Peak expiratory flow rate shows a gender-specific association with vitamin D deficiency

van Schoor, N.M.; de Jongh, R.T.; Daniels, J.M.A.; Heijmans, M.W.; Deeg, D.J.H.; Lips, P.T.A.M.

published in
Journal of Clinical Endocrinology and Metabolism
2012

DOI (link to publisher)
10.1210/jc.2011-3199

document version
Publisher's PDF, also known as Version of record

Peak Expiratory Flow Rate Shows a Gender-Specific Association with Vitamin D Deficiency

N. M. van Schoor, R. T. de Jongh, J. M. A. Daniels, M. W. Heymans, D. J. H. Deeg, and P. Lips

Department of Epidemiology and Biostatistics (N.M.v.S., M.W.H., D.J.H.D., P.L.), EMGO Institute for Health and Care Research, and Departments of Internal Medicine and Endocrinology (R.T.d.J., P.L.) and Pulmonary Diseases (J.M.A.D.), VU University Medical Center, 1081 BT Amsterdam, The Netherlands

Context: To our knowledge, no previous studies examined the longitudinal relationship between vitamin D status and pulmonary function in a population-based sample of older persons.

Objective: Our objective was to examine the cross-sectional as well as the longitudinal relationship between vitamin D status and peak expiratory flow rate (PEFR) in a representative sample of the Dutch older population.

Design, Setting, and Participants: Participants included men and women in the Longitudinal Aging Study Amsterdam, an ongoing cohort study in older people.

Main Outcome Measure: PEFR was measured using the mini-Wright peak flow meter.

Results: Men with serum 25-hydroxyvitamin D (25-OHD) levels below 10 ng/ml (25 nmol/liter) had a significantly lower PEFR in the cross-sectional analyses, and men with serum 25-OHD levels below 20 ng/ml (50 nmol/liter) had a significantly lower PEFR in the longitudinal analyses as compared with men with serum 25-OHD levels above 30 ng/ml (75 nmol/liter) (cross-sectional: $\beta = -47.0$, $P = 0.01$ for serum 25-OHD <10 ng/ml; longitudinal: $\beta = -45.0$, $P < 0.01$ for serum 25-OHD <10 ng/ml; and $\beta = -20.2$, $P = 0.03$ for serum 25-OHD $= 10–20$ ng/ml in the fully adjusted models). Physical performance ($\beta = -32.5$, $P = 0.08$ for serum 25-OHD <10 ng/ml) and grip strength ($\beta = -40.0$, $P = 0.03$ for serum 25-OHD <10 ng/ml) partly mediated the cross-sectional associations but not the longitudinal associations. In women, statistically significant associations between 25-OHD and PEFR were observed in the cross-sectional analyses after adjustment for age and season of blood collection but not in the fully adjusted models or in the longitudinal analyses.

Conclusions: A strong relationship between serum 25-OHD and PEFR was observed in older men, both in the cross-sectional as well as longitudinal analyses, but not in older women. The association in men could partly be explained by physical performance and muscle strength. **(*J Clin Endocrinol Metab* 97: 2164–2171, 2012)**

Low vitamin D status has been associated with respiratory diseases, such as pulmonary tuberculosis (1), chronic obstructive pulmonary disease (COPD) (2, 3), asthma (4, 5), and upper respiratory tract infections (6–8). One of the potential explanations for the observed association between low vitamin D status and respiratory tract infections might be a decrease of pulmonary function. In the literature, only two studies were found examining the association between serum 25-hydroxyvitamin D (25-OHD) and pulmonary function in the general population. In the Third National Health and Nutrition Examination Survey (NHANES III) , a strong cross-sectional association was found between serum 25-OHD and forced expiratory volume (FEV_1) and forced vital capacity

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2011-3199 Received November 22, 2011. Accepted March 13, 2012.
First Published Online April 3, 2012

Abbreviations: ATC, Anatomical Therapeutic Chemical; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume; FVC, forced vital capacity; LASA, Longitudinal Aging Study Amsterdam; NHANES III, Third National Health and Nutrition Examination Survey; 25-OHD, 25-hydroxyvitamin D; PEFR, peak expiratory flow rate.

(FVC) in adults, but not with FEV_1/FVC (9). In the Hertfordshire Cohort Study, serum 25-OHD was not related to FEV_1, FVC, or FEV_1/FVC in adults (10). To the best of our knowledge, longitudinal data on vitamin D and pulmonary function are not available in the general population.

Earlier studies showed that vitamin D status was strongly positively related to muscle strength and physical performance tests (11–13). Because pulmonary function depends on muscle function, muscle strength and physical performance will be considered as potential mediators in the current study.

The present study examines the cross-sectional as well as the longitudinal relationship between vitamin D status and peak expiratory flow rate (PEFR) in a representative sample of the Dutch older population. In addition, the mediating effects of muscle strength and physical performance will be examined. Finally, the optimal cutoff point for serum 25-OHD in the relationship with PEFR will be estimated. The following hypotheses will be tested: 1) lower serum 25-OHD levels are associated with decreasing PEFR, and 2) the relationship between serum 25-OHD and PEFR is mediated by physical performance and muscle strength.

