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Nonlinear association between serum 25-hydroxyvitamin D concentrations and lung function in the United States adult population with COPD

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Vitamin D has been studied for its potential protective effects against lung function decline in patients with COPD. However, conflicting results exist, the actual effect of vitamin D on lung function remains controversial. This study aimed to determine whether serum 25-hydroxyvitamin D (25-OHD) levels are correlated with lung function in community-dwelling individuals with COPD. We used data from the National Health and Nutrition Examination Survey (NHANES) to explore the relationship between serum 25-OHD concentration and the severity of airflow obstruction. Multivariable logistic regression, stratified analysis with interaction, restricted cubic splines (RCS), and threshold effect analysis were used to investigate the association between serum 25-OHD concentration and lung function.A total of 1384 patients with COPD were analyzed. Accordingly, the association between serum 25-OHD concentrations and lung function exhibited an inverse L-shaped curve in the RCS. Threshold analysis showed that in participants with 25-OHD concentrations < 90 nmol/L, lung function decreased with decrease in serum 25-OHD concentrations, whereas no significant association was observed in those with serum 25-OHD concentrations ≥ 90 nmol/L. An inverse L-shaped relationship was observed between serum 25-OHD concentration and airflow obstruction severity in the adult population with COPD in the United States.

Keywords 25-Hydroxyvitamin D, COPD, Lung function

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms caused by abnormal airways and/or alveoli that persist and often progressively obstruct airflow[1]. The diagnosis of COPD was confirmed by the establishment of irreversible airflow limitation (ratio of forced expiratory volume in 1 s to forced vital capacity [FEV1/FVC] < 0.7 post-bronchodilator), as measured by spirometry. In adults, lung function declines gradually with age; however, the disease state, risk factors (e.g., impaired lung development), and environmental exposure can modify this decline[2,3]. COPD is caused by a reduction in peak lung function during early adulthood and/or a rapid decrease in lung function later in life. Lung function declines more rapidly in patients with COPD than in those without, although the rate of decline varies from person to person[4]. The rapid decrease in lung function in COPD patients is associated with increased symptoms, worsened breathing, and a loss of fitness[1].

Vitamin D plays a hormonal role rather than acting solely as a vitamin, and its primary metabolites belong to two groups of secosteroids: cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). The liver hydroxylates vitamins D3 and D2, resulting in the formation of 25-hydroxy variants. These variants are further metabolized in the kidneys, leading to the production of biologically active 1,25-dihydroxy forms. 25-hydroxyvitamin D (25-OHD), the primary circulating form of vitamin D, is frequently used as a biomarker for assessing vitamin D status in an individual[5]. In addition to its role in calcium homeostasis, vitamin D has a role in muscle function[6]

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antimicrobial, anti-inflammatory, and immunomodulatory effects[7]. Vitamin D deficiency (VDD) is highly prevalent among adults in the general population[8–12] and particularly in patients with COPD[13–18]. Vitamin D potentially contributes to COPD pathogenesis and affects its severity through various mechanisms, including the reduction of respiratory infection frequency, impairment of pathogen response, and inhibition of airway smooth muscle proliferation[19]. However, most studies have been conducted on the incidence of exacerbations in COPD patients[13–16], fewer studies have examined how vitamin D status affects lung function in these patients[16–18]. To date, the effect of serum 25-OHD concentrations on COPD patients has not been established. This study aimed to evaluate the correlation between serum 25-OHD concentrations and the severity of airflow obstruction in community-dwelling individuals with COPD.

Results

Study population

Of the 30,442 participants interviewed, 1606 met the inclusion criteria (age range 40–79 years; pre-bronchodilator FEV1/FVC < 70%). Those participants lacking data on 25-OHD, height, and race were excluded. Ultimately, this analysis included 1384 participants from the 2007–2012 NHANES. We used multiple imputation, based on five replications and a chained equation approach method in the R mice procedure, to maximize statistical power and minimize bias that might occur because of missing data for 1384 patients. Figure 1 shows the selection flowchart for the participants.

Baseline characteristics

The participants had a mean age of 61.4 ± 10.7 years, and 845 (61.1%) were men. The mean baseline serum 25-OHD concentrations was 68.5 ± 26.7 nmol/L, and the prevalence of VDD was 24.5%, and 57.5% of VDDs were observed in men. Table 1 summarizes the characteristics of the population for different serum 25-OHD concentration groups (Q1 < 25 nmol/L, Q2 25–50 nmol/L, Q3 50–75 nmol/L, and Q4 ≥ 75 nmol/L). Participants with higher serum 25-OHD concentrations frequently were older, non-Hispanic whites, married or living with a partner, had a higher level of education and household income, had dietary supplements, had more milk and vitamin D2 + D3 intake, and had a lower incidence of asthma and gout. Serum 25-OHD concentrations were lower in current smokers and sedentary activity participants than in former and never-smokers, and participants engaged in moderate and vigorous physical activity. Moreover, obese participants (BMI ≥ 30 kg/m^2) had lower serum 25-OHD concentrations.

