079	0.001
Vitamin or mineral supplement use during past 30 days (%)	37.1 (2.8)	42.3 (0.8)	0.086	42.2 (0.9)	37.5 (3.1)	39.9 (2.5)	0.161	0.395	0.570
Frequency of alcohol use (times/month)	8.8 (0.9)	9.3 (0.5)	0.521	9.3 (0.5)	4.8 (0.7)	11.0 (1.0)	<0.001	0.100	<0.001
Systolic blood pressure (mm Hg)	124.3 (0.8)	119.1 (0.3)	<0.001	119.3 (0.3)	121.5 (0.8)	121.4 (0.6)	0.010	0.001	0.921
High-density lipoprotein cholesterol (mmol/l)	1.3 (<0.1)	1.3 (<0.1)	0.017	1.3 (<0.1)	1.2 (<0.1)	1.2 (<0.1)	0.002	<0.001	0.701
Non-high-density lipoprotein cholesterol (mmol/l)	4.1 (0.1)	4.0 (<0.1)	0.293	4.0 (<0.1)	4.2 (0.1)	4.1 (0.1)	0.008	0.080	0.357
Body mass index (kg/m <sup>2</sup> )	27.8 (0.3)	26.5 (0.1)	0.001	26.6 (0.1)	27.7 (0.4)	26.2 (0.3)	0.006	0.361	0.006
Albumin-creatinine ratio (mg/g)	46.8 (6.0)	13.2 (0.8)	<0.001	18.2 (1.8)	42.8 (9.8)	18.4 (1.6)	0.015	0.937	0.018
Glomerular filtration rate (ml/min/1.73 m <sup>2</sup> )	99.8 (0.7)	99.2 (0.3)	0.382	99.0 (0.3)	99.8 (0.8)	98.1 (0.7)	0.015	0.937	0.018
C-reactive protein >3 mg/l (%)	37.1 (2.5)	26.2 (1.2)	<0.001	25.7 (1.2)	41.5 (3.2)	28.7 (2.4)	<0.001	0.229	0.002
Good health status (%)	73.7 (2.8)	88.9 (0.7)	<0.001	87.7 (0.8)	77.5 (2.1)	86.8 (2.2)	<0.001	0.704	0.002
Diabetes (%)	13.3 (1.3)	5.4 (0.4)	<0.001	6.5 (0.5)	13.8 (1.7)	5.2 (0.9)	<0.001	0.307	<0.001
History of myocardial infarction (%)	4.9 (0.6)	1.5 (0.2)	<0.001	2.2 (0.3)	3.8 (0.8)	3.6 (0.8)	0.070	0.077	0.855
History of stroke (%)	3.6 (0.8)	1.0 (0.1)	0.002	1.3 (0.2)	2.9 (0.8)	1.7 (0.4)	0.043	0.304	0.129
Vitamin D (nmol/l)	70.3 (2.6)	74.5 (1.0)	0.106	74.4 (1.0)	65.8 (1.9)	75.7 (1.5)	<0.001	0.424	<0.001

Least-square adjusted mean concentrations of vitamin D among adults aged 20–79 years, by pulmonary function status, National Health and Nutrition Examination Survey III, 1988–1994

**Table 2**

	Normal (N = 8801)	Restrictive lung function (N = 685)	Mild obstructive lung function (N = 731)	Moderate-severe obstructive lung function (N = 578)	P-values					
					NLF vs RLF	NLF vs Mild OLF	NLF vs Mod + OLF	RLF vs Mild OLF	RLF vs Mod + OLF	Mild vs Mod + OLF
Model 1	75.3 (0.9)	66.5 (1.6)	76.2 (1.5)	69.5 (1.9)	<0.001	0.586	0.004	<0.001	0.217	0.004
Model 2	75.0 (0.7)	68.8 (1.8)	76.7 (1.6)	71.1 (1.7)	0.001	0.305	0.030	<0.001	0.310	0.007
Model 3	75.0 (0.7)	70.4 (1.8)	75.5 (1.5)	71.0 (1.9)	0.016	0.736	0.043	0.016	0.789	0.032

Abbreviations: Mod+, moderate/severe/very severe; NLF, normal lung function; OLF, obstructive lung function; RLF, restrictive lung function.