Subjects and Methods

Subjects

The Longitudinal Aging Study Amsterdam (LASA) is an ongoing multidisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional, and social functioning in older persons. A random sample of men and women aged 55 yr and over, stratified by age, sex, urbanization grade, and expected 5-yr mortality rate was drawn from the population registers of 11 municipalities in three regions of The Netherlands. In total, 3107 persons were enrolled in the baseline examination in 1992–1993 (14). Measurement cycles were repeated every 3 yr and included a main interview and medical interview. For the present study, persons who participated in the medical interview in 1995/1996 and were born in or before 1930 (aged 65 yr and older as of January 1, 1996), were selected (n = 1509). In 1352 of these persons, blood samples were drawn, and valid serum 25-OHD could be determined in 1320 samples. Data on serum 25-OHD, PEFR, and covariables were available for 596 men and 611 women in the cross-sectional analyses (1995/1996) and for 454 men and 496 women in the longitudinal analyses (1995/1996–1998/1999). The Medical Ethics Committee (Ethical Review Board) of the VU University Medical Center approved the study, and all persons gave informed consent.

Peak expiratory flow rate

PEFR is defined as a person's maximum speed of expiration. PEFR was measured using the mini-Wright peak flow meter in 1995/1996 and 1998/1999. All subjects received instructions about the use of the peak flow meter. For the measurements, the subjects were asked to take a maximum inspiration and to breathe out with maximum effort into the peak flow meter. The highest score of three measurements was used (15).

Serum 25-OHD

Morning blood samples were obtained in 1995/1996. Subjects were allowed to have tea and toast but no dairy products. The blood samples were centrifuged and stored at −20 C. Serum 25-OHD was determined using a competitive protein binding assay in 1997/1998 (Nichols Diagnostics, San Juan Capistrano, CA). The interassay coefficient of variation was 10%. All analyses were performed at the Endocrine Laboratory of the VU University Medical Center.

Potential effect modifiers

Because of differences in vitamin D status and PEFR between men and women, sex was identified as a potential effect modifier (16, 17).

Potential confounders

Potential confounders were age, sex (if no interaction effect was found), season of blood collection, education, weight, height, smoking, obstructive airway diseases (asthma, chronic bronchitis, or pulmonary emphysema), physical activity, and medication use (corticosteroids, estrogens, β-blockers, or benzodiazepines). Education level was assessed by asking the respondent for the highest education level completed. This was converted into elementary school or less, secondary school, or higher education. Body height was measured using a stadiometer. Body weight was measured without clothes and shoes using a calibrated bathroom balance scale. Smoking (never/stopped smoking >15 yr ago, stopped smoking ≤15 yr ago, or current smoker) was assessed by self-report. Presence of obstructive airway disease was assessed by self-report. Activity level was assessed in minutes per day by the LASA Physical Activity Questionnaire, a questionnaire covering the following areas: walking outside, bicycling, gardening, light household activities, heavy household activities, and a maximum of two sport activities during the previous 2 wk (18). Medication use was assessed by asking the respondents to show their medication containers to the interviewers. The medication names were recoded into Anatomical Therapeutic Chemical (ATC) classification system codes using the ATC index from the World Health Organization.

Potential mediators

Handgrip strength, an indicator of overall muscle strength (19), was assessed using a strain-gauged dynamometer (Takei TKK 5001; Takei Scientific Instruments Co. Ltd., Tokyo, Japan). Participants were asked to perform two maximum-force trials with each hand, while standing with their arm along the body. To calculate the total score, the maximum values of the right and the left hand were summed and divided by two (20). If only one hand could be used, the maximum value of that hand was taken. Physical performance was assessed by three tests: time needed to walk 3 m along a line, turn 180°, and walk back (walking test); time needed to stand up from and sit down on a chair five times with arms folded across the chest (chair stands test); and the ability to perform the tandem stand (one foot placed behind the other on a straight line) for at least 10 sec (13, 21). For the walking test and chair stands test, scores one (slowest) to four (fastest) were given according to the quartile of the distribution of time needed in the total LASA cohort. Score zero was given to those respondents who could not complete the test. The tandem stand was catego-

rized as follows: unable (score 0), able to hold position for 3–9 sec (score 2), and able to hold position for at least 10 sec (score 4). The total physical performance sum score ranged from zero (low physical performance) to 12 (high physical performance).

Statistical analyses

Vitamin D categories were made using common cutoff points (serum 25-OHD <10, 10–20, 20–30, or ≥30 ng/ml or <25, 25–50, 50–75, or ≥75 nmol/liter) (22). First, baseline differences between vitamin D categories were tested. Depending on the distribution of the variable, differences in mean were tested using one-way ANOVA, differences in median were tested using Kruskal-Wallis *H* test, and differences in frequencies were tested using Pearson χ^2 test. Second, sex was tested as an effect modifier using univariable linear regression analysis with serum 25-OHD in dummies (serum 25-OHD <10, 10–20, 20–30, or ≥30 ng/ml = reference). Third, the analyses were adjusted for potential confounders. Physical performance and grip strength were included in separate models, because these variables could mediate the relationship under study. In the longitudinal analyses, all models were adjusted for baseline PEFR. The assumptions of linear regression analyses were checked by making histograms and normal probability plots of the standardized residuals. Multicollinearity was checked by calculating correlation coefficients between the independent variables. These were sufficiently low to enter all variables ($r < 0.4$). Fourth, two sensitivity analyses were performed. First, corticosteroids, estrogens, β-blockers, and benzodiazepines, respectively, were added as confounders to the fully adjusted models in both the cross-sectional as well as the longitudinal analyses. Second, persons having self-reported obstructive airway diseases at baseline were excluded from the longitudinal analyses. The above analyses were performed using SPSS version 15.0.1.

