Relationship Between Serum 25-Hydroxyvitamin D and Lung Function Among Korean Adults in Korea National Health and Nutrition Examination Survey (KNHANES), 2008–2010

Chang-Jin Choi, Min Seo, Whan-Seok Choi, Kyung-Soo Kim, Sang-Ah Youn, Tony Lindsey, Yun-Jung Choi, and Churl-Min Kim

Department of Family Medicine (C.-J.C., W.-S.C., K.-S.K., S.-A.Y., C.-M.K.), Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 137-701, Korea; Department of Parasitology (M.S.) College of Medicine, Dankook University, Chonan 330-715, Korea; NASA Ames Research Center (T.L.), Moffett Field, California 94035; and Metabolex, Inc (Y.-J.C.), Hayward, California 94545

Context: The relationship between vitamin D status and pulmonary function has not been investigated for an East Asian population.

Objective: The aim of the present study was to examine the relationship of serum 25-hydroxyvitamin D [25(OH)D] with lung function in Korean adults.

Design and Setting: The analysis used data from the Korea National Health and Nutrition Examination Survey (KNHANES), a cross-sectional survey of Korean civilians, conducted from 2008 to 2010.

Participants: A total of 10 096 people aged 19 years and older were selected from 16 administrative districts in South Korea.

Main Outcome Measures: Serum 25(OH)D levels with lung function [forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC)].

Results: Serum 25(OH)D concentration was positively associated with lung function after controlling for age, sex, height, and season. For FEV_1 and FVC, the differences between top and bottom quartiles in 25(OH)D were 51 mL (SE, 17 mL, *P* trend <.001) and 58 mL (SE, 20 mL, *P* trend <.005) greater volume, respectively. Association of serum 25(OH)D with FEV_1 and FVC was only slightly attenuated after adjustment for body mass index, lifestyle and socioeconomic factors, and respiratory illness. The subjects with a history of pulmonary tuberculosis showed a much higher increase in FEV_1; the difference between top and bottom quartiles in 25(OH)D was 229 mL (SE, 87 mL, *P* trend <.01).

Conclusion: Serum 25(OH)D levels have a positive correlation with pulmonary function. This relationship appears prominent in subjects with susceptibility to pulmonary tuberculosis. **(*J Clin Endocrinol Metab* 98: 1703–1710, 2013)**

It has been well established that vitamin D is important for bone health (1). Recent evidence suggests that adequate vitamin D levels reduce the risk for various ailments such as cancer and cardiovascular, autoimmune, and respiratory diseases (2). Observational population studies on the relationship between lung function and vitamin D concentrations have shown mixed results. Two national studies performed in the United States (3) and United

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

Received November 14, 2012. Accepted February 8, 2013.
First Published Online March 26, 2013

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; 25(OH)D, 25-hydroxyvitamin D; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; KNHANES IV, Fourth Korea National Health and Nutrition Examination Surveys; PSU, primary sampling unit; TB, tuberculosis.

Kingdom (4) indicated that higher vitamin D status, ie, serum 25-hydroxyvitamin D [25(OH)D] concentrations, is associated with improved lung function. However, this relationship was not confirmed in a recent cross-sectional study of older adults in the United Kingdom (5).

The relative risk for upper respiratory tract infection was elevated among participants with severe vitamin D deficiency, and the association appeared stronger for those with asthma and chronic obstructive pulmonary disease (COPD) (6). Vitamin D deficiency was extensive in patients with asthma (7), COPD (8), and pulmonary tuberculosis (TB) (9). Although the precise mechanism is unclear, vitamin D is an important innate immune modulator that influences barrier function for viral and bacterial infection (10, 11). In addition, vitamin D restrains inflammation in the airways to maintain respiratory health (12).

Despite observational studies and laboratory evidence, the results of clinical trials using vitamin D supplements to prevent respiratory diseases are not definitive (13, 14). Current recommended 25(OH)D levels are based on bone health, and levels for optimal immunological outcome (nonskeletal) measures are currently unknown.