Relationship between serum 25-OHD concentrations and FEV1% predicted and FVC% predicted

Univariate analysis revealed that sex, BMI, marital status, education level, family income, smoking status, alcohol intake, vitamin C, vitamin D2 + D3, vitamin E, magnesium, dietary supplements, physical activity, asthma, HBP, DM, CHD, stroke, and 25-OHD were correlated with the FEV1% predicted and FVC% predicted (Supplementary Table S1). After adjusting for potential confounders, a significant positive association was found between FEV1% predicted or FVC% predicted and serum concentrations of 25-OHD when analyzed in quartiles. In comparison with individuals with lower serum 25-OHD concentration Q1 (< 25 nmol/L), the adjusted β values for 25-OHD and FEV1% predicted in Q2 (25–50 nmol/L), Q3 (50–75 nmol/L), and Q4 (≥ 75 nmol/L) were 3.86 (95% CI − 1.34 to 9.07, $p = 0.146$), 5.25 (95% CI 0.07–10.43, $p = 0.047$), and 6.72 (95% CI 1.44–12, $p = 0.013$), respectively (Table 2). Based on the same model and analysis, the adjusted β for FVC% predicted in Q2, Q3, and Q4 groups were 1.49 (95% CI − 3.47 to 6.45, $p = 0.557$), 3.91 (95% CI − 1.02 to 8.85, $p = 0.121$), and 4.69 (95% CI − 0.35 to 9.72, $p = 0.068$) (Table 2), respectively, with Q1 group as the reference. Accordingly, an inverse L-shaped curve (nonlinear, $p = 0.012$ and $p = 0.026$, respectively) was observed in the spline (Fig. 2) for the relationship between serum 25-OHD concentrations and FEV1% predicted or FVC% predicted. In the threshold analysis, the β for FEV1% predicted and FVC% predicted were 0.78 (95% CI 0.16–1.41, $p = 0.014$) and 0.73 (95% CI 0.12–1.34,

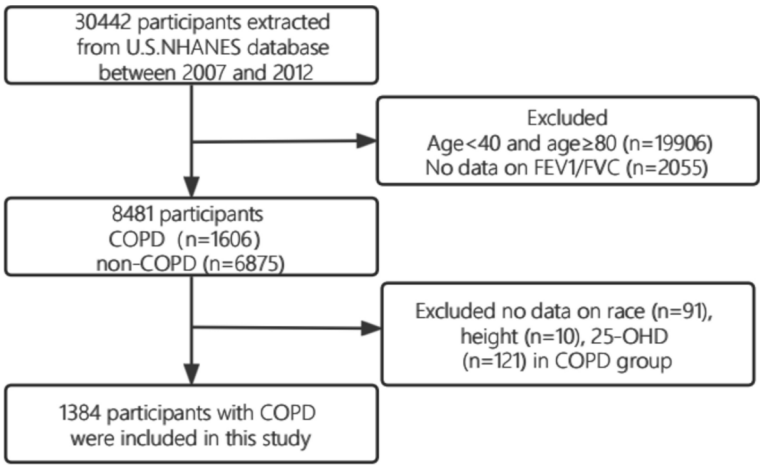

Fig. 1. Flowchart of study participant selection.

Variables	Total (n = 1384)	25-OHD(nmol/l)				
		Q1(< 25 nmol/l) (n = 49)	Q2(25-50 nmol/l) (n = 290)	Q3(50-75 nmol/l) (n = 514)	Q4(≥ 75 nmol/l) (n = 531)	*p*-value
Sex, n (%)						0.007
Male	845 (61.1)	24 (49)	171 (59)	342 (66.5)	308 (58)	
Female	539 (38.9)	25 (51)	119 (41)	172 (33.5)	223 (42)	
Age(years), Mean ± SD	61.4 ± 10.7	59.7 ± 10.4	60.2 ± 10.3	60.9 ± 11.1	62.6 ± 10.4	0.004
Height(cm), Mean ± SD	170.0 ± 9.5	168.7 ± 9.4	169.6 ± 8.9	170.5 ± 9.4	169.8 ± 9.7	0.355
BMI(kg/m2), Mean ± SD	28.0 ± 6.1	28.0 ± 8.8	28.8 ± 7.2	28.5 ± 6.1	27.2 ± 5.1	0.001
Race, n (%)						< 0.001
Non-Hispanic White	897 (64.8)	13 (26.5)	129 (44.5)	331 (64.4)	424 (79.8)	
Non-Hispanic Black	271 (19.6)	29 (59.2)	104 (35.9)	90 (17.5)	48 (9)	
Hispanic	216 (15.6)	7 (14.3)	57 (19.7)	93 (18.1)	59 (11.1)	
Education level (year), n (%)						0.06
< 9	154 (11.1)	5 (10.2)	36 (12.4)	64 (12.5)	49 (9.2)	
9–12	597 (43.1)	25 (51)	141 (48.6)	214 (41.6)	217 (40.9)	
> 12	633 (45.7)	19 (38.8)	113 (39)	236 (45.9)	265 (49.9)	
Marital status, n (%)						< 0.001
Married or living with partner	863 (62.4)	15 (30.6)	163 (56.2)	320 (62.3)	365 (68.7)	
Living alone	521 (37.6)	34 (69.4)	127 (43.8)	194 (37.7)	166 (31.3)	
Family income, n (%)						< 0.001
Low	406 (29.3)	27 (55.1)	100 (34.5)	148 (28.8)	131 (24.7)	
Medium	516 (37.3)	14 (28.6)	108 (37.2)	200 (38.9)	194 (36.5)	
High	462 (33.4)	8 (16.3)	82 (28.3)	166 (32.3)	206 (38.8)	
Physical activity, n (%)						< 0.001
Sedentary	816 (59.0)	35 (71.4)	198 (68.3)	312 (60.7)	271 (51)	
Moderate	417 (30.1)	9 (18.4)	71 (24.5)	139 (27)	198 (37.3)	
Vigorous	151 (10.9)	5 (10.2)	21 (7.2)	63 (12.3)	62 (11.7)	
Dietary Supplements, n (%)						< 0.001
No	635 (45.9)	37 (75.5)	214 (73.8)	234 (45.5)	150 (28.2)	
Yes	749 (54.1)	12 (24.5)	76 (26.2)	280 (54.5)	381 (71.8)	
Milk intake, n (%)						< 0.001
Never	252 (18.2)	21 (42.9)	69 (23.8)	75 (14.6)	87 (16.4)	
Rarely	186 (13.4)	7 (14.3)	34 (11.7)	74 (14.4)	71 (13.4)	
Sometimes	373 (27.0)	14 (28.6)	103 (35.5)	150 (29.2)	106 (20)	
Often	573 (41.4)	7 (14.3)	84 (29)	215 (41.8)	267 (50.3)	
Alcohol, n (%)						0.558
No	263 (19.0)	7 (14.3)	62 (21.4)	98 (19.1)	96 (18.1)	
Yes	1121 (81.0)	42 (85.7)	228 (78.6)	416 (80.9)	435 (81.9)	
Smoke, n (%)						< 0.001
No	387 (28.0)	11 (22.4)	75 (25.9)	148 (28.8)	153 (28.8)	
Current	478 (34.5)	24 (49)	130 (44.8)	172 (33.5)	152 (28.6)	
Former	519 (37.5)	14 (28.6)	85 (29.3)	194 (37.7)	226 (42.6)	
Asthma, n (%)						0.031
No	1200 (86.7)	39 (79.6)	241 (83.1)	445 (86.6)	475 (89.5)	
Yes	184 (13.3)	10 (20.4)	49 (16.9)	69 (13.4)	56 (10.5)	
HBP, n (%)						0.608
No	830 (60.0)	27 (55.1)	175 (60.3)	318 (61.9)	310 (58.4)	
Yes	554 (40.0)	22 (44.9)	115 (39.7)	196 (38.1)	221 (41.6)	
DM, n (%)						0.017
No	902 (84.7)	40 (81.6)	229 (79)	442 (86)	461 (86.8)	
Yes	212 (15.3)	9 (18.4)	61 (21)	72 (14)	70 (13.2)	
CHD, n (%)						0.024
No	1285 (92.8)	49 (100)	268 (92.4)	467 (90.9)	501 (94.4)	
Yes	99 (7.2)	0 (0)	22 (7.6)	47 (9.1)	30 (5.6)	
Stroke, n (%)						0.084
No	1322 (95.5)	47 (95.9)	274 (94.5)	500 (97.3)	501 (94.4)	