Finally, we used restricted cubic spline functions and spline plots to estimate an optimal cutoff point for serum 25-OHD in the cross-sectional and longitudinal relationship with PEFR. Cubic splines are piecewise polynomial functions that are constrained to join smoothly at points called knots. These spline functions provide better insight into dose-response relationships compared with analyses using categorized variables. Restricted cubic spline functions use all data points to estimate the risk at each level of exposure, as opposed to step functions using categorical variables, which assume a constant risk within categories. Cubic spline functions were tested in regression models at three knots using spline plots and likelihood ratio tests. Eventually, the best fitting spline regression model was identified. All spline regression analyses were performed using R version 2.10.0 (23).

Results

Mean serum 25-OHD was 23.5 ng/ml in men (SD = 9.8) and 19.7 ng/ml in women (SD = 9.2). In men, 8.1% had a serum 25-OHD level below 10 ng/ml, 38.1% below 20 ng/ml, and 75.8% below 30 ng/ml. In women, 13.4% had a serum 25-OHD level below 10 ng/ml, 56.3% below 20 ng/ml, and 86.9% below 30 ng/ml.

Baseline data are presented in Tables 1 and 2. Men having lower serum 25-OHD levels were older and had

TABLE 1. Baseline characteristics in men

	25-OHD				
	<10 ng/ml, n = 48	**10–20 ng/ml, n = 179**	**20–30 ng/ml, n = 225**	**≥30 ng/ml, n = 144**	***P* value**
Age[a]	78.8 ± 6.0	77.7 ± 6.8	74.9 ± 6.1	72.2 ± 5.5	<0.01
Season (% winter)	64.6	60.9	50.2	50.7	0.06
Education (%)					
Less than high school	25.0	31.3	28.0	25.7	<0.01
High school graduate	43.8	52.0	61.8	53.5	
Postsecondary school	31.3	16.8	10.2	20.8	
Height[a]	171.2 ± 7.4	172.2 ± 6.6	172.8 ± 6.6	174.6 ± 6.2	<0.01
Weight[a]	76.9 ± 12.8	77.8 ± 11.9	78.5 ± 12.1	78.8 ± 11.3	0.74
Smoker (%)					
Never/stopped >15 yr ago	45.8	54.7	54.2	51.4	0.13
Stopped ≤15 yr ago	14.6	19.0	24.9	25.0	
Current	39.6	26.3	20.9	23.6	
Obstructive airway diseases (% yes)	22.9	17.3	16.0	13.2	0.44
Corticosteroids (% yes)	2.1	0.6	3.6	0.7	0.10
β-blockers (% yes)	16.7	17.9	16.9	13.9	0.81
Benzodiazepines (% yes)	18.8	5.0	6.2	6.3	<0.01
Physical activity (min/d)[b]	95.7 (43.4–165.4)	94.3 (47.1–154.3)	112.0 (69.1–175.6)	121.1 (60.2–177.7)	0.03
Physical performance[a]	5.6 ± 3.2	7.5 ± 3.0	8.4 ± 2.6	9.0 ± 2.3	<0.01
Grip strength (kg)[a]	30.5 ± 7.1	34.3 ± 7.8	36.4 ± 7.3	38.8 ± 7.9	<0.01
PEFR in 1995/1996[a]	366.7 ± 145.4	414.7 ± 128.8	439.3 ± 122.3	476.0 ± 117.1	<0.01
PEFR in 1998/1999[a,c]	360.0 ± 123.7	422.5 ± 124.5	457.0 ± 123.1	490.8 ± 122.8	<0.01

Differences in means were tested using one-way ANOVA, differences in median were tested using Kruskal-Wallis *H* test, and differences in frequencies were tested using Pearson χ^2 test. To convert 25-OHD values from nanograms per milliliter to nanomoles per liter, multiply by 2.496.

[a] Mean ± SD are presented.

[b] Median (interquartile range) is presented.

[c] Numbers of persons are 29, 130, 177, and 118 in 25-OHD groups ranging from 25-OHD <10 to 25-OHD ≥30 ng/ml.

