

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

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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 func-

tion. 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 (FEV₁) and forced vital capacity

(FVC) in adults, but not with FEV₁/FVC (9). In the Hertfordshire Cohort Study, serum 25-OHD was not related to FEV₁, FVC, or FEV₁/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 \leq 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				P value
	<10 ng/ml, n = 48	10–20 ng/ml, n = 179	20–30 ng/ml, n = 225	≥ 30 ng/ml, n = 144	
Age ^a	78.8 \pm 6.0	77.7 \pm 6.8	74.9 \pm 6.1	72.2 \pm 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 \pm 7.4	172.2 \pm 6.6	172.8 \pm 6.6	174.6 \pm 6.2	<0.01
Weight ^a	76.9 \pm 12.8	77.8 \pm 11.9	78.5 \pm 12.1	78.8 \pm 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 \pm 3.2	7.5 \pm 3.0	8.4 \pm 2.6	9.0 \pm 2.3	<0.01
Grip strength (kg) ^a	30.5 \pm 7.1	34.3 \pm 7.8	36.4 \pm 7.3	38.8 \pm 7.9	<0.01
PEFR in 1995/1996 ^a	366.7 \pm 145.4	414.7 \pm 128.8	439.3 \pm 122.3	476.0 \pm 117.1	<0.01
PEFR in 1998/1999 ^{a,c}	360.0 \pm 123.7	422.5 \pm 124.5	457.0 \pm 123.1	490.8 \pm 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 \pm 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				P value
	<10 ng/ml, n = 82	10–20 ng/ml, n = 262	20–30 ng/ml, n = 187	≥30 ng/ml, n = 80	
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.

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* ≥ 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

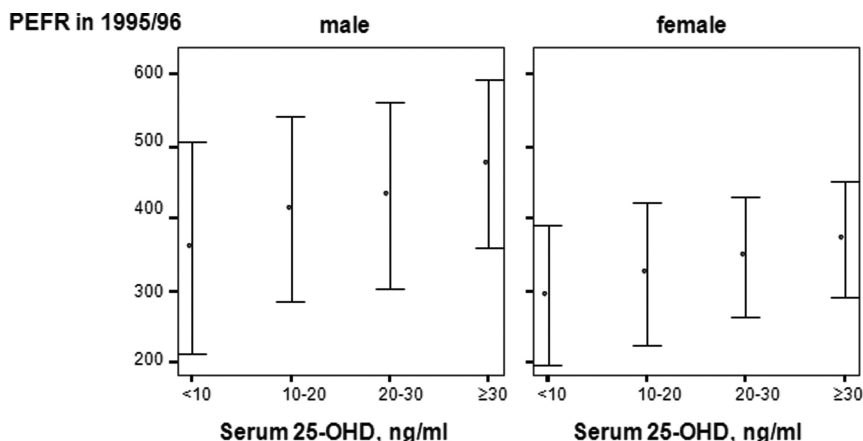


FIG. 1. Cross-sectional association between serum 25-OHD in categories and PEFR. Presented are the mean and 95% confidence intervals.

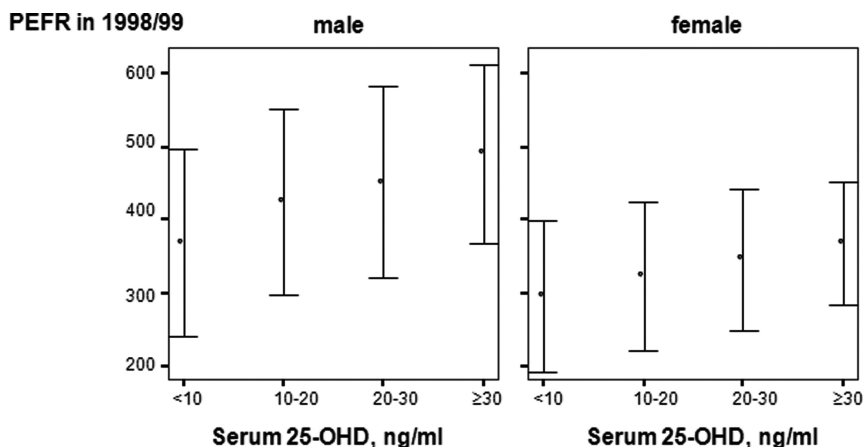


FIG. 2. Longitudinal association between serum 25-OHD in categories and PEFR.

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 ad-

justed 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

25-OHD	Model 1		Model 2		Model 3		Model 4	
	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.

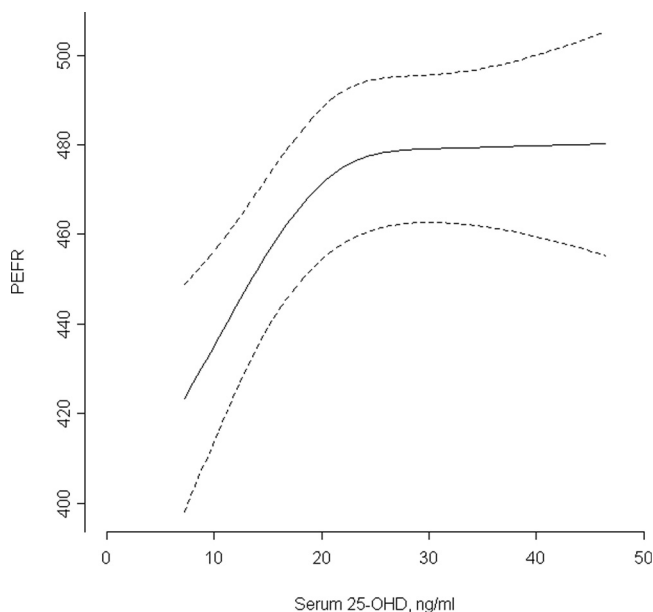


FIG. 3. Longitudinal association between serum 25-OHD and PEFR in men. The dotted line represents 95% confidence interval.

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 FEV₁ and FVC in adults (9). In contrast, in the Hertfordshire Cohort Study, serum 25-OHD was not significantly related to FEV₁, FVC, or FEV₁/FVC (10). The latter study did find significant positive

associations between dietary vitamin D intake and FEV₁ and FEV₁/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 FEV₁ and FEV₁/FVC ratio were observed (24). In addition, in a small study in asthma patients, serum 25-OHD was positively associated with FEV₁ (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 FEV₁) 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 FEV₁ (30). Furthermore, it has been shown that *VDR* knockout mice had increased influx of inflammatory cells, phospho-acetylation of nuclear factor- κ B associated with increased pro-inflammatory 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 FEV₁ 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.

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