Continued

Variables	Total (n = 1384)	25-OHD(nmol/l)				
		Q1(< 25 nmol/l) (n = 49)	Q2(25-50 nmol/l) (n = 290)	Q3(50-75 nmol/l) (n = 514)	Q4(≥ 75 nmol/l) (n = 531)	*p*-value
Yes	62 (4.5)	2 (4.1)	16 (5.5)	14 (2.7)	30 (5.6)	
Gout, n (%)						0.009
No	1295 (93.6)	48 (98)	280 (96.6)	484 (94.2)	483 (91)	
Yes	89 (6.4)	1 (2)	10 (3.4)	30 (5.8)	48 (9)	
25-OH-vitaminD(nmol/L), Mean ± SD	68.5 ± 26.7	20.2 ± 3.5	38.0 ± 6.9	63.1 ± 7.0	94.8 ± 18.4	< 0.001
VitaminE(mg),Median (IQR)	6.3 (4.2, 9.9)	5.0 (3.5, 8.6)	5.8 (4.1, 9.3)	6.4 (4.3, 9.8)	6.7 (4.3, 10.2)	0.031
Beta-carotene(ug), Median (IQR)	717.5 (257.0, 2169.0)	443.0 (122.0, 1029.0)	680.5 (238.0, 1840.0)	692.5 (251.0, 2279.0)	812.0 (283.5, 2277.0)	0.026
VitaminC(mg), Median (IQR)	49.5 (20.0, 111.3)	30.5 (12.0, 86.3)	48.3 (17.6, 107.0)	48.5 (21.4, 116.4)	51.6 (21.8, 111.0)	0.223
VitaminD2 + D3(ug), Median (IQR)	3.2 (1.4, 5.9)	2.3 (0.9, 4.2)	2.9 (1.1, 5.0)	2.9 (1.3, 5.8)	3.7 (1.7, 6.7)	< 0.001
Magnesium(mg), Median (IQR)	268.5 (191.0, 373.0)	206.0 (159.0, 338.0)	258.5 (177.5, 357.2)	267.5 (197.0, 382.5)	283.0 (203.5, 380.0)	0.002
Selenium(ug), Median (IQR)	96.3 (65.8, 135.8)	91.7 (59.5, 136.3)	102.2 (69.8, 143.4)	96.2 (67.7, 136.2)	93.6 (64.5, 130.2)	0.227
FEV1%predicted, Mean ± SD	80.5 ± 18.7	71.8 ± 21.7	76.8 ± 18.1	80.6 ± 19.0	83.3 ± 17.8	< 0.001
FVC%predicted, Mean ± SD	96.7 ± 17.6	91.8 ± 20.1	93.2 ± 17.0	97.0 ± 18.1	98.7 ± 16.7	< 0.001

Table 1. Baseline characteristics of the study population according to 25-OHD (nmol/L). 25-OHD, 25-hydroxyvitamin D; FEV1% predicted, forced expiratory volume in 1 s percent of predicted; FVC% predicted, forced vital capacity percent of predicted; BMI, body mass index; HBP, high blood pressure; CHD, coronary heart disease; DM, diabetes mellitus; CI, confidence interval.