TABLE 2. Baseline characteristics in women

	25-OHD in women				
	<10 ng/ml, n = 82	**10–20 ng/ml, n = 262**	**20–30 ng/ml, n = 187**	**≥30 ng/ml, n = 80**	***P* value**
Age[a]	80.6 ± 5.7	76.3 ± 6.3	72.9 ± 5.5	72.1 ± 5.3	<0.01
Season (% winter)	68.3	59.5	51.3	47.5	0.02
Education (%)					
Less than high school	56.1	53.8	48.1	53.8	0.82
High school graduate	35.4	38.2	44.4	40.0	
Postsecondary school	8.5	8.0	7.5	6.3	
Height[a]	157.1 ± 5.9	160.0 ± 6.9	161.3 ± 6.0	162.4 ± 5.5	<0.01
Weight[a]	69.8 ± 15.4	71.5 ± 13.2	71.4 ± 10.8	69.0 ± 10.8	0.34
Smoker (%)					
Never/stopped > 5 yr ago	80.5	75.2	80.7	87.5	0.20
Stopped ≤15 yr ago	4.9	9.9	9.1	6.3	
Current	14.6	14.9	10.2	6.3	
Obstructive airway diseases (% yes)	9.8	14.1	9.1	8.8	0.30
Corticosteroids (% yes)	3.7	1.5	3.2	2.5	0.60
Estrogens (% yes)	2.4	1.1	1.6	1.3	0.86
β-blockers (% yes)	13.4	16.8	17.1	12.5	0.70
Benzodiazepines (% yes)	28.0	21.0	17.1	13.8	0.09
Physical activity (min/d)[b]	128.2 (76.8–188.9)	155.0 (103.9–217.2)	172.5 (121.4–240.0)	191.8 (121.1–241.1)	<0.01
Physical performance[a]	4.7 ± 3.1	6.4 ± 3.2	7.9 ± 3.0	8.2 ± 3.0	<0.01
Grip strength (kg)[a]	17.9 ± 4.2	20.8 ± 4.7	22.3 ± 4.7	23.1 ± 4.0	<0.01
PEFR in 1995/1996[a]	293.5 ± 99.3	325.5 ± 97.8	348.9 ± 80.8	372.4 ± 81.0	<0.01
PEFR in 1998/1999[a,c]	302.7 ± 103.9	325.1 ± 98.9	349.8 ± 93.6	369.7 ± 84.2	<0.01

Differences in means were tested using one-way ANOVA, differences in median were tested using Kruskal-Wallis *H* test, and differences in frequencies were tested using Pearson χ^2 test.

[a] Mean ± SD are presented.

[b] Median (interquartile range) is presented.

[c] Numbers of persons are 56, 208, 160, and 72 in 25-OHD groups ranging from 25-OHD <10 to 25-OHD ≥30 ng/ml.

lower height, less physical activity, lower physical performance, lower grip strength, and lower PEFR as compared with men having higher serum levels. In addition, there were differences in educational level between different vitamin D groups. Women having lower serum 25-OHD levels were older, were more often studied in winter, and had lower height, less physical activity, lower physical performance, lower grip strength, and lower PEFR as compared with women having higher serum levels.

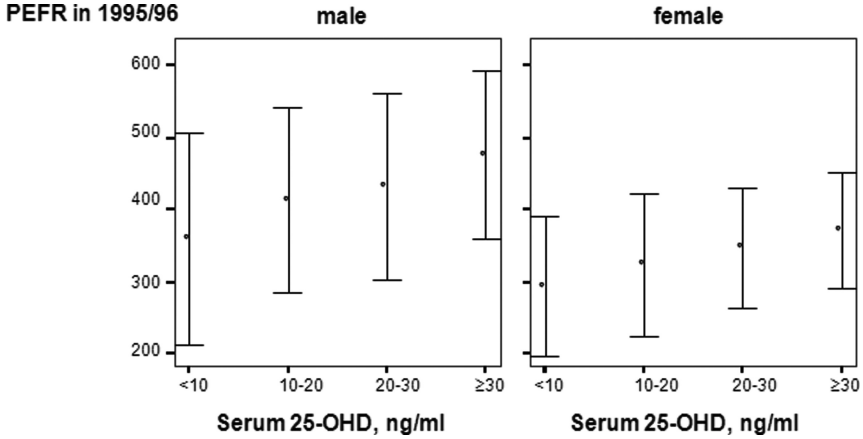

FIG. 1. Cross-sectional association between serum 25-OHD in categories and PEFR. Presented are the mean and 95% confidence intervals.

An interaction effect between vitamin D status and sex was observed in the longitudinal analyses ($P = 0.09$ for serum 25-OHD <10 ng/ml as compared with 25-OHD ≥ 30 ng/ml) but not in the cross-sectional analyses ($P \geq 0.12$). For comparability reasons, all analyses were stratified for sex.

In Figs. 1 and 2, the unadjusted cross-sectional and longitudinal associations between serum 25-OHD groups and PEFR are presented stratified according to sex. In both men and women, a higher PEFR was observed for higher vitamin D categories.

In Table 3, the cross-sectional and longitudinal associations between serum 25-OHD and PEFR are presented in men and women. In men, a strong relationship between vitamin D status and PEFR was observed for serum 25-OHD levels up to 20 ng/ml. In the cross-sectional analyses, this association was no longer statistically significant for serum 25-OHD levels between 10 and 20 ng/ml in the fully adjusted model ($P = 0.13$) but remained statistically significant for serum 25-OHD levels below 10 ng/ml ($P = 0.01$). In the longitudinal

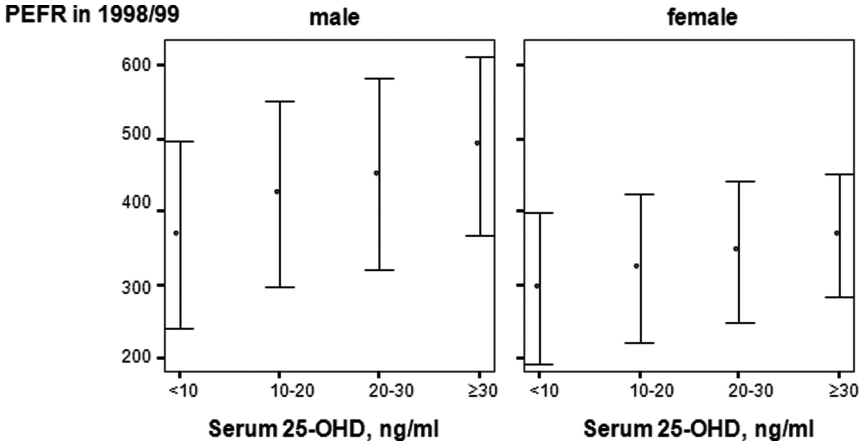

FIG. 2. Longitudinal association between serum 25-OHD in categories and PEFR.

