Journal of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci. 2012 June;67A(6):683–689
doi:10.1093/gerona/glr213

Advance Access published on December 7, 2011

Serum 25-Hydroxyvitamin D and Pulmonary Function in Older Disabled Community-Dwelling Women

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Background. Recent studies have expanded the functions of vitamin D to a possible role in pulmonary function. Our objective was to examine the relationship between serum 25-hydroxyvitamin D (25[OH]D), serum parathyroid hormone, and pulmonary function in older women.

Methods. We examined the relationship of serum 25(OH)D and parathyroid hormone with pulmonary function (forced expiratory volume in one second [FEV_1], forced vital capacity [FVC], and FEV_1/FVC ratio) in a cross-sectional study of 646 moderately to severely disabled women, 65 years or more, living in the community in Baltimore, Maryland, who participated in the Women's Health and Aging Study I.

Results. Overall, median (25th, 75th percentile) serum 25-hydroxyvitamin D concentrations were 19.9 (14.7, 26.7) ng/mL. Serum 25(OH)D was positively associated with FEV_1 ($p = .03$), FVC ($p = .18$), and FEV_1/FVC ($p = .04$) in multivariable linear regression models adjusting for age, race, education, smoking, height, physical activity, cognition, interleukin-6, chronic diseases, and other potential confounders. In the same models, serum parathyroid hormone was not significantly associated with FEV_1, FVC, or FEV_1/FVC.

Conclusions. These findings support the idea that vitamin D deficiency is independently associated with poor pulmonary function in older disabled women.

Key Words: Aging—Lung function—Parathyroid hormone—Vitamin D—Women.

Received April 1, 2011; Accepted October 27, 2011

Decision Editor: Darryl Wieland, PhD

PULMONARY function declines slowly through adult life and, after age 70 years, is characterized by a more progressive rate of decline (1). Reduced pulmonary function, assessed by forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), is prevalent in older adults and is most commonly associated with chronic obstructive pulmonary disease, asthma, or fibrotic lung disease (2). Pulmonary function is an independent predictor of impaired physical performance (3) and higher all-cause and cardiovascular mortality (4,5).

Vitamin D has recently been implicated in lung health (6). Vitamin D deficiency is common among adults (7) and associated with increased risk of osteopenia, osteoporosis, muscle weakness, poor physical performance (8), falls (9), and fractures (10). Vitamin D plays an important role in the regulation of calcium and phosphorus, bone metabolism, cellular differentiation, immune function, and skeletal muscle performance (11,12). Human vitamin D status depends on both sunlight exposure and dietary intake of vitamin D–rich foods, such as oily fish, vitamin D–fortified dairy products, and dietary supplements containing vitamin D. Despite the tremendous progress that has been made in nutrition in the last several decades, vitamin D deficiency remains a serious public health problem (13). Both sunlight exposure and dietary intake of vitamin D are inadequate in many populations (11). More severe vitamin D deficiency can contribute to the development of elevated circulating parathyroid hormone (PTH) concentrations (11).

A recent study showed that among adults, aged 20 years or more, who participated in the Third National Health and Nutrition Examination Survey, serum 25-hydroxyvitamin D concentrations were independently associated with pulmonary function (14). Vitamin D deficiency is also common in adults with chronic obstructive pulmonary disease, and the extent of deficiency correlates with the severity of lung disease (15). Vitamin D may influence pulmonary function

through effects on the musculoskeletal system (14,15). The relationship between vitamin D status and pulmonary function has not been examined among older women, who are highly susceptible to vitamin D deficiency and worsening airflow limitation with age. We hypothesized that vitamin D deficiency and elevated PTH concentrations were associated with reduced pulmonary function in older women. To address this hypothesis, we measured serum 25-hydroxyvitamin D and PTH concentrations and assessed pulmonary function in a population-based study of older, moderately to severely disabled women living in the community.

