Vitamin D Deficiency, Smoking, and Lung Function in the Normative Aging Study

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Rationale: **Vitamin D has immunomodulatory and antiinflammatory effects that may be modified by cigarette smoke and may affect lung function.**

Objectives: **To examine the effect of vitamin D deficiency and smoking on lung function and lung function decline.**

Methods: **A total of 626 men from the Normative Aging Study had 25-hydroxyvitamin D levels measured at three different times between 1984 and 2003 with concurrent spirometry. Vitamin D deficiency was defined as serum level $\leq$ 20 ng/ml. Statistical analysis was performed using multivariable linear regression and mixed effects models.**

Measurements and Main Results: **In the overall cohort, there was no significant effect of vitamin D deficiency on lung function or on lung function decline. In both cross-sectional and longitudinal multivariable models, there was effect modification by vitamin D status on the association between smoking and lung function. Cross-sectional analysis revealed lower lung function in current smokers with vitamin D deficiency (FEV_1, FVC, and FEV_1/FVC; $P \leq 0.0002$), and longitudinal analysis showed more rapid rates of decline in FEV_1 ($P = 0.023$) per pack-year of smoking in subjects with vitamin D deficiency as compared with subjects who were vitamin D sufficient.**

Conclusions: **Vitamin D deficiency was associated with lower lung function and more rapid lung function decline in smokers over 20 years in this longitudinal cohort of elderly men. This suggests that vitamin D sufficiency may have a protective effect against the damaging effects of smoking on lung function. Future studies should seek to confirm this finding in the context of smoking and other exposures that affect lung function.**

Keywords: vitamin D; vitamin D deficiency; lung function decline; smoking; effect modification

Vitamin D deficiency is common in the United States and throughout the world, even in areas near the equator where sun exposure is presumed to be high (1). In addition to its known effects on calcium homeostasis, vitamin D has a variety of functions, including immunomodulatory and antiinflammatory effects (2). Many diseases have been associated with vitamin D deficiency, including cancers and inflammatory diseases (3), although the exact mechanisms are still being elucidated.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Several cross-sectional studies have shown an association between low vitamin D levels and lower lung function.

What This Study Adds to the Field

This study presents evidence that vitamin D sufficiency, defined as vitamin D $>$ 20 ng/ml, may protect against lower lung function and more rapid lung function decline in smokers.

Prior epidemiologic studies have shown a cross-sectional association between lung function and vitamin D levels (4, 5). Despite the limitations of cross-sectional investigations, it is plausible that vitamin D could be causally related to lung function. Genetic studies have shown associations between polymorphisms in the vitamin D binding protein and both lung function and chronic obstructive pulmonary disease (COPD) diagnosis (5–7) as well as bronchiectasis (8) and the rate of decline in lung function (9), implicating the vitamin D pathway in relation to lung function. In smoking-related lung disease, lung destruction is mediated in part through inflammation (10, 11), oxidative stress (12–14), and increased proteases (12, 15). Many of these processes are modulated by vitamin D (2, 16–19). Moreover, *in vitro* studies and animal models suggest that cigarette smoke may interfere with the local antiinflammatory effects of vitamin D (20, 21). However, a recent longitudinal study in subjects with COPD showed no association between baseline vitamin D levels and rate of lung function decline over time (22).

We examined the association between vitamin D deficiency (VDD), smoking, lung function, and rate of lung function decline in a cohort of adult white men from The Normative Aging Study (NAS). Our data set included lung function measures and vitamin D levels over a 20-year period beginning in the 1980s. Given the immunomodulatory properties of vitamin D and prior studies suggesting local interactions between cigarette smoke and vitamin D (20, 21), we investigated whether there was effect modification by VDD on the relationship between smoking and lung function. To our knowledge, no prior epidemiologic studies have looked for an interaction between vitamin D and smoking in association with lung function. Some of the results of these studies have been previously reported in the form of an abstract (23).

METHODS

Population

Study participants were from the Veterans Administration Normative Aging Study, an ongoing longitudinal study of aging established in 1963 (24). This is a cohort of 2,280 healthy male volunteers from the

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Author Contributions: N.E.L. designed the study, performed the data analysis, and prepared the manuscript. D.S. and P.V. were involved in conception of the study and critical revision of the manuscript. A.A.L. designed the study, obtained funding, assisted with the data analysis, and provided critical revision of the manuscript.