analyses, the relationships remained statistically significant up to a serum 25-OHD level of 20 ng/ml. Adjustment for physical performance or grip strength did not change these results in the longitudinal analyses. However, in the cross-sectional analyses, the relationship between serum 25-OHD and PEFR was no longer statistically significant after adding the potential mediator grip strength ($P = 0.08$ for serum 25-OHD <10 ng/ml). In women, serum 25-OHD levels below 20 ng/ml were significantly associated with lower PEFR in the cross-sectional analyses after adjustment for age and season. However, the associations were no longer statistically significant after adding smoking or height to the model (data not shown) or in the fully adjusted model (Table 3). In addition, no statistically significant associations were observed after adjustment for potential mediators or in the longitudinal models.

When adding corticosteroids, estrogens, β-blockers, and benzodiazepines, respectively, to the fully adjusted models, the results were highly similar in both the cross-sectional as well as the longitudinal analyses (data not shown).

Persons reporting obstructive airway diseases at baseline had similar 25-OHD levels (median = 19.5 ng/ml, interquartile range = 14.2–27.3) as compared with persons not reporting obstructive airway diseases (median = 20.4 ng/ml, interquartile range = 14.4–27.3). When excluding persons having self-reported obstructive airway diseases at baseline in the longitudinal analyses, similar associations were observed. Men having serum 25-OHD levels below 10 ng/ml showed somewhat stronger associations ($\beta = -49.9$, $P < 0.01$ in the fully adjusted model; $\beta = -48.8$, $P < 0.01$ after adjustment for physical performance; $\beta = -46.8$, $P < 0.01$ after adjustment for grip strength). Men having serum 25-OHD levels between 10 and 20 ng/ml showed similar associations (data not shown). However, these were only borderline statistically significant ($P = 0.05$ in the fully adjusted mod-

TABLE 3. Cross-sectional and longitudinal association between serum 25-OHD and PEFR

	Model 1		Model 2		Model 3		Model 4	
25-OHD	**β (SE)**	***P* value**	**β (SE)**	***P* value**	**β (SE)**	***P* value**	**β (SE)**	***P* value**
Men								
Cross-sectional, n = 596								
<10 ng/ml	−73.3 (20.8)	<0.01	−47.0 (18.1)	0.01	−32.5 (18.2)	0.08	−40.0 (18.3)	0.03
10–20 ng/ml	−30.9 (14.2)	0.03	−18.9 (12.3)	0.13	−16.3 (12.2)	0.18	−16.6 (12.3)	0.18
20–30 ng/ml	−21.5 (13.0)	0.10	−14.3 (11.3)	0.21	−13.6 (11.1)	0.22	−13.1 (11.3)	0.25
≥30 ng/ml	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Longitudinal, n = 454								
<10 ng/ml	−50.1 (14.8)	<0.01	−45.0 (14.8)	<0.01	−43.0 (15.0)	<0.01	−42.4 (15.1)	<0.01
10–20 ng/ml	−22.8 (9.3)	0.01	−20.2 (9.3)	0.03	−19.9 (9.3)	0.03	−19.5 (9.3)	0.04
20–30 ng/ml	−1.0 (8.4)	0.91	−0.2 (8.4)	0.98	−0.3 (8.4)	0.97	0.1 (8.4)	0.99
≥30 ng/ml	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Women								
Cross-sectional, n = 611								
<10 ng/ml	−33.8 (14.6)	0.02	−26.1 (14.2)	0.07	−18.9 (14.1)	0.18	−17.8 (14.1)	0.21
10–20 ng/ml	−24.7 (11.3)	0.03	−17.1 (11.0)	0.12	−13.8 (10.9)	0.21	−13.8 (10.9)	0.20
20–30 ng/ml	−18.9 (11.5)	0.10	−17.7 (11.1)	0.11	−17.6 (10.9)	0.11	−15.6 (10.9)	0.15
≥30 ng/ml	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Longitudinal, n = 496								
<10 ng/ml	8.3 (12.4)	0.51	12.2 (12.5)	0.33	14.3 (12.5)	0.25	15.4 (12.4)	0.22
10–20 ng/ml	−1.0 (9.1)	0.91	−0.6 (9.1)	0.95	0.7 (9.1)	0.94	1.0 (9.0)	0.92
20–30 ng/ml	4.3 (9.2)	0.64	1.2 (9.1)	0.90	1.1 (9.1)	0.90	1.6 (9.0)	0.86
≥30 ng/ml	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference

Model 1 was adjusted for age, season (and baseline PEFR in longitudinal analyses). Model 2 was additionally adjusted for education, height, weight, smoking, obstructive airway diseases, and physical activity. Model 3 is the same as model 2 and additionally adjusted for physical performance. Model 4 is the same as model 2 and additionally adjusted for grip strength.