Model 1 is adjusted for month of examination. Model 2 is adjusted for variables in model 1 plus age, gender, race or ethnicity and education. Model 3 is adjusted for variables in model 2 plus smoking status, alcohol use, leisure-time physical activity, use of vitamin or mineral supplements, systolic blood pressure, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, body mass index, C-reactive protein, albumin-creatinine ratio, health status, diabetes, history of myocardial infarction and history of stroke.

Table 3

Hazard ratios (95% confidence limits) for all-cause mortality in function of concentrations of vitamin D among US adults aged 20–79 years, by pulmonary function status, National Health and Nutrition Examination Survey III Linked Mortality Study 1988–1994 to 2006

	Vitamin D (nmol/l)				P-adjusted Wald F
	<25	25–<50	50–<75	75	
<i>Total</i>					
Unweighted no. of deaths	64	559	604	565	
Unweighted no. at risk	378	3293	3694	3430	
Unadjusted rate per 1000 person-years (s.e.)	11.9 (2.0)	11.3 (0.8)	9.4 (0.6)	7.4 (0.7)	
Age-adjusted rate per 1000 person-years (s.e.)	19.9 (3.0)	13.1 (0.9)	10.9 (0.6)	10.1 (0.7)	
Model 1	1.62 (1.09, 2.41)	1.53 (1.21, 1.92)	1.27 (1.02, 1.59)	1.00	0.007
Model 2	2.00 (1.41, 2.83)	1.41 (1.13, 1.75)	1.11 (0.92, 1.33)	1.00	0.002
Model 3	1.37 (0.91, 2.05)	1.23 (0.99, 1.54)	1.04 (0.86, 1.26)	1.00	0.179
<i>Normal pulmonary function</i>					
Unweighted no. of deaths	37	319	348	308	
Unweighted no. at risk	316	2681	3022	2782	
Unadjusted rate per 1000 person-years (s.e.)	7.6 (1.7)	7.6 (0.6)	6.4 (0.6)	4.4 (0.5)	
Age-adjusted rate per 1000 person-years (s.e.)	18.0 (2.8)	10.7 (0.8)	8.8 (0.7)	7.6 (0.6)	
Model 1	1.71 (1.07, 2.73)	1.70 (1.26, 2.28)	1.43 (1.08, 1.90)	1.00	0.010
Model 2	2.17 (1.36, 3.45)	1.54 (1.13, 2.09)	1.22 (0.94, 1.57)	1.00	0.015
Model 3	1.76 (1.03, 3.00)	1.31 (0.94, 1.83)	1.16 (0.88, 1.53)	1.00	0.226
<i>Restrictive pulmonary function</i>					
Unweighted no. of deaths	11	78	70	49	
Unweighted no. at risk	28	266	237	154	
Unadjusted rate per 1000 person-years (s.e.)	22.9 (10.1)	19.6 (3.2)	15.9 (3.2)	16.9 (3.5)	
Age-adjusted rate per 1000 person-years (s.e.)	50.3 (13.6)	17.2 (2.7)	15.8 (1.7)	15.9 (3.1)	
Model 1	1.18 (0.37, 3.78)	1.19 (0.65, 2.17)	0.92 (0.52, 1.62)	1.00	0.690
Model 2	1.55 (0.70, 3.44)	0.96 (0.54, 1.70)	0.84 (0.53, 1.34)	1.00	0.473
Model 3	0.85 (0.33, 2.22)	0.84 (0.47, 1.52)	0.77 (0.47, 1.26)	1.00	0.733
<i>Obstructive pulmonary function</i>					
Unweighted no. of deaths	16	162	186	208	

	Vitamin D (nmol/l)				P-adjusted Wald F
	<25	25–<50	50–<75	75	
Unweighted no. at risk	34	346	435	494	
Unadjusted rate per 1000 person-years (s.e.)	25.4 (8.8)	32.7 (3.5)	28.5 (2.7)	25.7 (2.5)	
Age-adjusted rate per 1000 person-years (s.e.)	22.6 (6.6)	17.6 (2.1)	15.3 (1.8)	15.8 (1.7)	
Model 1	0.89 (0.40, 1.95)	1.31 (0.98, 1.75)	1.10 (0.82, 1.46)	1.00	0.204
Model 2	1.16 (0.61, 2.21)	1.28 (0.94, 1.73)	1.06 (0.83, 1.36)	1.00	0.420
Model 3	0.65 (0.29, 1.48)	1.21 (0.89, 1.66)	0.97 (0.78, 1.19)	1.00	0.268

Model 1 is adjusted for month of examination. Model 2 is adjusted for variables in model 1 plus age, gender, race or ethnicity and education. Model 3 is adjusted for variables in model 2 plus smoking status, alcohol use, leisure-time physical activity, use of vitamin or mineral supplements, systolic blood pressure, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, body mass index, C-reactive protein, albumin-creatinine ratio, health status, diabetes, history of myocardial infarction and history of stroke.