	Unadjusted		Model 1		Model 2		Model 3	
	β(95%CI)	*P*-value	β(95%CI)	*P*-value	β(95%CI)	*P*-value	β(95%CI)	*P*-value
FEV1%predicted								
25-OHD[a]	− 0.79 (− 1.16 to − 0.42)	< 0.001	− 0.28 (− 0.66 to 0.11)	0.159	− 0.27 (− 0.66 to 0.11)	0.167	− 0.25 (− 0.63 to 0.14)	0.215
Groups								
Q1(< 25 nmol/l)	0(Ref)		0(Ref)		0(Ref)		0(Ref)	
Q2(25–50 nmol/l)	4.94 (− 0.65 to 10.53)	0.083	3.89 (− 1.32 to 9.1)	0.144	3.92 (− 1.29 to 9.13)	0.141	3.86 (− 1.34 to 9.07)	0.146
Q3(50–75 nmol/l)	8.74 (3.33 to 14.15)	0.002	5.95 (0.79 to 11.11)	0.024	5.36 (0.18 to 10.54)	0.043	5.25 (0.07 to 10.43)	0.047
Q4(≥ 75 nmol/l)	11.45 (6.05 to 16.85)	< 0.001	7.17 (1.9 to 12.44)	0.008	6.91 (1.62 to 12.19)	0.011	6.72 (1.44 to 12)	0.013
Trend.test		< 0.001		0.003		0.005		0.007
FVC%predicted								
25-OHD[a]	− 0.61 (− 0.96 to − 0.27)	0.001	− 0.26 (− 0.63 to 0.1)	0.161	− 0.3 (− 0.67 to 0.06)	0.105	− 0.29 (− 0.66 to 0.08)	0.127
Groups								
Q1(< 25 nmol/l)	0(Ref)		0(Ref)		0(Ref)		0(Ref)	
Q2(25–50 nmol/l)	1.48 (− 3.8 to 6.76)	0.582	1.39 (− 3.58 to 6.36)	0.584	1.46 (− 3.5 to 6.43)	0.563	1.49 (− 3.47 to 6.45)	0.557
Q3(50–75 nmol/l)	5.29 (0.18 to 10.4)	0.043	4.38 (− 0.54 to 9.3)	0.081	3.94 (− 1 to 8.87)	0.118	3.91 (− 1.02 to 8.85)	0.121
Q4(≥ 75 nmol/l)	6.9 (1.8 to 12)	0.008	4.75 (− 0.28 to 9.77)	0.064	4.77 (− 0.27 to 9.8)	0.064	4.69 (− 0.35 to 9.72)	0.068
Trend.test		< 0.001		0.008		0.008		0.01

Table 2. Multivariable-adjust β and 95%CI of the 25-OHD(nmol/L) groups associated with FEV1% predicted and FVC% predicted. [a]25-OHD was a continuous variable per 10 nmol/l decrease. Model1: BMI, race, family income, smoking status, dietary supplements, physical activity, asthma and CHD. Model2: Model1 + sex, education, marriage, Vitamin E, Vitamin C, Vitamin D(D2 + D3), Magnesium, Selenium, the frequency of intake of milk, HBP, DM, stroke. Model3: Model2 + age, height, alcohol, Beta-carotene, gout. 25-OHD, 25-hydroxyvitamin D; FEV1% predicted, forced expiratory volume in 1 s percent of predicted; FVC% predicted, forced vital capacity percent of predicted; BMI, body mass index; HBP, high blood pressure; CHD, coronary heart disease; DM, diabetes mellitus; CI, confidence interval.

$p = 0.019$), in participants with serum 25-OHD concentrations < 90 nmol/L (Table 3), indicating that the FEV1% predicted and FVC% predicted are increased by 0.78 and 0.73, respectively, for every 10 nmol/L increase in serum 25-OHD concentrations. Participants with serum 25-OHD concentrations ≥ 90 nmol/L showed no association between serum 25-OHD concentrations and predicted FEV1% predicted or FVC% (Table 3) indicating that FEV1% predicted and FVC% predicted did not increase with increasing serum 25-OHD concentrations.