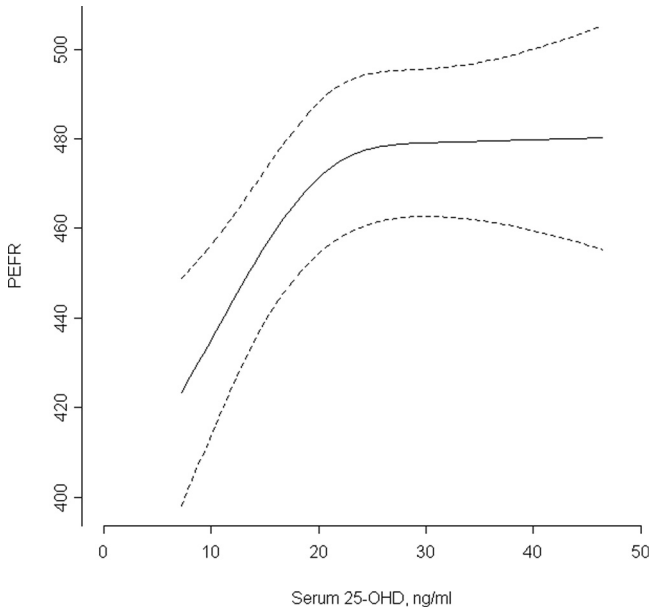

FIG. 3. Longitudinal association between serum 25-OHD and PEFR in men. The *dotted line* represents 95% confidence interval.

el; $P = 0.06$ after adjustment for physical performance or grip strength). In women, no statistically significant associations were observed. However, a trend toward significance was observed after adjustment for physical performance ($P = 0.08$) or grip strength ($P = 0.07$).

Figure 3 shows the multivariable longitudinal association between serum 25-OHD and PEFR in men. The spline plot shows increasing PEFR up to a serum 25-OHD level of 24 ng/ml (60 nmol/liter). At the lower and higher end of the spline plot, the confidence interval becomes wider due to lower numbers of persons having lower or higher 25-OHD levels. The multivariable cross-sectional association between serum 25-OHD and PEFR in men did not show a cutoff point and was best fit by a linear function (data not shown).

Discussion

Serum 25-OHD was strongly related to PEFR in men, both in the cross-sectional as well as in the longitudinal analyses. In the longitudinal analyses, a cutoff point was observed in men at a serum 25-OHD level of 24 ng/ml. In women, the results were less consistent, showing only statistically significant results in the cross-sectional analyses. The results were very similar when excluding persons having self-reported obstructive airway diseases at baseline.

In NHANES III, a strong relationship was found between serum 25-OHD and FEV_1 and FVC in adults (9). In contrast, in the Hertfordshire Cohort Study, serum 25-OHD was not significantly related to FEV_1, FVC, or FEV_1/FVC (10). The latter study did find significant positive associations between dietary vitamin D intake and FEV_1 and FEV_1/FVC but not between genotypes of the vitamin D receptor and lung function (10). According to the authors, the observed associations between dietary vitamin D intake and lung function may be explained by other nutrients in the diet that are correlated to dietary vitamin D. In Chinese asthma patients, significant associations between serum 25-OHD and FEV_1 and FEV_1/FVC ratio were observed (24). In addition, in a small study in asthma patients, serum 25-OHD was positively associated with FEV_1 (25). However, in the Lung Health Study 3 cohort, baseline 25-OHD levels were not predictive of subsequent pulmonary function decline in cases (smokers having the most rapid decline in FEV_1) *vs.* controls (smokers having the least decline) (26). In patients with COPD, 25-OHD levels correlated significantly with FEV1 (3).

From the above studies, only NHANES III and the Hertfordshire Cohort Study were performed in the general population (NHANES III: aged 20+ with 4329 persons aged 60 yr and over; Hertfordshire Cohort Study: aged 59–73 yr). Although pulmonary function was measured by PEFR in the current study, our study confirms the results observed in NHANES III. In both NHANES III and the Hertfordshire Cohort Study, however, the longitudinal association between serum 25-OHD and pulmonary function was not examined. In our study, a longitudinal relationship between serum 25-OHD and PEFR was observed only in men but not in women. The reason for this is unclear. It may be more difficult to find a statistically significant result in women, because women showed less variation in PEFR than men. In addition, women had lower PEFR values than men, and fewer women reported obstructive airway diseases at baseline. When excluding women having obstructive airway diseases at baseline, a trend toward significance was observed after additional adjustment for physical performance and grip strength, respectively.

In the cross-sectional analyses, a statistically significant lower PEFR was observed in women having serum 25-OHD levels below 10 ng/ml. This association disappeared after adjustment for height or smoking. In a systematic review on sex differences in COPD, it was postulated that women may be more susceptible to COPD than men (27). One of the reasons may be that women have smaller lungs and that these smaller lungs result in a relatively greater dose of smoke to their lungs as compared with men. This may explain the large impact of height and smoking on the association between serum 25-OHD and PEFR in women in our study. In addition, in women, other factors may be more important, *e.g.* a higher genetic susceptibility to develop severe obstruction (27). Future studies are needed to confirm the interaction effect with sex and the explanation

behind this. In addition, the longitudinal association between 25-OHD and PEFR in the general population should be confirmed. In addition to the above analyses, in our study, the optimal cutoff point for the relationship between serum 25-OHD and PEFR was examined. Interestingly, the observed cutoff point is similar to the observed cutoff point for the association of 25-OHD with physical performance (28). It is important to validate the cutoff point for PEFR in other datasets.