Methods

Participants

Participants in this study were women, aged 65 years and older, who participated in the Women's Health and Aging Study (WHAS) I, a population-based study designed to evaluate the causes and course of physical disability in older disabled women living in the community. WHAS I participants were recruited from an age-stratified random sample of women, aged 65 years and older, selected from Medicare enrollees residing in 12 contiguous zip code areas in Baltimore (16). WHAS I enrolled the one-third most disabled women aged 65 years and older, those with disability in two or more domains. Of the 1,409 women who met study eligibility criteria, 1,002 agreed to participate in the study in 1992. There were no major differences in sociodemographic or reported health characteristics between eligible participants and those who declined to participate (16).

Data Collection

Standardized questionnaires were administered in the participant's home by trained interviewers. Race was assessed in a questionnaire as black, white, or other; smoking in terms of never, former, or current smoker; and education as 0–8, 9–11, 12, or more than 12 years as the highest level of formal education achieved. Physical activity was assessed through self-report of total minutes per week spent in six moderate-intensity activities (walking for exercise, heavy household chores, heavy outdoor work, regular exercise, dancing, and bowling) using a modified version of the Minnesota Leisure Time Activity Questionnaire (16). Women were classified as being inactive, having low activity, or moderate-to-high physical activity if they reported 0, 0–149, or 150 min/wk or more of activity, respectively. Two weeks later, a trained, registered full-time study nurse practitioner examined each study participant in her home, using a standardized evaluation of physical performance and physical exam. Approximately 75% of women also consented to phlebotomy performed during a separate visit by a trained phlebotomist who followed a standardized protocol.

The definitions for most of the chronic diseases reported in this study were adjudicated by WHAS coinvestigators based on standardized algorithms that combined information from the questionnaire, physical examination, medical records, and physician contact (16). The diagnosis of chronic obstructive pulmonary disease was defined on the basis of a diagnostic algorithm that included review of spirometry results (if available), respiratory medications, respiratory symptoms, and physician diagnosis by a study pulmonologist. The Mini-Mental State Examination (17) was administered at enrollment. An Mini-Mental State Examination score of less than 24 was defined as cognitive impairment (17). Further details on the methods and sampling design of the WHAS studies are published elsewhere (16).

Pulmonary function was assessed using spirometry (16). A PJ5 spirometer (Burdick Inc., Deerfield, WI) with pneumotachograph was connected to a portable computer using software for spirometry developed by the National Institute for Occupational Safety and Health. Nurses who conducted the examination had received training and certification in a National Institute for Occupational Safety and Health–approved course on spirometry. Participants with bronchodilators were told not to use them for 6 hours prior to testing. Readings were reviewed by the National Institute for Occupational Safety and Health reading center. Field technicians sought to obtain three acceptable spirograms (FEV_1 and FVC within 5%) using the American Thoracic Society Criteria Guidelines (18). Of the 840 participants who underwent spirometry, 693 participants completed acceptable spirograms. Readings deemed "not acceptable" were usually the result of a participant's inability to sustain force expiration after repeated attempts. FEV_1% and FVC predicted were calculated as per Knudson and colleagues (19). There were 646 women with acceptable spirograms who also had serum 25-hydroxyvitamin D and PTH measurements. The median 25(OH)D concentration among women who were not included in the analysis due to unacceptable spirograms was 18.2 ng/mL. The Johns Hopkins University School of Medicine Institutional Review Board approved the study protocol, and written informed consent was obtained from all participants.