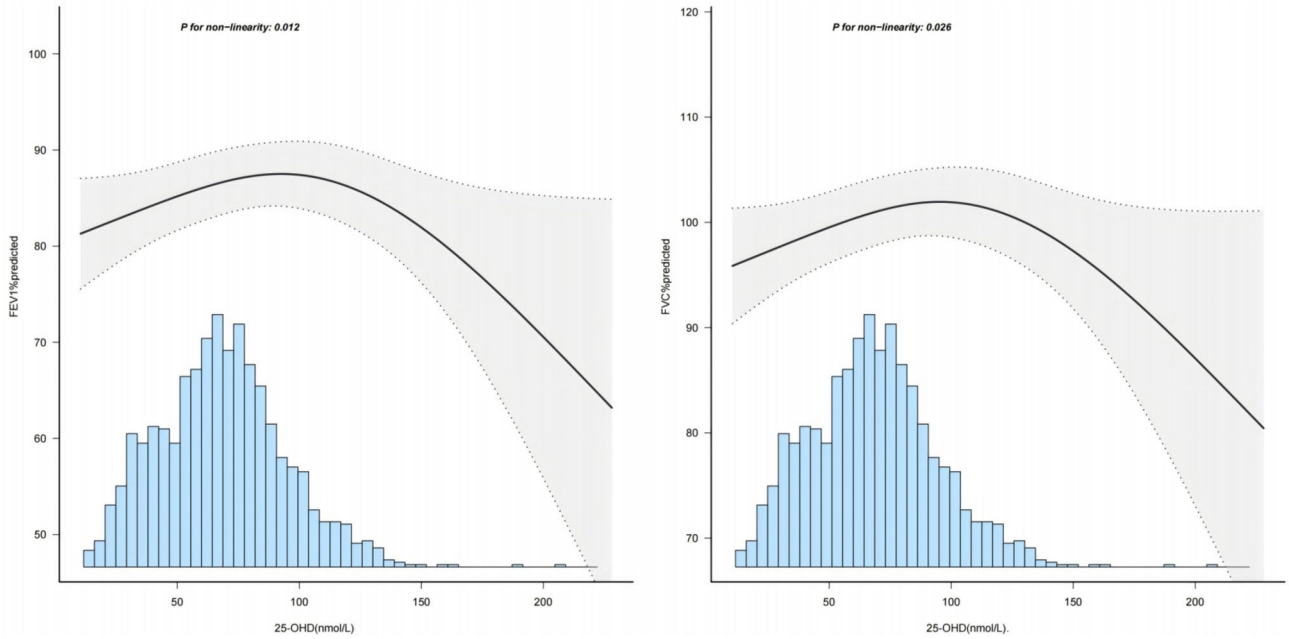

Fig. 2. Associations between 25-OHD with FEV1% predicted and FVC% predicted. Solid and dashed lines represent FEV1 (or FVC)%predicted value and 95% confidence interval. X-axis: 25-OHD concentrations. Y-axis: FEV1 (or FVC)%predicted. FEV1 (or FVC)%predicted value was adjusted for age, sex, race, height, BMI, marital status, education level, family income, smoking status, alcohol intake, vitamin C, vitamin D2 + D3, vitamin E, beta-carotene, selenium and magnesium, the frequency of intake of milk, dietary supplements, physical activity, asthma, HBP, DM, CHD, stroke and gout. P for non-linearity < 0.05 indicates a non-linear relationship. 25-OHD, 25-hydroxyvitamin D; FEV1% predicted, Forced expiratory volume in one second percent of predicted; FVC% predicted, Forced vital capacity percent of predicted; BMI, Body mass index; HBP, High blood pressure; CHD, Coronary heart disease; DM, Diabetes mellitus

	FEV1% predicted		FVC% predicted	
25-OHD(nmol/L)[a]	β(95%CI)	*P*-value	β(95%CI)	*P*-value
< 90	0.78(0.16 to 1.41)	0.014	0.73(0.12 to 1.34)	0.019
≥ 90	− 0.93(− 2.28 to 0.42)	0.178	− 0.47(− 1.68 to 0.74)	0.447
Likelihood Ratio test		0.01		0.047

Table 3. Threshold effect analysis of the relationship of 25-OHD and FEV1% predicted and FVC% predicted. [a]25-OHD was a continuous variable per 10 nmol/l increase. Only 99.8% of the data is shown. 25-OHD, 25-hydroxyvitamin D; FEV1% predicted, forced expiratory volume in 1 s percent of predicted; FVC% predicted, forced vital capacity percent of predicted; CI, confidence interval.

Subgroup analyses based on adjusted potential effect confounders

Subgroup analyses were conducted to evaluate the possible effect of serum 25-OHD concentrations on FEV1% predicted and FVC% predicted. After stratifying the data according to age, sex, BMI, race, smoking status, physical activity, dietary supplements, frequency of milk intake, and asthma, no significant interactions were found among any of the subgroups (Fig. 3).

Sensitivity analysis

Sensitivity analysis was performed to assess the reliability of the results. To avoid confusing results with COPD participants combined with asthma, we excluded data on participants with COPD and asthma and repeated the main results (n = 1195) for comparison(Supplementary Figure S1), and the relationship between 25-OHD and FEV1% predictedor FVC% predicted remained stable.

Discussion

This cross-sectional study showed an inverse L-shaped correlation between 25-OHD and the severity of airflow obstruction in 1384 US adults with COPD, with inflection point values of approximately 90 nmol/L. The results were independent of multiple potential covariates including age, sex, BMI, race, smoking status, physical activity, dietary supplements, frequency of milk intake, and asthma (all *P* for interaction > 0.05). Sensitivity analyses