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greater Boston, Massachusetts area who were 21 to 80 years of age at entry and who enrolled after an initial health screening determined that they were free of known chronic medical conditions. Participants were reevaluated every 3 to 5 years using detailed on-site physical examinations and questionnaires. This study was approved by the Human Studies Subcommittee of the Department of Veterans Affairs Medical Center and the Institutional Review Board of the Brigham and Women's Hospital, and all participants provided written informed consent. Because the start date for the current analysis is 20 years after enrollment for the original study, some subjects developed chronic conditions (including respiratory disease such as COPD) since the initiation of the original study (1963). These subjects remain part of the current analysis.

For this study, white individuals who had blood samples drawn at least three times between 1984 and 2003 and who had concomitant spirometry data at those times were selected. This included 626 subjects. By 1984, loss to follow up in the whole cohort (20 yr after initiation) was 22%.

Measures

Spirometry was performed as previously described (25), and acceptability of spirograms was judged according to ATS standards (26, 27). 25-Hydroxyitamin D (vitamin D) levels were measured using the chemiluminescence method (Liaison; Diasorin, Saluggia [Vercelli], Italy) and reported in ng/ml (28, 29). VDD was defined as a serum vitamin D level $\leq$ 20 ng/ml ($\leq$ 50 nmol/l) as per the 2010 Institute of Medicine report (30).

Statistical Analysis

Linear regression was used for cross-sectional analyses, and mixed effects models were used for longitudinal analyses using repeated measures. Covariates in multivariable models were chosen for their clinical relevance and strong univariate associations ($P < 0.05$) with lung function and included age, height, pack-years of cigarette smoking, and body mass index (BMI). Season of blood draw was also included because vitamin D measurements can vary by time of year. Smoking was considered as a continuous variable (pack-years of smoking) and as a dichotomous variable (current smokers vs. ex- and never-smokers). Smoking status was included in all models that examined the interaction between vitamin D level and smoking (either pack-years or smoking status). The third time point was used for cross-sectional analyses because the widest variance in lung function occurred at this point; however, all analyses were also performed on the earlier time points as well. In longitudinal models, time was considered as a continuous variable. Interaction between vitamin D levels was performed using the dichotomized value based on the Institute of Medicine definition of deficiency ($\leq$ 20 ng/ml) (30). The same analyses were explored using vitamin D as a continuous variable, though the relationship between vitamin D and end-organ effects is unlikely to be linear. Percent predicted values for FEV_1 and FVC were calculated using equations by Crapo and colleagues (31). Student's *t* test was used to compare FEV_1 percent predicted values between individuals with and without VDD in Figure E3 in the online supplement. SAS version 9.1 (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Baseline characteristics of the cohort at all three time points (Time 1: 1984–1989; Time 2: 1992–1999; Time 3: 1995–2003) are shown in Table 1. There was a broad range of levels of lung function at all three time points, though mean levels were normal. Many subjects had a significant smoking history; however, only a small percentage had COPD by GOLD criteria (15) at Time 1 (GOLD $\geq$ 1; n = 98 or 16%); this proportion increased at Time 3 (n = 165 or 26%). VDD was common throughout the study. There was no significant association between smoking and vitamin D level ($P = 0.7$ for pack-years; $P = 0.2$ for smoking status). As expected, smoking was significantly and inversely associated with lung function (FEV_1) ($P < 0.0001$ for pack-years, [Figure E1]; $P = 0.05$ for smoking status). The mean overall decline in lung function over the period of the study was 16.4% for FEV_1, 15.8% for FVC, and 0.6% for FEV_1/FVC ratio. Subjects not included but still participating in the cohort study at the initial time point for inclusion for this analysis were on average slightly older, had lower lung function and higher mean pack-years of smoking, and more were current smokers (Table E1).