The prevalence of vitamin D deficiency has increased worldwide during the last few decades (15, 16), and Korea is no exception. A nationwide survey conducted in 2008 revealed that vitamin D insufficiency (<20 ng/mL) was 55.9% with the most common cases occurring in the 20- to 29-year age group (17). Among the Korean population, it has been suggested that vitamin D deficiency is a risk factor for metabolic syndrome (18) and various cardiovascular diseases (19). However, the relationship between vitamin D status and pulmonary function has not been thoroughly studied in Korea. The aim of the present study was to examine the relationship of serum 25(OH)D with lung function in Korean adults.

Subjects and Methods

Study population

This study was based on data obtained from the second (2008) and third years (2009) of the Fourth Korea National Health and Nutrition Examination Surveys (KNHANES IV) and the first year (2010) of KNHANES V. KNHANES was a cross-sectional survey designed to examine the health and nutritional status of the noninstitutionalized Korean population conducted by the Division of Chronic Disease Surveillance, Korea Centers for Disease Control and Prevention (KCDC). Data were collected by a variety of means including household interviews, physical examinations, and nutritional status assessment. KNHANES followed a multistage cluster probability sampling design to ensure an independent and homogeneous sampling for each year in addition to nationally representative sampling. The sampling frame for KNHANES IV (2007–2009) relied upon 2005 Population and Housing Census data, whereas KNHANES V (2010–2012) used 2009 Registered Population and 2008 apartment complex price data. The primary sampling units (PSUs) for KNHANES IV and non-apartment complex of KNHANES V were enumeration districts consisting of 60 households on average. The apartment complex PSU of KNHANES V consisted of an average of 120 apartment housing units. There were 264 186 PSUs in KNHANES IV and 201 677 PSUs in KNHANES V. For sampling, PSUs were divided into 42 strata based on administrative region, city (rural or urban), and house type. Per year, 200 and 192 PSUs were selected in KNHANES IV and KNHANES V, respectively. Within a PSU, 20 to 23 final target households were sampled from the dwelling unit list of the PSU by systematic sampling.

Among 29 235 subjects age 19 and older, we constrained eligibility to those who successfully completed spirometry tests (n = 18 526). The subjects without 25(OH)D measurement (n = 597) or those exhibiting estimated glomerular filtration rate <30 mL/min (n = 16) were excluded from the study. A total of 10 096 participants were eligible for our study. The presence of asthma and pulmonary TB was determined by their response to the following question: “Have you ever been diagnosed with asthma (or pulmonary TB) by a physician?” All examination (or testing) protocols were approved by the KCDC Institutional Review Board with each subject providing written informed consent before participating.

Measurement of serum 25(OH)D

Levels of the serum 25(OH)D were assayed according to an agreed upon protocol. Blood samples were collected from each participant during the survey, processed, immediately refrigerated, and transported in cold storage to the Central Testing Institute in Seoul, Korea. All blood samples were analyzed within 24 hours after arrival at the testing facility. Serum 25(OH)D levels were measured by RIA (DiaSorin, Stillwater, Minnesota) using a γ-counter (1470 Wizard; PerkinElmer, Turku, Finland). The interassay coefficients of variation were 11.7%, 10.5%, 8.6%, and 12.5% at 8.6, 22.7, 33.0, and 49.0 ng/mL.

Measurement of lung function

Lung function was measured using a dry rolling seal spirometer (model 2130; SensorMedics, Yorba Linda, California) according to the American Thoracic Society/European Respiratory Society criteria for standardization (20). Spirometric data obtained on site by clinical technicians were transferred to an internet review center for processing. The data were carefully examined and compared against criteria metrics for acceptability, reproducibility, and quality control. A principal investigator validated and stored the data in a KCDC repository management system. Obstructive lung disease is defined by a decrease below 70% of the forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC).

Statistical analyses

Data were analyzed using the survey procedures of SAS version 9.2 (SAS Institute Inc, Chicago, Illinois). To produce an unbiased national estimate, a sample weight was assigned for the participating individuals to represent the Korean population. Sampling weights were constructed to account for the complex survey design, survey nonresponse, and poststratification. First, sampling was reflected by sampling weights with inverse probability of selection for PSUs and households. The inverse probability of selection was then adjusted for household and individual nonresponse. In addition to the survey design and nonresponse adjustments, the weights were modified by adjustment for sex and age demographics.