Although several mechanisms have been proposed, it is not fully understood how vitamin D affects pulmonary function. In our study, we tested the hypothesis whether the positive association between vitamin D and pulmonary function could be explained by higher muscle strength. With the exception of men having serum 25-OHD levels below 10 ng/ml (cross-sectional analyses), adding physical performance or grip strength to the model did not lead to major changes in the association between serum 25-OHD and PEFR. Several other mechanisms have been proposed. First, *in vitro* studies revealed that vitamin D modulates the activity of various defense and immune cells (29). Vitamin D deficiency could result in altered host defense of the lung with subsequent growth of abnormal flora that triggers inflammation (29). High vitamin D-binding protein levels are associated with lower free vitamin D metabolite levels and may lead to increased macrophage activation and lower FEV_1 (30). Furthermore, it has been shown that *VDR* knockout mice had increased influx of inflammatory cells, phospho-acetylation of nuclear factor-κB associated with increased proinflammatory mediators, and up-regulation of matrix metalloproteinases in the lung (31). This was associated with emphysema and decline in pulmonary function (31). These results indicate that absence of the *VDR* may lead to an early onset of emphysema, possibly due to inflammation, immune dysregulation, and lung destruction (31). Second, in a mouse model, it was shown that vitamin D deficiency decreases pulmonary function. This was primarily explained by a deficit in lung volume and could not be explained by alterations in somatic growth (32).

Strengths of our study are that LASA is a large representative sample of Dutch older men and women and contains longitudinal data on PEFR. Limitations include that causality cannot be established within the setting of a cohort study, although the observed longitudinal relationship in men does support causality. Second, data on FEV_1 and FVC were not available. However, we do think that PEFR is a valid outcome, because it is an effort-independent measure of expiratory flow limitation, which might play a role in the observed association between vitamin D status and respiratory tract infections. In addition, PEFR is related to physical functioning, cognitive functioning, and mortality (33–35). Third, we did not have data on fat mass, which may be a more important confounder than body weight (36). Body weight is a poor predictor of fat mass and was not related to serum 25-OHD levels in our study. Finally, we have only self-reported data on obstructive airway diseases and no objective assessment of specific types of respiratory diseases such as COPD.

In conclusion, a strong relationship between serum 25-OHD and PEFR was observed in older men, both in the cross-sectional as well as longitudinal analyses, but not in older women. This association could partly be explained by physical performance or muscle strength. Randomized controlled trials are needed to assess a causal effect of vitamin D on pulmonary function and respiratory tract infections.

Acknowledgments

Address all correspondence and requests for reprints to: N. M. van Schoor, EMGO Institute for Health and Care Research, VU University Medical Center, Van der Boechorststraat 7 (Room A-517), 1081 BT Amsterdam, The Netherlands. E-mail: nm.vanschoor@vumc.nl.

The Longitudinal Aging Study Amsterdam is largely supported by a grant from The Netherlands Ministry of Health Welfare and Sports, Directorate of Long-Term Care. The writing of the manuscript is funded by the EMGO Institute for Health Care Research, VU University Medical Center.

Disclosure Summary: The authors have nothing to disclose.

References

1. **Nnoaham KE, Clarke A** 2008 Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. Int J Epidemiol 37:113–119
2. **Franco CB, Paz-Filho G, Gomes PE, Nascimento VB, Kulak CA, Boguszewski CL, Borba VZ** 2009 Chronic obstructive pulmonary disease is associated with osteoporosis and low levels of vitamin D. Osteoporos Int 20:1881–1887
3. **Janssens W, Bouillon R, Claes B, Carremans C, Lehouck A, Buysschaert I, Coolen J, Mathieu C, Decramer M, Lambrechts D** 2010 Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. Thorax 65:215–220
4. **Litonjua AA, Weiss ST** 2007 Is vitamin D deficiency to blame for the asthma epidemic? J Allergy Clin Immunol 120:1031–1035
5. **Brehm JM, Celedón JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, Laskey D, Sylvia JS, Hollis BW, Weiss ST, Litonjua AA** 2009 Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. Am J Respir Crit Care Med 179:765–771
6. **Ginde AA, Mansbach JM, Camargo Jr CA** 2009 Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med 169:384–390
7. **Laaksi I, Ruohola JP, Tuohimaa P, Auvinen A, Haataja R, Pihlajamäki H, Ylikomi T** 2007 An association of serum vitamin D concentrations <40 nmol/L with acute respiratory tract infection in young Finnish men. Am J Clin Nutr 86:714–717
8. **Sabetta JR, DePetrillo P, Cipriani RJ, Smardin J, Burns LA, Landry ML** 2010 Serum 25-hydroxyvitamin D and the incidence of acute