TABLE 1. BASELINE CHARACTERISTICS OF *626* WHITE MALE SUBJECTS FROM THE NORMATIVE AGING STUDY AT THREE TIME POINTS*

	Time 1	Time 2	Time 3
Age, yr	59.9 (6.9)	66.5 (6.7)	73.3 (6.9)
BMI	27.2 (3.3)	28.0 (3.7)	28.4 (4)
FEV_1	3.21 (0.63)	2.98 (0.65)	2.68 (0.63)
FEV_1, %pred	89.5 (14.8)	88.1 (16.5)	84.4 (17.3)
FVC	4.24 (0.74)	4.02 (0.76)	3.57 (0.71)
FVC, %pred	93.3 (12.8)	92.4 (14.0)	86 (14.4)
FEV_1/FVC ratio	75.5 (6.8)	74.0 (7.3)	75 (8.3)
Pack-years	19.2 (22.3)	20 (23.2)	20.3 (23.8)
Current smoking, n (% yes)	64 (10%)	33 (5%)	27 (4%)
Vitamin D level, ng/ml	23.2 (9.4)	29.8 (12.2)	26.9 (10.7)
Vitamin D deficient ($\leq$ 20 ng/ml)	284 (45%)	115 (18%)	154 (25%)
COPD (GOLD $\geq$ 1)	98 (16%)	153 (24%)	165 (26%)
GOLD			
0	528 (84%)	473 (76%)	461(74%)
1	36 (6%)	54 (9%)	30 (5%)
2	53 (8%)	84 (13%)	75 (12%)
3	5 (1%)	10 (2%)	16 (3%)
4	4 (0.5%)	5 (1%)	44 (7%)

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; %pred = %predicted.

Values are mean (SD) or n (%).

*Time 1: 1984–1989; Time 2: 1992–1999; Time 3: 1995–2003.

Main Effects of Vitamin D

In unadjusted analyses, VDD was associated with lower FEV_1 ($\beta = -0.119$; $P = 0.048$; reference group was individuals without VDD; therefore, negative effect estimates indicate lower values in subjects with VDD) and showed a trend toward association with lower FVC ($\beta = -0.123$; $P = 0.07$) at Time 3. However, after adjustment for covariates (age, height, pack-years, BMI, and season), these relationships were no longer statistically significant (FEV_1, $P = 0.15$; FVC, $P = 0.42$; FEV_1/FVC, $P = 0.083$). Table E2 shows the effect estimates and *P* values at all three time points using VDD. There was no significant relationship between vitamin D as a continuous variable and lung function in unadjusted or adjusted analyses (*see* Figure E2 for unadjusted analyses; for adjusted analyses: FEV_1, $P = 0.98$; FVC, $P = 0.83$; FEV_1/FVC, $P = 0.70$).

Similarly, in longitudinal models, using three repeated measures of lung function and three concurrent measurements of vitamin D, there was no significant association between VDD and rate of decline in unadjusted or adjusted models (Table E3). In models analyzing vitamin D as a continuous variable, there was an inverse relationship between vitamin D level and FVC decline, but relationships were not significant with FEV_1 or FEV_1/FVC (Table E3; Figure E3).

Smoking and Vitamin D Interaction

We considered an interaction of vitamin D levels with smoking by examining the relationship with pack-years of smoking and

with smoking status using cross-sectional and longitudinal models. When we plotted FEV_1 simultaneously with vitamin D levels and pack-years of smoking, there was a suggestion of a combined effect of these exposures on lung function (Figure 1).

In a cross-sectional analysis using a multivariable model adjusted for age, height, pack-years, BMI, season, and smoking status, there were significant interactions ($P \leq 0.02$) between VDD and pack-years of smoking for all spirometric measures of lung function (FEV_1, $P = 0.007$; FVC, $P = 0.02$; FEV_1/FVC, $P = 0.004$). Effects were also significant ($P \leq 0.01$) when analyzed by smoking status. A similar direction of effect, though not consistently significant, was seen at earlier time points (Table E4) and when analyzed using vitamin D as a continuous variable (Table E5).

In longitudinal models, which included interactions with time, there were significant interactions between VDD and pack-years of smoking in association with the rate of FEV_1 decline ($P = 0.02$) and a trend toward significance with FVC decline ($P = 0.08$) and with smoking status in relation to FEV_1 ($P = 0.052$) and to FEV_1/FVC decline ($P = 0.02$), where smokers with VDD had greater lung function decline compared with those without VDD. This reinforced the cross-sectional findings associating VDD with lower lung function by pack-years of smoking, suggesting that vitamin D sufficiency may mitigate the effect of smoking on the rate of lung function decline as measured by FEV_1 (Table 2) (for smoking status, *see* Table E6). Findings were not significant when vitamin D was analyzed as a continuous variable but were in the same direction of effect and showed a trend toward significance with FEV_1 ($P = 0.07$) (Table E7).