For analysis of the relationship between 25(OH)D and lung function, potential confounders were categorized. Body mass index (BMI) was categorized as <23, 23 to <25, and ≥25 kg/m^2, which are the cutoff points for, respectively, normal (including underweight), overweight, and obesity for Asian populations. Cigarette use was divided into 3 categories: current smoker, past smoker, and no history of smoking, which correlated to fewer than 100 cigarettes ever smoked. Subjects who had smoked 100 or more cigarettes were classified as past or current smokers, based on current use estimates. Occupation was classified into 4 groups: clerical (sales and service, clerical staff, administration, and specialists), manual (agriculture, forestry, fishery, and manual labor), technical (engineering, assembling, and technical work), and unemployed (no job, students, housewives). The criteria for season, regular exercise, and residential area were described by a previous study (17).

The differences in social and lifestyle factor means were evaluated using linear regression. The mean for 25(OH)D was standardized by sex and age. The means for FEV_1 and FVC were standardized by sex, age, and height. Analysis of covariance, with age and sex as covariate variables, was used to examine group difference for various types of respiratory disease. The association of 25(OH)D with FEV_1 and FVC was modeled by multiple linear regression or logistic regression in the presence of respiratory disease. Deviations of linearity across quartiles of 25(OH)D were assessed by the likelihood test for the quadratic term. All tests were 2-sided, with $P < .05$ being considered statistically significant.

Table 1. Serum 25(OH)D and Lung Function by Social and Lifestyle Characteristics (n = 10 096)[a]

Variable	n	25(OH)D, ng/mL	*P* Value	FEV_1, mL	*P* Value	FVC, mL	*P* Value
25(OH)D, ng/mL			<.0001		<.05		.0737
<10	636	8.6 (0.1)		2809 (24)		3553 (28)	
10 to <20	5384	15.2 (0.1)		2815 (8)		3574 (10)	
20 to <30	3274	24.0 (0.1)		2850 (9)		3606 (11)	
≥30	802	33.9 (0.2)		2850 (20)		3619 (23)	
Gender			<.0001		<.0001		<.0001
Male	4569	20.6 (0.2)		3046 (11)		3887 (14)	
Female	5527	17.5 (0.2)		2611 (9)		3286 (11)	
Age, y			<.0001		<.0001		<.0001
19–39	1928	17.1 (0.3)		3254 (14)		3858 (15)	
40–69	7040	19.4 (0.2)		2838 (8)		3611 (9)	
≥70	1128	19.8 (0.4)		2292 (19)		3162 (19)	
BMI, kg/m^2			.3872		<.0001		<.0001
<23	3619	19.2 (0.2)		2773 (10)		3541 (12)	
23 to <25	2706	18.9 (0.2)		2853 (9)		3620 (11)	
≥25	3757	19.0 (0.2)		2864 (9)		3603 (11)	
Smoking			.0656		<.01		.4003
Never	5885	19.2 (0.2)		2856 (10)		3572 (12)	
Ex-smoker	1929	19.3 (0.3)		2811 (17)		3584 (19)	
Current	2262	18.6 (0.3)		2800 (14)		3600 (16)	
Exercise[b]			<.0001		<.005		<.0001
No	7389	18.8 (0.2)		2819 (7)		3572 (8)	
Yes	2664	19.9 (0.3)		2857 (11)		3628 (12)	
Occupation[c]			<.0001		<.0001		<.0001
Clerical	3212	18.4 (0.2)		2857 (10)		3597 (12)	
Manual	2036	20.9 (0.4)		2817 (14)		3611 (16)	
Technical	1092	19.7 (0.3)		2869 (17)		3656 (19)	
Unemployed	3694	18.5 (0.2)		2793 (11)		3537 (13)	
Region[d]			<.0001		.6334		.1562
Rural	2534	20.8 (0.4)		2827 (13)		3607 (16)	
Urban	7562	18.6 (0.2)		2829 (7)		3580 (9)	
Season			<.0001		.3648		.2357
Spring	2574	16.2 (0.2)		2816 (13)		3579 (16)	
Summer	2700	21.8 (0.3)		2821 (12)		3568 (16)	
Fall	2672	21.0 (0.3)		2835 (10)		3590 (13)	
Winter	2150	16.8 (0.2)		2847 (15)		3614 (17)	

[a] Data are expressed as mean (SE). 25(OH)D was adjusted for age and sex. FEV_1 and FVC were adjusted for age, sex, and height. *P* values are associated with analysis of covariance.