Nonfasting blood samples were obtained by venipuncture. Processing and aliquoting of samples were carried out at the Core Genetics Laboratory of the Johns Hopkins University School of Medicine following a standardized protocol. One set of blood samples was placed on ice and sent the same day to the central laboratory of Quest Diagnostics (formerly Corning Clinical Laboratories and MedPath) in Teterboro, New Jersey, for analysis. Serum 25-hydroxyvitamin D (25[OH]D) was measured using a radioreceptor assay (Nichols Institute Diagnostics, San Juan Capistrano, CA (20)), with interassay and intraassay coefficients of variation of 9.6% and 7.5%, respectively. Serum 25(OH)D was analyzed as a continuous variable and also as a categorical variable using generally accepted cutoff point to define vitamin D deficiency (<20 ng/mL), inadequacy (20–29 ng/mL), and sufficiency (≥30 ng/mL (11)). Serum 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) was measured with the use of extraction,

chromatography, and radioreceptor assay (21) with interassay and intraassay coefficients of variation of 10.9% and 7.5%, respectively. Intact serum PTH was measured using chemiluminescence (22) with interassay and intraassay coefficients of variation of 6.7% and 5.7%, respectively. Complete blood count, phosphate, calcium, and creatinine were measured at Quest Diagnostics Laboratories. Chronic kidney disease was defined as estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease equation of Levey and colleagues (23). Anemia was defined as hemoglobin less than 11 g/dL (24). Serum samples were aliquoted and stored continuously at −70°C until the time of analyses of serum interleukin-6 (IL-6) was measured using a commercial ELISA (Quantikine Human IL-6; R&D Systems, Minneapolis, MN) in the laboratory of one of the investigators (R.D.S.). The minimum detection limit for the IL-6 ELISA reported by the manufacturer is 0.039 pg/mL. Intraassay and interassay coefficients of variation for IL-6 measurements were 4% and 6%, respectively. IL-6 concentration less than 2.5 pg/mL was used as an indicator of inflammation (25).

Statistical Analysis

Medians (25th, 75th percentiles) and proportions were used to describe the study population. Variables that were skewed, that is, serum IL-6, were log transformed to achieve a normal distribution. Bivariate and multivariable linear regression models were used to examine the relationship between serum 25(OH)D, PTH, and other variables with FEV_1, FVC, and FEV_1/FVC ratio, respectively, where FEV_1, FVC, and FEV_1/FVC ratio were the dependent variable in the models. Variables that reached statistical significance in bivariate models were included in the multivariable linear regression models. Since serum 25(OH)D and PTH are closely related, multivariable models were run with the same covariates but with inclusion of either serum 25(OH)D or PTH and finally both 25(OH)D and PTH in the model. All analyses were performed using SAS (v. 9.1.3; SAS Institute, Inc., Cary, NC) with a type I error of 0.05.

Results

Serum 25(OH)D and PTH concentrations, pulmonary function, demographic and other characteristics of the participants are shown in Table 1. The prevalence of chronic diseases was fairly high in this population-based sample of women representing the one-third most disabled women living in the community. Data were examined for a possible threshold relationship between 25(OH)D and FEV_1, FVC, and FEV_1/FVC, respectively, and the relationship was linear with no evidence of a threshold. There were no significant differences in log 25(OH)D, log PTH, or 1,25-hydroxyvitamin D concentrations between 202 women with and 444 women without chronic obstructive pulmonary disease (results not shown). There were no women with evidence of primary hyperparathyroidism, defined as calcium more than 10.2 mg/dL and PTH more than 65 pg/mL.

Table 1. Characteristics of Participants in the Women's Health and Aging Studies I