Stratified Analysis

To further explore and clarify the interpretation of these interactions, we performed a stratified analysis on the cross-sectional data. To examine the interaction between pack-years of smoking and VDD, we stratified by vitamin D status (deficient vs. not deficient), and pack-years was maintained as a continuous variable. In subjects with VDD, the number of pack-years of smoking was associated with lower lung function as compared with subjects who were not deficient for all spirometric measures (Table 3).

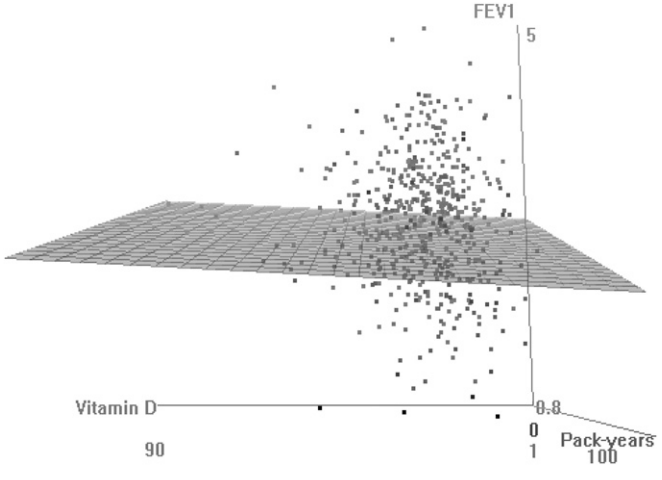

Figure 1. Three-way relationship between FEV_1, vitamin D levels, and smoking (pack-years). Shown here is the unadjusted relationship between FEV_1, pack-years of smoking, and vitamin D levels as a continuous variable, viewed from the side of the graph where pack-years are highest. This suggests that FEV_1 is higher in subjects with higher vitamin D levels compared with subjects with lower vitamin D levels and the same number of pack-years of smoking.

TABLE 2. MULTIVARIABLE LONGITUDINAL ANALYSIS OF THE CHANGE IN LUNG FUNCTION OVER TIME; INTERACTION OF VITAMIN D DEFICIENCY AND SMOKING (PACK-YEARS)*

	β	*P* Value
FEV_1	−0.0002	0.023
FVC	−0.0002	0.08
FEV_1/FVC	−0.003	0.1

Negative effect estimates suggest that in subjects with vitamin D deficiency, the same number of pack-years led to a faster rate of decline as compared with subjects without vitamin D deficiency.

*Effect estimates and *P* values are for the interaction term with vitamin D deficiency, time (in years), and pack-years of smoking.

For example, for subjects with VDD, for each 1 unit increase in pack-years, mean FEV_1 was 12 ml lower ($P < 0.0001$). However, the value in subjects who were not deficient was half this amount, or 6.5 ml ($P < 0.0001$), suggesting that higher vitamin D level may protect somewhat against the damage in lung function caused by higher pack-years of smoking (Figure 2). Stratified analyses were done using Time 3, but findings were similar and significant at other time points. Findings were similar in stratified longitudinal models, showing greater rates of decline per pack-year of smoking for all three spirometric measures in subjects with VDD ($P < 0.01$).

When stratified by smoking status, in current smokers there was a significant association between VDD and lung function, such that in current smokers, those with VDD had a lower mean FEV_1, FVC, and FEV_1/FVC ($P < 0.05$) than smokers without VDD (Figure E4). The relationship between VDD and lung function was not significant in ex-smokers or never-smokers.

We repeated these analyses after excluding the 165 subjects who developed COPD during the course of follow-up of this analysis. Although the results for the stratified cross-sectional analysis were not statistically significant, the direction of effect was consistent with the results in the full cohort (data not shown). In the stratified longitudinal analysis examining lung function decline in non-COPD subjects, we found a significant difference with a greater effect of pack-years of smoking on FEV_1 decline in those with vitamin D deficiency ($P = 0.04$), though this was not statistically significant for FVC ($P = 0.12$) or FEV_1/FVC ($P = 0.2$). This was likely due to the small number of subjects.

DISCUSSION

In a longitudinal cohort of North American older men, we examined the relationship between vitamin D deficiency and lung function using cross-sectional and longitudinal models to examine the effect on lung function rate of decline. We also investigated whether vitamin D deficiency modified the relationship between smoking and lung function, examining smoking status and pack-years of smoking. We found no main effect of vitamin D deficiency on lung function. However, we found that VDD modified the effect of smoking on lung function, suggesting that in vitamin D-deficient subjects, the same number of pack-years of smoking was associated with lower lung function when compared with subjects who were not vitamin D deficient. Importantly, in longitudinal models, VDD exacerbated the effect of pack-years of smoking on FEV_1 decline over time. This suggests that maintaining vitamin D sufficiency may have a protective effect against the more rapid lung function decline seen in smokers.