**Table 4**

Hazard ratios (95% confidence limits) for all-cause mortality in function of concentrations of vitamin D among US adults aged 20–79 years, by pulmonary function status, National Health and Nutrition Examination Survey III Linked Mortality Study 1988–1994 to 2006

	Vitamin D (nmol/l)			<i>P</i> -adjusted Wald F
	<30	30–<50	50	
<i>Total</i>				
Unweighted no. of deaths	133	490	1169	
Unweighted no. at risk	794	2877	7124	
Unadjusted rate per 1000 person-years (s.e.)	12.4 (2.0)	11.1 (0.8)	8.2 (0.5)	
Age-adjusted rate per 1000 person-years (s.e.)	18.6 (2.1)	12.7 (0.9)	10.5 (0.5)	
Model 1	1.50 (1.05, 2.15)	1.34 (1.12, 1.60)	1.00	0.003
Model 2	1.85 (1.37, 2.50)	1.30 (1.08, 1.56)	1.00	<0.001
Model 3	1.47 (1.06, 2.04)	1.18 (0.99, 1.41)	1.00	0.044
<i>Normal lung function</i>				
Unweighted no. of deaths	78	278	656	
Unweighted no. at risk	654	2343	5804	
Unadjusted rate per 1000 person-years (s.e.)	8.4 (1.8)	7.4 (0.6)	5.2 (0.4)	
Age-adjusted rate per 1000 person-years (s.e.)	15.1 (2.3)	10.4 (0.8)	8.1 (0.5)	
Model 1	1.57 (0.99, 2.50)	1.39 (1.11, 1.75)	1.00	0.015
Model 2	1.94 (1.21, 3.13)	1.34 (1.07, 1.70)	1.00	0.016
Model 3	1.63 (1.03, 2.58)	1.17 (0.93, 1.47)	1.00	0.116
<i>Restrictive lung function</i>				
Unweighted no. of deaths	22	67	119	
Unweighted no. at risk	67	227	391	
Unadjusted rate per 1000 person-years (s.e.)	23.7 (8.6)	19.1 (3.2)	16.4 (2.5)	
Age-adjusted rate per 1000 person-years (s.e.)	34.4 (7.4)	16.7 (3.0)	15.6 (2.1)	
Model 1	1.46 (0.68, 3.12)	1.20 (0.75, 1.89)	1.00	0.526
Model 2	1.37 (0.77, 2.43)	1.06 (0.66, 1.69)	1.00	0.554
Model 3	1.07 (0.57, 2.00)	1.00 (0.65, 1.52)	1.00	0.977
<i>Obstructive lung function</i>				
Unweighted no. of deaths	33	145	394	
Unweighted no. at risk	73	307	929	
Unadjusted rate per 1000 person-years (s.e.)	29.4 (7.9)	32.5 (3.9)	26.9 (1.7)	
Age-adjusted rate per 1000 person-years (s.e.)	19.1 (4.2)	17.6 (2.5)	15.7 (1.3)	
Model 1	1.07 (0.61, 1.87)	1.24 (0.98, 1.58)	1.00	0.190
Model 2	1.39 (0.83, 2.30)	1.21 (0.91, 1.60)	1.00	0.167
Model 3	1.00 (0.57, 1.77)	1.20 (0.90, 1.62)	1.00	0.464

Model 1 is adjusted for month of examination. Model 2 is adjusted for variables in model 1 plus age, gender, race or ethnicity and education. Model 3 is adjusted for variables in model 2 plus smoking status, alcohol use, leisure-time physical activity, use of vitamin or mineral supplements, systolic blood pressure, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, body mass index, C-reactive protein, albumin–creatinine ratio, health status, diabetes, history of myocardial infarction and history of stroke.