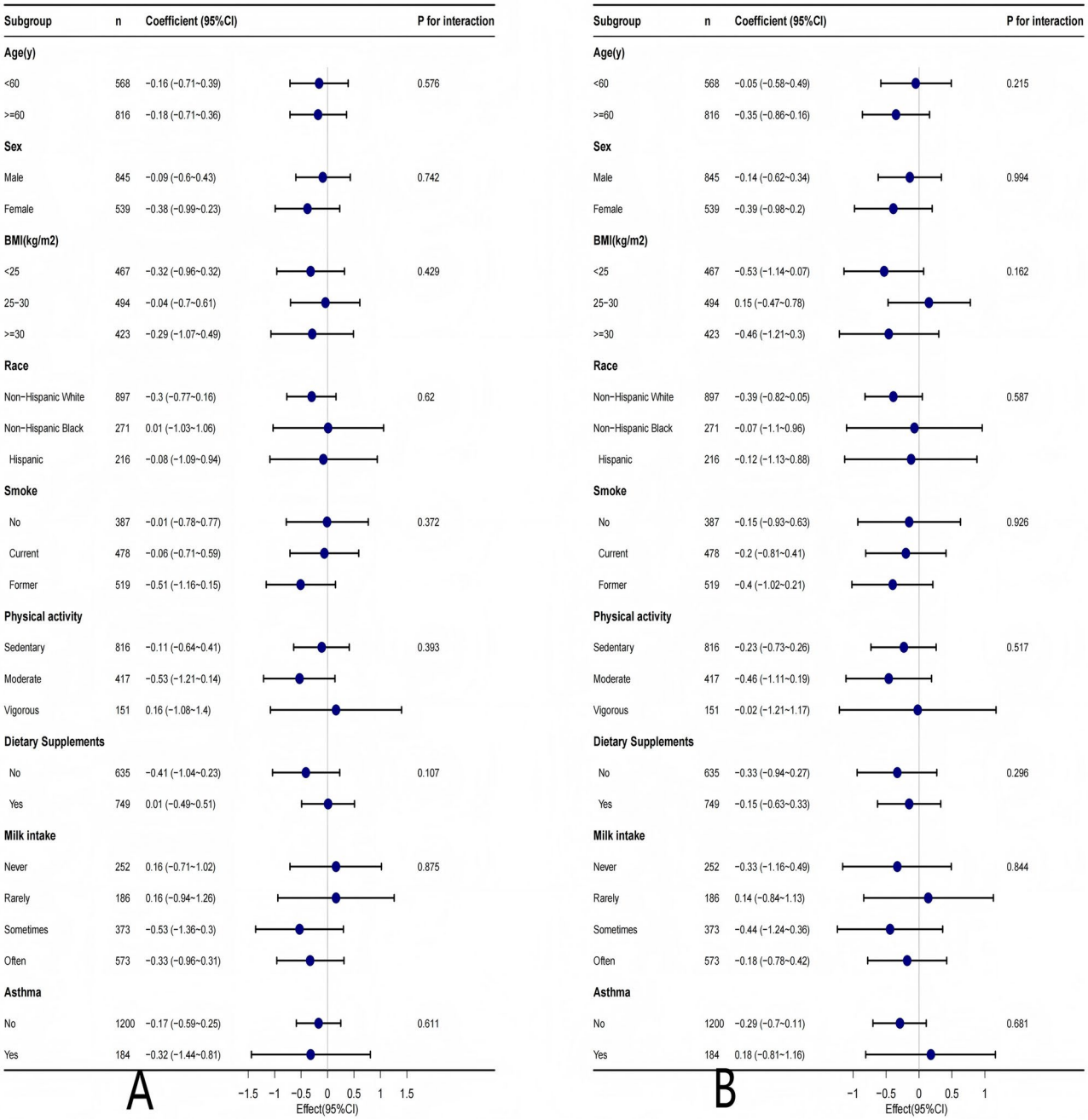

Fig. 3. Subgroup analyses of the association between 25-OHD and FEV1% predicted (**A**) and FVC% predicted (**B**). Except stratification component itself, each stratification factor was adjusted for all other variables (age, sex, race, height, BMI, marital status, education level, family income, smoking status, alcohol intake, vitamin C, vitamin D2 + D3, vitamin E, beta-carotene, selenium and magnesium, the frequency of intake of milk, dietary supplements, physical activity, asthma, HBP, DM, CHD, stroke and gout). Dots indicate Betas, with horizontal lines indicating 95% Cls. 25-OHD, 25-hydroxyvitamin D; FEV1% predicted, forced expiratory volume in one second percent of predicted; FVC% predicted, forced vital capacity percent of predicted; BMI, body mass index; CI, confidence interval

demonstrated the robustness of the correlation between 25-OHD levels and the severity of airflow obstruction. VDD is frequently observed in patients with COPD, and this association can be attributed to a history of smoking, current smoking habits, or the presence of more advanced pulmonary ailments[20]. Our findings revealed a VDD prevalence of 24.5% among the participants and suggested an association with younger age, black race, lower education level, lower family income, current smoking status, sedentary activity, obesity, and asthma.

Lung function typically follows a course normally divided into three phases throughout an individual's lifetime: growth (from birth to early adulthood), plateau (lasting for a few years), and decline (due to physiological aging of the lungs). As the lungs mature and grow, lung function peaks at approximately 20–25 years (earlier

in women)[21]. However, several factors alter this normal course, affecting lung growth, shortening the plateau, and/or accelerating the aging process during pregnancy, childbirth, childhood, and adolescence[22]. Fletcher and Peto[23] reported a normal decline in FEV1 in older adults and an accelerated decline in FEV1 in smokers. Consistent with this finding, our study found that smoking status was a risk factor for FEV1% predicted and FVC% predicted declines, independent of 25-OHD. The synthesis of 25-OHD is reduced, and the expression of 25-OHD receptor is affected by cigarette smoke, as described by Mousavi[24]. Existing studies on the overall population revealed that the relationship between decreased lung function due to low vitamin D levels may vary depending on the smoking history[10,12,25].

Other risk factors unrelated to smoking were highlighted by Agusti[22], who described several processes of lung impairment in nonsmoking individuals, including immature lungs in utero or in infancy, recurrent exacerbations, and uncontrolled asthma leading to COPD. Consistent with this observation, our study identified asthma as a risk factor for lower FEV1% predicted and FVC% predicted, independent of 25-OHD. VDD may have a detrimental impact on lung growth during pregnancy, potentially leading to a decrease in the maximum attainable lung function in adults[26]. Rodent studies conducted by Yurt have shown that offspring with VDD exhibited reduced lung volume, compromised lung function, and elevated tracheal contractility compared with their counterparts with sufficient vitamin D levels[27]. These effects may be attributable to the anti-inflammatory and antioxidant properties of 25-OHD.