Characteristic	Median (25th, 75th percentile) or %
Age (y)	76.0 (71.0, 85.0)
Race (%)	
White	73.5
Black	26.5
Education <12 y (%)	63.1
Smoking (%)	
Never	52.6
Former	36.4
Current	11.0
Height (cm)	155 (151, 160)
Physical activity (%)	
Inactive	69.2
Low	17.3
Moderate-to-high	13.5
FEV_1 (L)	1.43 (1.11, 1.76)
FEV_1% predicted	78.0 (77.0, 79.0)
FVC (L)	1.97 (1.57, 2.38)
FVC% predicted	87.5 (73.1, 104.3)
FEV_1/FVC ratio	0.73 (0.66, 0.80)
Parathyroid hormone (pg/mL)	73.0 (52.0, 106.0)
Parathyroid hormone >65 pg/mL (%)	58.8
25(OH)D (%)	
<20 ng/mL	50.1
20–29 ng/mL	30.4
≥30 ng/mL	19.5
25-Hydroxyvitamin D (ng/mL)	19.9 (14.7, 26.7)
1,25-Dihydroxyvitamin D (pg/mL)	35.4 (27.5, 45.3)
Use of vitamin D supplements (%)	10.0
Serum phosphate (mg/dL)	3.6 (3.3, 4.0)
Serum calcium (mg/dL)	9.3 (9.0, 9.5)
MMSE <24 (%)	16.1
Anemia (%)	20.4
Interleukin-6 >2.5 pg/mL (%)	55.6
Hypertension (%)	56.7
Angina (%)	22.3
Heart failure (%)	8.4
Peripheral artery disease (%)	19.2
Stroke (%)	5.6
Diabetes mellitus (%)	15.6
Chronic obstructive pulmonary disease (%)	31.3
Depression (%)	16.1
Cancer (%)	10.4
Chronic kidney disease (%)	53.9
Season (%)*	
Winter	19.3
Spring	18.3
Summer	30.7
Autumn	31.7

Notes: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; MMSE, Mini-Mental State Examination.

*Season at the time of blood drawing.

Separate bivariate linear regression models were used to examine the relationship between serum 25(OH)D, serum PTH, demographic factors, inflammation, and chronic diseases with FEV_1, FVC, and FEV_1/FVC, respectively. Age, low education, serum PTH, cognitive impairment, anemia, IL-6 less than 2.5 pg/mL, heart failure, peripheral artery disease,

Table 2. Bivariate Linear Regression Models for Relationship of Serum 25(OH)D and Other Participant Characteristics With FEV_1, FVC, and FEV_1/FVC, Respectively, Among Women in WHAS I

	FEV_1		FVC		FEV_1/FVC	
Characteristic	β (*SE*)	*p* Value	β (*SE*)	*p* Value	β (*SE*)	*p* Value
Age (y)	−0.020 (0.002)	<.0001	−0.028 (0.002)	<.0001	0.0008 (0.0006)	.18
Race, white	0.114 (0.040)	.005	0.241 (0.053)	<.0001	−0.046 (0.011)	<.0001
Education <12 y	−0.149 (0.037)	<.0001	−0.234 (0.048)	<.0001	0.016 (0.010)	.11
Smoking*						
Former	−0.093 (0.059)	.11	−0.065 (0.051)	0.20	−.051 (0.010)	<.0001
Current	−0.144 (0.038)	0.0002	0.021 (0.078)	0.79	−0.053 (0.016)	0.001
Height (cm)	0.016 (0.002)	<.0001	0.029 (0.003)	<.0001	−0.003 (0.0005)	<.0001
Physical activity†						
Low	0.186 (0.047)	.0001	0.459 (0.069)	<.0001	−0.025 (0.013)	.07
Moderate-to-high	0.300 (0.053)	<.0001	0.325 (0.063)	<.0001	−0.018 (0.015)	.24
Log parathyroid hormone (pg/mL)	−0.133 (0.029)	<.0001	−0.206 (0.039)	<.0001	0.009 (0.008)	.26
Parathyroid hormone >65 pg/mL	−0.155 (0.037)	<.0001	−0.233 (0.048)	<.0001	0.007 (0.010)	.48
Log 25(OH)D (ng/mL)	0.152 (0.034)	<.0001	0.208 (0.046)	<.0001	−0.002 (0.009)	.84
1,25-Dihydroxyvitamin D (pg/mL)	−0.0007 (0.001)	.55	0.0002 (0.002)	.89	−0.0005 (0.0003)	.13
Use of vitamin D supplements	0.053 (0.061)	.38	0.019 (0.080)	.81	0.026 (0.017)	.13
Serum phosphate (mg/dL)	−0.012 (0.037)	.74	−0.032 (0.049)	.52	0.008 (0.010)	.43
Serum calcium (mg/dL)	0.089 (0.039)	.02	0.069 (0.052)	.19	0.016 (0.011)	.13
MMSE < 24	−0.217 (0.048)	<.0001	−0.363 (0.063)	<.0001	0.041 (0.014)	.003
Anemia	−0.105 (0.046)	.02	−0.225 (0.060)	.0002	0.037 (0.013)	.004
Interleukin-6 < 2.5 pg/mL	0.127 (0.036)	.0004	0.158 (0.048)	.001	0.004 (0.010)	.70
Hypertension	0.008 (0.036)	.82	−0.027 (0.048)	.57	0.008 (0.010)	.42
Angina	0.018 (0.043)	.66	0.015 (0.057)	.78	0.005 (0.012)	.68
Heart failure	−0.176 (0.064)	.006	−0.200 (0.085)	.02	−0.005 (0.018)	.78
Peripheral artery disease	−0.147 (0.045)	.001	−0.149 (0.060)	.01	−0.020 (0.013)	.11
Stroke	−0.030 (0.078)	.69	−0.236 (0.103)	.02	0.089 (0.022)	<.0001
Diabetes mellitus	0.027 (0.049)	.57	−0.062 (0.065)	.34	0.035 (0.014)	.01
Chronic obstructive pulmonary disease	−0.358 (0.036)	<.0001	−0.142 (0.051)	.005	−0.138 (0.009)	<.0001
Depression	−0.056 (0.048)	.25	−0.096 (0.064)	.14	0.007 (0.014)	.60
Cancer	0.089 (0.058)	.13	0.133 (0.078)	.09	−0.010 (0.017)	.52
Chronic kidney disease	0.031 (0.037)	.39	−0.006 (0.048)	.90	0.017 (0.010)	.09
Season‡						
Spring	−0.027 (0.059)	.63	−0.047 (0.078)	.54	−0.009 (0.015)	.52
Summer	−0.054 (0.052)	.30	−0.065 (0.070)	.35	−0.005 (0.016)	.74
Autumn	−0.055 (0.052)	.29	−0.089 (0.069)	.20	−0.0003 (0.015)	.98