viral respiratory tract infections in healthy adults. PLoS One 5:e11088
9. **Black PN, Scragg R** 2005 Relationship between serum 25-hydroxyvitamin D and pulmonary function in the third national health and nutrition examination survey. Chest 128:3792–3798
10. **Shaheen SO, Jameson KA, Robinson SM, Boucher BJ, Syddall HE, Sayer AA, Cooper C, Holloway JW, Dennison EM** 2011 Relationship of vitamin D status to adult lung function and COPD. Thorax 66:692–698
11. **Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, Dawson-Hughes B** 2004 Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged ≥60 y. Am J Clin Nutr 80: 752–758
12. **Visser M, Deeg DJ, Lips P** 2003 Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab 88:5766–5772
13. **Wicherts IS, van Schoor NM, Boeke AJ, Visser M, Deeg DJ, Smit J, Knol DL, Lips P** 2007 Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab 92:2058–2065
14. **Deeg DJH, van Tilburg T, Smit JH, de Leeuw ED** 2002 Attrition in the Longitudinal Aging Study Amsterdam: the effect of differential inclusion in side studies. J Clin Epidemiol 55:319–328
15. **Cook NR, Evans DA, Scherr PA, Speizer FE, Vedal S, Branch LG, Huntley JC, Hennekens CH, Taylor JO** 1989 Peak expiratory flow rate in an elderly population. Am J Epidemiol 130:66–78
16. **Hagenau T, Vest R, Gissel TN, Poulsen CS, Erlandsen M, Mosekilde L, Vestergaard P** 2009 Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis. Osteoporos Int 20:133–140
17. **Boezen HM, Schouten JP, Postma DS, Rijcken B** 1994 Distribution of peak expiratory flow variability by age, gender and smoking habits in a random population sample aged 20–70 yrs. Eur Respir J 7:1814–1820
18. **Stel VS, Smit JH, Pluijm SM, Visser M, Deeg DJ, Lips P** 2004 Comparison of the LASA Physical Activity Questionnaire with a 7-day diary and pedometer. J Clin Epidemiol 57:252–258
19. **Rantanen T, Era P, Heikkinen E** 1994 Maximal isometric strength and mobility among 75-year-old men and women. Age Ageing 23: 132–137
20. **Kallman DA, Plato CC, Tobin JD** 1990 The role of muscle loss in the age-related decline of grip strength: cross-sectional and longitudinal perspectives. J Gerontol 45:M82–M88
21. **Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB** 1994 A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 49:M85–M94
22. **Snijder MB, van Schoor NM, Pluijm SM, van Dam RM, Visser M, Lips P** 2006 Vitamin D status in relation to one-year risk of recurrent falling in older men and women. J Clin Endocrinol Metab 91:2980–2985
23. **Steenland K, Deddens JA** 2004 A practical guide to dose-response analyses and risk assessment in occupational epidemiology. Epidemiology 15:63–70
24. **Li F, Peng M, Jiang L, Sun Q, Zhang K, Lian F, Litonjua AA, Gao J, Gao X** 2011 Vitamin D deficiency is associated with decreased lung function in Chinese adults with asthma. Respiration 81:469–475
25. **Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DY** 2010 Vitamin D levels, lung function, and steroid response in adult asthma. Am J Respir Crit Care Med 181:699–704
26. **Kunisaki KM, Niewoehner DE, Singh RJ, Connett JE** 2011 Vitamin D status and longitudinal lung function decline in the Lung Health Study. Eur Respir J 37:238–243
27. **Ohar J, Fromer L, Donohue JF** 2011 Reconsidering sex-based stereotypes of COPD. Prim Care Respir J 20:370–378
28. **Kuchuk NO, Pluijm SM, van Schoor NM, Looman CW, Smit JH, Lips P** 2009 Relationships of serum 25-hydroxyvitamin D to bone mineral density and serum parathyroid hormone and markers of bone turnover in older persons. J Clin Endocrinol Metab 94:1244–1250
29. **Herr C, Greulich T, Koczulla RA, Meyer S, Zakharkina T, Branscheidt M, Eschmann R, Bals R** 2011 The role of vitamin D in pulmonary disease: COPD, asthma, infection, and cancer. Respir Res 12:31
30. **Wood AM, Bassford C, Webster D, Newby P, Rajesh P, Stockley RA, Thickett DR** 2011 Vitamin D-binding protein contributes to COPD by activation of alveolar macrophages. Thorax 66:205–210
31. **Sundar IK, Hwang JW, Wu S, Sun J, Rahman I** 2011 Deletion of vitamin D receptor leads to premature emphysema/COPD by increased matrix metalloproteinases and lymphoid aggregates formation. Biochem Biophys Res Commun 406:127–133
32. **Zosky GR, Berry LJ, Elliot JG, James AL, Gorman S, Hart PH** 2011 Vitamin D deficiency causes deficits in lung function and alters lung structure. Am J Respir Crit Care Med 183:1336–1343
33. **Cook NR, Albert MS, Berkman LF, Blazer D, Taylor JO, Hennekens CH** 1995 Interrelationships of peak expiratory flow rate with physical and cognitive function in the elderly: MacArthur Foundation studies of aging. J Gerontol A Biol Sci Med Sci 50:M317–M323
34. **Fragoso CA, Gahbauer EA, Van Ness PH, Concato J, Gill TM** 2008 Peak expiratory flow as a predictor of subsequent disability and death in community-living older persons. J Am Geriatr Soc 56: 1014–1020
35. **Starr JM, Deary IJ, Whalley LJ** 2008 All-cause mortality in the Aberdeen 1921 birth cohort: effects of socio-demographic, physical and cognitive factors. BMC Public Health 8:307
36. **Snijder MB, van Dam RM, Visser M, Deeg DJ, Dekker JM, Bouter LM, Seidell JC, Lips P** 2005 Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. J Clin Endocrinol Metab 90:4119–4123