The association between serum 25-OHD concentrations and FEV1%predicted or FVC% predicted exhibited an inverse L-shaped curve. The protective effect of increasing 25-OHD levels on airflow obstruction appeared to peak in individuals with sufficient serum 25-OHD concentrations. In particular, the severity of airflow obstruction decreased with increasing 25-OHD in those with serum 25-OHD concentrations < 90 nmol/L, whereas airflow obstruction severity no longer reduced with increasing 25-OHD in those with serum 25-OHD concentrations ≥ 90 nmol/L. Several factors could drive changes in this relationship, particularly at higher levels of 25-OHD. Vitamin D is known to influence the immune system and inflammation. At lower levels, increasing vitamin D may reduce inflammation in the lungs, thereby improving lung function. However, at very high levels, vitamin D could potentially lead to dysregulation of calcium metabolism, which may have no effect on respiratory function. On the other hand, there may be a physiological saturation point beyond which additional vitamin D does not confer further benefits. This could be due to receptor saturation or other regulatory mechanisms in the body. Therefore, prospective studies investigating the clinical effects of vitamin D in patients with COPD are warranted. Although previous trials have been conducted, the small sample size, short duration, and administration of excessively high doses of vitamin D supplementation in these trials were considered potential limitations[28,29]. Consequently, it is imperative to delve deeper into the potential existence of a continuous dose–response effect or threshold effect of vitamin D supplementation in COPD patients, as well as to identify the specific subset of patients who would derive the greatest benefit from such supplementation.

A key strength of this study is the use of predicted values to accurately interpret lung function impairment. We used FEV1% predicted and FVC% predicted, which were calculated according to the age, height, and race of the participants, instead of FEV1 and FVC, to compare lung function among individuals of different ages. With FEV1% predicted and FVC% predicted, we obtained more meaningful insights into lung function across varying age groups. However, this study had several limitations. First, because this was a cross-sectional study, we could not prove causation between 25-OHD concentrations and severity of airflow obstruction. Second, as the study included only US civilians, the findings cannot be generalized to other ethnic groups. Third, because the 2007–2012 NHANES data were collected only during the study period, we were unable to use them for further validation. Fourth, despite the use of regression models, stratified analyses, and sensitivity analyses, some residual confounding factors remain. Fifth, owing to the lack of post-bronchodilator spirometry tests in the 2007–2012 NHANES, COPD was defined as measured lung function before bronchodilator administration; however, several studies[29,30] have also used this approach to define COPD.

Materials and methods

Data source

The present analysis was based on a cross-sectional design and relied on data obtained from the National Health and Nutrition Examination Survey (NHANES) conducted between 2007 and 2012. This study integrated various sources of information, including demographic characteristics, spirometry test outcomes, disease documentation, laboratory findings, and questionnaire responses. Data were retrieved from the NHANES cycles carried out in specific periods, namely 2007–2008, 2009–2010, and 2011–2012, which were conducted by the Centers for Disease Control and Prevention (CDC)[31]. To ensure a representative sample of the non-institutionalized US population, the NHANES methodology employed a stratified multistage probability survey[32]. This comprehensive assessment gauges both the health status and nutritional well-being of individuals residing in the country through a combination of in-home interviews, physical measurements, and laboratory examinations, all of which were conducted within specially outfitted nation-wide mobile examination centers (MECs).Written informed consent was obtained from all participants at enrollment, and the NHANES was approved by the National Center for Health Statistics Research Ethics Review Board (Continuation of Protocol #2007–12). Given the nature of this analysis as a secondary investigation, approval from the Institutional Review Board was waived[33]. The CDC website provides access to the NHANES data and can be visited at the following link: http://www.cdc.gov/nchs/nhanes.htm, enabling the retrieval of necessary information.

Spirometry test and measurement of 25-OHD concentrations

Participants who met the specific inclusion criteria for the 2007–2012 NHANES cycle and had undergone spirometry testing in accordance with guidelines established by the American Thoracic Society and European Respiratory Society were evaluated for lung function[34].

Participants who had recent symptoms of chest pain or manifested physical difficulties with forceful expiration; individuals receiving supplemental oxygen therapy; individuals who recently underwent eye, chest, or abdominal surgery; those with a recent history of heart attacks, strokes, tuberculosis exposure, or who had recently experienced hemoptysis; adults with a personal background of retinal detachment or lung collapse; and youngsters enduring distressing infections in the ear were excluded. Based on the spirometry test results, the FEV1 and FVC values were determined and predicted using estimates from Hankinson et al., which were based on ethnicity, sex, and age[35]. FEV1% predictedand FVC% predicted were then calculated. The CDC Environment Health Laboratory tested blood specimens collected in the MEC examination after processing and stored at − 30 °C. Measurements of 25-hydroxyvitamin D3 (25-OHD3), epi-25-hydroxyvitamin D3 (epi-25-OHD3), and 25-hydroxyvitamin D2(25-OHD2) levels were performed using ultra-high-performance liquid chromatography-tandem mass spectrometry. The total 25-OHD was the sum of the 25-OHD3 and 25-OHD2 levels. A 25-OHD concentration of < 50 nmol/L was defined as VDD, whereas vitamin D sufficiency was defined as a serum 25-OHD concentration exceeding 75 nmol/L[36].