Notes: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; MMSE, Mini-Mental State Examination; WHAS I, Women's Health and Aging Study I.

*Reference category is never smoking.

†Reference category is inactive.

‡Season at time of blood drawing. Winter is the reference category.

stroke, and chronic obstructive pulmonary disease were significantly and negatively associated with both FEV_1 and FVC (Table 2). Cognitive impairment, anemia, stroke, and chronic obstructive pulmonary disease were associated with FEV_1/FVC but no significant relationship was found between FEV_1/FVC and age, education, IL-6, heart failure, and peripheral artery disease. White race, height, serum 25(OH)D, and physical activity were significantly and positively associated with both FEV_1 and FVC. Serum calcium was positively associated with FEV_1 but not with FVC or FEV_1/FVC. Current smoking was negatively associated with FEV_1 and FEV_1/FVC but not with FVC.

1,25-Dihydroxyvitamin D, use of vitamin D supplements, serum phosphate, angina, depression, cancer, and chronic kidney disease were not significantly associated with FEV_1, FVC, or FEV_1/FVC. Stroke was not significantly associated with FEV_1 but was significantly and negatively associated with FVC. There was no significant relationship between season and FEV_1, FVC, or FEV_1/FVC.

Multivariable linear regression models were used to examine the relationship between serum 25(OH)D, serum PTH, and other factors with FEV_1 (Table 3). Serum 25(OH)D was associated with FEV_1 when included with all covariates except PTH (Model 1; $p = .03$). Serum PTH was not associated with FEV_1 when included with all covariates except serum 25(OH)D (Model 2; $p = .34$). Both serum 25(OH)D and serum PTH were included with all covariates in Model 3; serum 25(OH)D was associated with FEV_1 ($p = .03$), but the association of serum PTH and FEV_1 was not significant ($p = 0.42$). When an interaction term between log serum 25(OH)D and log PTH was added with all the covariates in Model 3, the interaction term was not significant.