Our study extends the work of prior investigations into the relationship between vitamin D and lung function. A large cross-sectional study in NHANES III of over 14,000 subjects showed a strong positive association between vitamin D level

TABLE 3. STRATIFIED CROSS-SECTIONAL ANALYSIS FOR THE EFFECT OF VITAMIN D DEFICIENCY AND SMOKING ON LUNG FUNCTION

	FEV_1		FVC		FEV_1/FVC	
	β	*P* Value	β	*P* Value	β	*P* Value
Deficient	−0.012	<0.0001	−0.009	0.0002	−0.176	<0.0001
Not deficient	−0.0065	<0.0001	−0.004	0.0002	−0.108	<0.0001

The table shows β and *P* values for pack-years in multivariable models in subjects with and without vitamin D deficiency adjusted for age, height, body mass index, pack-years, smoking status, and season of blood draw. In vitamin D–deficient subjects, number of pack-years of smoking had a more negative effect on lung function than in subjects who were not vitamin D deficient.

and lung function (4), prompting much speculation on the possible biological effects of vitamin D on lung function (32–34). In that study, the effect appeared to be stronger in smokers, though this was not statistically significant. Smaller studies have demonstrated a high prevalence of VDD in subjects with advanced lung disease (35), though this is also common in the general population (1, 36), as well as an association between lung function and vitamin D level in patients with asthma (37–40). A study of smokers found that in subjects with COPD there was an association between vitamin D levels and lung function (5), similar to our findings. However, each of these studies was cross-sectional. Except for the NHANES III study, all studies involved subjects with lung disease. One study examined vitamin D and lung function decline over 6 years in the Lung Health Study, a cohort of smokers with COPD (22). In this study, patients were divided into "rapid" and "slow" decliners based on the change in lung function between two time points, and mean initial vitamin D levels were compared between the two groups. The authors found no significant differences in vitamin D levels in rapid versus slow decliners and concluded that vitamin D had no effect on the rate of lung function decline.

Our study design has several advantages over the Lung Health study. Although the Lung Health study was well powered to detect a difference in mean vitamin D levels between rapid versus slow decliners, dichotomizing lung function decline as such may decrease power and obscure the ability to detect subtle differences in rates of decline that are possible when analyzing lung function as a continuous measure, as we did in our study. Additionally, that study had only one measurement of vitamin D and two of lung function over a total of 6 years, whereas we have three measurements of vitamin D and of lung function over approximately 20 years, increasing power and precision. This is particularly important because vitamin D levels fluctuate over time. Furthermore, our study has three times the number of subjects and includes subjects with and without obstructive airways disease as well as smokers and nonsmokers.

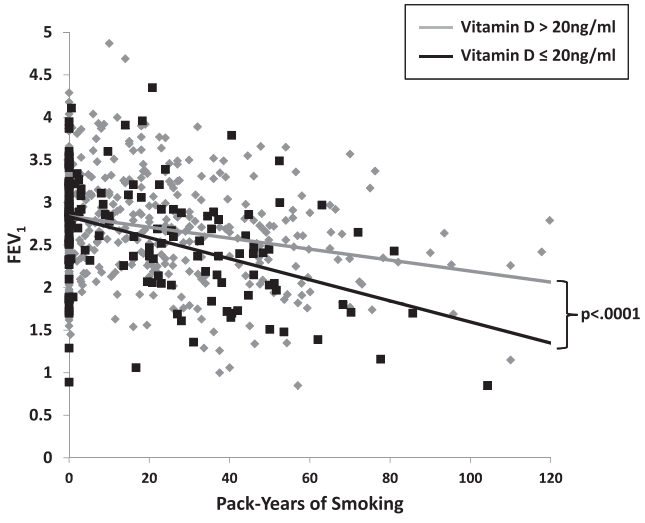

Figure 2. Relationship between lung function, vitamin D deficiency, and smoking (pack-years). Shown here is the cross-sectional relationship between FEV_1% predicted and pack-years of smoking in subjects who were vitamin D deficient (vitamin D ⩽ 20 ng/ml) compared with those who were not (vitamin D > 20 ng/ml). In subjects who were vitamin D deficient, the effect of pack-years of smoking on FEV_1 was twice as severe as in subjects without vitamin D deficiency.