Definitions

Individuals with COPD were identified as adults aged 40–79 years who were diagnosed with spirometry-defined COPD. Because few participants had undergone a post-bronchodilator spirometry test, pre-bronchodilator testing was used to define COPD as an FEV1/FVC ratio < 70%[4]. The study included various potential covariates based on previous studies[16–18], including age, sex, race, height, body mass index (BMI), marital status, education level, family income, smoking status, alcohol intake, vitamin C, vitamin D2 + D3, vitamin E, beta-carotene, selenium, magnesium, frequency of intake of milk, dietary supplements, physical activity, asthma, hypertension (HBP), diabetes mellitus (DM), coronary heart disease (CHD), stroke, and gout. Race was categorized as non-Hispanic white, non-Hispanic black, or Hispanic (Hispanic was defined as Mexican American or other Hispanic). According to the CDC guidelines, obesity was defined as a body mass index (BMI) ≥ 30 kg/m^2, and a BMI between 25 and ˂ 30 kg/m^2 was defined as overweight[37]. Marital status was categorized as being married, cohabiting with a partner, or living alone. Educational status was divided into three categories: ˂ 9 years of education, 9–12 years of education, and ≥ 12 years of education. To determine family income, the poverty income ratio (PIR), as outlined in a report by the US government was utilized[38]. Three income categories were established: low (PIR ≤ 1.3), medium (PIR ranging from 1.3 to 3.5), and high (PIR ˃ 3.5). Based on smoking habits, participants were grouped into three categories: never smokers (individuals who had smoked < 100 cigarettes in their lifetime), current smokers (individuals who had smoked > 100 cigarettes in their lifetime and were still current smokers), and former smokers (individuals who had smoked > 100 cigarettes in their lifetime but had quit smoking)[39]. Alcohol intake was divided into two groups: drinking and non-drinking, based on whether the participants had consumed 12 or more alcoholic beverages in their lifetime[40]. Physical activity was classified as sedentary, moderate (moderate activity that induces a slight elevation in breathing or heart rate, such as brisk walking, cycling, swimming, or golf, for a minimum of 10 uninterrupted min), or vigorous (vigorous activities that result in a considerable increase in breathing or heart rate, such as running or basketball, for a minimum of 10 uninterrupted min). The dietary recall interview was conducted face-to-face at the MEC facility to collect the previous 24-h nutritional information, including vitamin C, vitamin D2 + D3, vitamin E, beta-carotene, selenium, and magnesium. Dietary supplementation was determined using a questionnaire (Did you take any vitamins, minerals, or dietary supplements in the last 30 days?). The frequency of milk intake was classified as never, rarely (less than once a week), sometimes (one or more times per week but less than once a day), or often (once or more per day). Pre-existing conditions (asthma, HBP, DM, CHD, stroke, and gout) were identified based on the questionnaire (Have a physician or other health professional ever told you that you have …?).

Statistical analysis

This descriptive study was conducted with all participants. Normally distributed variables were compared using analysis of variance and presented as the mean (standard deviation). Skewed variables were compared using Kruskal–Wallis tests and presented as medians (interquartile range, 25–75%). The chi-square test for multiple comparisons was used to compare categorical variables as frequencies (percentages) among groups. The association between 25-OHD and FEV1% predicted and FVC% predicted were determined using univariate and multivariate linear regression models, the beta (β), and 95% confidence interval (95% CI). A total of three models were used: Model 1 was adjusted for variables (BMI, race, family income, smoking status, dietary supplements, physical activity, asthma, and CHD), and if the addition of a variable caused a change of at least 10 percent in the matched β, it was added to this model. Model 2 was adjusted for the same factors as those in Model 1, in addition to factors with p values < 0.05 in the univariate analysis (sex, BMI, race, education level, marital status, family income, smoking status, vitamin C, vitamin D2 + D3, vitamin E, beta-carotene, selenium, magnesium, frequency of milk intake, dietary supplements, physical activity, asthma, HBP, CHD, DM, and stroke). Model 3 was fully adjusted for all covariates. Additionally, we evaluated the linear relationship and explored the dose–response curve between 25-OHD and FEV1% predicted and FVC% predicted using cubic spline (RCS) regression. A two-piece-wise linear regression model with smoothing was employed to examine the association threshold between 25-OHD and FEV1% predicted and FVC%predicted. The inflection point was deduced using the likelihood ratio test and bootstrap resampling. This analysis considers various factors in Model 3. Furthermore, to observe any potential modifications and interactions, a stratified multivariate linear regression model was implemented along with the likelihood ratio test for age, sex, BMI, race, smoking status,frequency of milk intake, dietary supplements, physical activity, and asthma subgroups.

We used multiple imputations based on the chained equation approach in the R mice package with five replications to account for missing data. We evaluated the robustness of the results by comparing the complete data (n = 1106) with the main analyses.

Power estimates were not performed prior to the analysis. The sample size was determined based on the available data. The R statistical package (R Foundation, http://www.R-project.org) and version 1.7.1 of the Free Statistical Software[41] were utilized to conduct all statistical analyses. A p-value < 0.05 for a two-tailed test indicated statistical significance.

Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

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Author contributions

Q.H.: Data curation, Writing- Original draft preparation. J.Y., X.X.: Formal analysis. M.D., Y.H.: Writing- Reviewing and Editing. L. W., G.L.: Conceptualization. All authors reviewed the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval and consent to participate

The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital institutional review board determined the study to be exempt because it used publicly available data, and informed consent was waived.

Consent for publication

Written informed consent was obtained from all participants prior to involvement in the study.

Additional information

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