Multivariable linear regression models were used to examine the relationship between serum 25(OH)D, serum PTH,

Table 3. Multivariable Linear Regression Models of the Relationship Between Serum 25(OH)D, PTH, and FEV_1, FVC, and FEV_1/FVC, Respectively, Among Women in WHAS I*

	Model 1, Vitamin D but Not PTH		Model 2, PTH but Not Vitamin D		Model 3, Both Vitamin D and PTH	
Characteristic	β (*SE*)	*p* Value	β (*SE*)	*p* Value	β (*SE*)	*p* Value
FEV_1 as dependent variable						
Log 25(OH)D (ng/mL)	0.039 (0.017)	.03			0.038 (0.018)	.03
Log PTH (ng/mL)			−0.018 (0.018)	.34	−0.015 (0.019)	.42
FVC as dependent variable						
Log 25(OH)D (ng/mL)	0.032 (0.023)	.15			0.031 (0.023)	.18
Log PTH (ng/mL)			−0.014 (0.024)	.33	−0.015 (0.024)	.53
FEV_1/FVC as dependent variable						
Log 25(OH)D (ng/mL)	0.011 (0.005)	.03			0.011 (0.005)	.04
Log PTH (ng/mL)			−0.006 (0.006)	.27	−0.004 (0.005)	.41

Notes: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; WHAS I, Women's Health and Aging Study I.

*All models adjusted for age, race, education, smoking, height, physical activity, Mini-Mental State Examination score, IL-6, anemia, congestive heart failure, peripheral artery disease, and stroke.

and other factors with FVC (Table 3). Serum 25(OH)D was not associated with FVC when included with all covariates except PTH (Model 1; $p = .15$). Serum PTH was not associated with FVC when included with all covariates except serum 25(OH)D (Model 2; $p = .33$). Both serum 25(OH)D and serum PTH were included with all covariates in Model 3; neither serum PTH ($p = .53$) nor serum 25(OH)D ($p = .18$) was associated with FVC. When an interaction term between log serum 25(OH)D and log PTH was added to all the covariates in Model 3, the interaction term was not significant.

Multivariate linear regression models were used to examine the relationship between serum 25(OH)D, serum PTH, and other factors with FEV_1/FVC (Table 3). Serum 25(OH)D was associated with FEV_1/FVC when included with all covariates except PTH (Model 1; $p = .03$). Serum PTH was not associated with FEV_1/FVC when included with all covariates except serum 25(OH)D ($p = .27$). When both serum 25(OH)D and serum PTH were included with all covariates in Model 3, serum 25(OH)D was associated with FEV_1/FVC ($p = .04$) but serum PTH was not ($p = .41$). There was no significant interaction between log serum 25(OH)D and log PTH when entered with the same covariates as in Model 3.

Discussion

The present study shows that serum 25(OH)D is independently associated with pulmonary function in older disabled women living in the community. These results corroborate the findings of Black and colleagues (14) that showed a positive relationship between vitamin D status and pulmonary function in the Third National Health and Nutrition Examination Survey study. In addition, the present study extends the findings to older and more disabled community-dwelling women. The percent predicted FEV_1 and FVC values suggest that most of the women in this cohort had at least mild restrictive or obstructive pulmonary disease. No significant correlation was found between 1,25-hydroxyvitamin D and pulmonary function, but 1,25-hydroxyvitamin D is not considered a long-term indicator of vitamin D status.