Our most novel and important finding was the interaction between VDD and smoking in the effect on lung function in cross-sectional models examining level of lung function and in longitudinal models examining rates of lung function decline over time. These results suggest that vitamin D potentially mitigates the damaging effects of smoking on lung function. In additional exploratory analyses, we noted that we had similar findings of the protective effect of vitamin D sufficiency on FEV_1 decline when subjects with COPD were excluded, implying that smokers who have not yet developed COPD may have the potential for protection based on vitamin D status. There are several possible mechanisms whereby higher vitamin D levels could have a protective effect against damage caused by smoking on lung function.

In subjects with COPD, exacerbations, usually due to infections, increase the rate of decline of lung function (41) due to worsening inflammation (10), and vitamin D may protect against this. Vitamin D decreases viral-induced inflammation without compromising viral clearance (42) and may decrease the risk of respiratory infections (36). Cigarette smoke decreases the production of the active form of vitamin D (1,25-dihydroxyvitamin D) in lung epithelial cells (20), which may be overcome with higher serum levels of the substrate (25-hydroxyvitamin D). Additionally, cigarette smoke may affect expression levels of the vitamin D receptor (21). Furthermore, COPD is increasingly coming to be understood as a systemic inflammatory disease (11), and vitamin D has immunomodulatory and antiinflammatory effects (2). TNF-α, a key cytokine implicated in lung destruction of COPD (43), is down-regulated by vitamin D (17, 19). Enzymes implicated in smoking-related COPD, such as matrix metalloproteinases (44, 45), may be modulated by vitamin D (18). Vitamin D can act as an antioxidant (46) or induce production of antioxidants (47), which may be beneficial in exposure to the oxidative stress of cigarette smoking that leads to lung damage (15).

Our findings must be interpreted within the context of our study design. A major strength of our cohort is that it includes smokers and nonsmokers and those with and without abnormal lung function, which is in contrast to many prior studies that focus on those with established lung disease. However, it included only men, all of whom were older and white, limiting generalizability. Future studies in more diverse cohorts are needed to confirm our findings. Vitamin D levels vary over time; the intraclass correlation (within subjects) was moderate ($r = 0.48$) in our cohort. We were not able to confirm prior findings from NHANES III showing an association between vitamin D and lung function in the general population; however, few subjects with abnormal lung function may have made an effect difficult to detect in the overall cohort. Additionally, the current accepted definition of VDD (⩽ 20 ng/ml) is based on bone health, and the level required to confer extraskeletal benefits is unknown. We had similar, though not significant, findings when examining vitamin D levels as a continuous variable. The biological effects of vitamin

D are unlikely to be linear, and this may suggest a threshold effect of vitamin D, though we may have had limited power to determine a specific threshold because of clustering of the distribution of vitamin D levels (the majority of the cohort was between 20 and 40 ng/ml). We did find a significant inverse relationship between vitamin D and FVC decline though the actual incremental change (0.3 ml/yr per 1 ng/ml change in vitamin D level) was very small. To clarify and understand these relationships, these analyses should be explored in different cohorts. Subjects not included in this analysis because they did not have blood samples and lung function measures at three time points were older, had lower lung function, and had higher pack-years of smoking, which would likely bias our results toward the null given that those included were healthier. Finally, we adjusted for season of measurement but did not adjust for latitude; however, all subjects were from the greater Boston, Massachusetts area and therefore were within roughly the same latitude.

In summary, we examined VDD in relation to lung function over a 20-year period in a longitudinal cohort of elderly white men. In the overall cohort, there was no significant effect of VDD on lung function or lung function decline. However, in smokers, vitamin D sufficiency appeared to have a protective effect on lung function and the rate of lung function decline, modifying the effect of smoking. This may be due to the antiinflammatory and antioxidant properties of vitamin D. If confirmed, our findings could have immense public health importance in the potential for prevention of COPD and other exposure-related lung diseases, although smoking cessation and avoidance of exposures remain the most important interventions. Additional investigations as to whether vitamin D may protect against lung damage from other sources, such as biomass fuel or air pollution, would also have profound import. Long-term interventional studies of vitamin D supplementation, including several ongoing trials in COPD, will be essential to further explore these associations.

Author disclosures are available with the text of this article at www.atsjournals.org.

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