A strength of the study is that it involved a population-based sample of older disabled women living in the community. Chronic diseases were carefully adjudicated, and pulmonary function was assessed in a standardized manner by highly trained nurses. The analyses were adjusted for inflammation, which has previously been associated with lower pulmonary function (26). A limitation of the study is the cross-sectional nature of the study, as a causal direction of the association between vitamin D status and pulmonary function cannot be established. It is possible that women with low pulmonary function had lower physical activity and less exposure to ultraviolet type B rays, resulting in low vitamin D levels. However, physical activity was included as a covariate in the multivariable analyses. In addition, as with any epidemiological study, it is not possible to measure all factors that might influence pulmonary function; thus, there may be unmeasured confounding factors. The older generation assay used to measure 25(OH)D in the present study is considered less accurate than more recent assays, such as the DiaSorin assay that distinguishes vitamin $25(OH)D_3$ and $25(OH)D_2$ forms equally. Another limitation of the study is that chronic obstructive pulmonary disease was classified on the basis of a diagnostic algorithm rather than post-bronchodilator fixed ratio of 0.7.

Further studies are needed to determine if older adults with low serum 25(OH)D levels are at higher risk of developing a greater decline in pulmonary function over time. A recent nested case–control study showed that adults with lower plasma 25(OH)D concentrations at baseline were not at higher risk of rapid decline in pulmonary function over 6 years of follow-up (27). This study differs significantly from the present study, in that all the study participants were mostly middle-aged males who were continuous smokers.

Vitamin D status may affect pulmonary function through biological mechanisms involving calcium and bone, skeletal

muscle function, and immunity. Vitamin D protects against osteoporosis, and osteoporosis can lead to loss of vertebral height and vertebral fractures. Both vital capacity and total lung capacity are decreased in patients with thoracic vertebral fractures (28,29) and reduced vertebral height (30). Low serum 25(OH)D and high serum PTH levels are predictive of the loss of muscle strength and muscle mass in older men and women (31). Vitamin D deficiency is associated with impaired physical performance (8) and with poorer improvement in exercise capacity after pulmonary rehabilitation in patients with chronic obstructive pulmonary disease (32). Vitamin D supplementation increases muscle strength in adults who are vitamin D deficient (33). Vitamin D deficiency could potentially affect skeletal muscles that are involved in respiration and compromise pulmonary function. Moreover, vitamin D plays an important role in both innate and adaptive immunities. Vitamin D is involved in maintaining epithelial barrier function and production of antimicrobial defenses such as cathelicidin and some defensins and in T-cell activation (34). A recent epidemiological study in Great Britain involving over 6,000 participants, aged 45 years and older, showed that circulating 25(OH)D concentrations had a positive linear correlation with lung function and a negative linear correlation with respiratory infections (35), implicating a biological role for vitamin D in immune defense of the lung. Thus, scientific evidence exists to support the idea that vitamin D can influence pulmonary function through effects on bone, skeletal muscle, and immune function.

Most of the circulating vitamin D is bound to vitamin D–binding globulin. Polymorphisms in vitamin D–binding protein gene (*GC*) have been associated with an increased risk of chronic obstructive pulmonary disease (36). Vitamin D can be taken up by cells either in bound or unbound forms, and whether levels of vitamin D–binding globulin or affinity of vitamin D–binding globulin to 25(OH)D affect the action of 25(OH)D is not well understood. Further genome-wide studies may help corroborate the relationship between polymorphisms in the vitamin D–binding protein gene and pulmonary function.

Low circulating 25(OH)D concentrations have been associated with an increasing number of nonskeletal aging-related phenotypes, such as bladder dysfunction, cardiovascular disease, age-related macular degeneration, and Alzheimer's disease (37–39), as well as increased mortality (40). The Institute of Medicine recently concluded that serum 25(OH)D concentrations of at least 20 ng/mL were sufficient to ensure skeletal health and that the evidence for the effects of vitamin D on nonskeletal outcomes was still inconclusive (41).

If the link between vitamin D status and lung function proves to be causal, the problem of poor pulmonary health may be growing with the increasing prevalence of deficiency in the United States (42). Further work is needed to determine whether vitamin D status is an independent predictor of a decline in pulmonary function in community-dwelling adults. Pulmonary function should be included as an outcome measure in vitamin D supplementation studies in adults. Clinical trials of vitamin D supplementation for patients with chronic obstructive pulmonary disease are currently in progress (43).

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