[b] Exercise was consistently defined as either moderate or severe (for more than 30 minutes at a time and more than 5 times per week in the case of moderate exercise; for more than 20 minutes at a time and more than 3 times per week in the case of severe exercise).

[c] Occupations were classified as clerical (sales and service, clerical staff, administration, and specialists), manual (agriculture, forestry, fishery, and manual labor), technical (engineering, assembling, and technical work), and unemployed (no job, students, and housewives).

[d] Regions were designated as rural (Gangwon, Chungbuk, Chungnam, Jeonbuk, Jeonnam, Gyeongbuk, Gyeongnam, and Jeju) and urban (Seoul, Gyeonggi, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) areas.

Table 2. Serum 25(OH)D According to Respiratory Diseases

	n	25(OH)D[a]	*P* value[b]
Asthma[c]			
Yes	335	18.6 (0.5)	.277
No	9747	19.1 (0.2)	
Airway obstruction[d]			
Yes	1060	18.4 (0.3)	<.05
No	9036	19.2 (0.2)	
Pulmonary TB[e]			
Yes	556	18.2 (0.4)	<.05
No	9526	19.1 (0.2)	

[a] 25(OH)D is expressed as mean (SE), adjusted for age, sex, and season.

[b] *P* values represent Student's *t* test.

[c] Asthma was defined by physician diagnosis history of asthma.

[d] Airway obstruction was defined by FEV_1/FVC of less than 70%.

[e] Pulmonary TB was defined by physician diagnosis history of pulmonary tuberculosis.

Results

The serum 25(OH)D levels and lung functions of subjects according to baseline characteristics are shown in Table 1. Of the 10 096 subjects, 636 (6.3%) had serum 25(OH)D levels less than 10 ng/mL, 5384 (53.3%) were in the 10 to <20 ng/mL group, 3274 (32.4%) in the 20 to <30 ng/mL group, and only 802 (7.9%) in the group of >30 ng/mL. The serum 25(OH)D level was significantly higher in males, and their lung function was better compared with females. Regular exercise positively influenced the serum 25(OH)D and lung function ($P < .001$), whereas cigarette smoking and BMI appeared to have an insignificant effect. Occupation and residence also influenced the 25(OH)D, FEV_1, and FVC values. The 25(OH)D showed trends that increased with advancing age, whereas lung function indicated decreasing trends. There were significant seasonal variations in 25(OH)D, which was highest during the summer, followed by autumn, winter, and spring. The data analysis did not indicate significant seasonal differences in FEV_1 and FVC (Table 1). As for respiratory diseases, the subjects with a history of asthma failed to show significant differences in 25(OH)D (Table 2). However, subjects with airway obstruction or a history of pulmonary TB showed significantly lower levels of 25(OH)D ($P < .05$) (Table 2).

Quartile (Q) cutoff values of 25(OH)D (ng/mL) were Q1 < 15.3, Q2 15.3 to <19.6, Q3 19.6 to <24.9, and Q4 ≥ 24.9 for men, and Q1 < 12.8, Q2 12.8 to <16.5, Q3 16.5 to <21.4, and Q4 ≥ 21.4 for women.

There was a strong association of 25(OH)D with both FEV_1 and FVC, which persisted after adjusting for all other variables (Table 3). After controlling for age, sex, height, and season, 25(OH)D was positively associated with lung function. For FEV_1 and FVC, differences between top and bottom quartiles in serum 25(OH)D levels were 51 mL (SE 17, *P* trend <.001) and 58 mL (SE 20, *P* trend <.005), respectively (model 1). Although mean differences were decreased, these increased trends were maintained after additional adjustment for smoking and exercise (model 2), BMI, occupation, and region (model 3) as well as 3 respiratory diseases: asthma, pulmonary TB, and obstructive lung disease (model 4).

As seen in Table 4, after adjusting for potential confounders (model 3), the subjects with a history of pulmonary TB displayed a much higher increase in FEV_1, the differences between top and bottom quartiles in 25(OH)D were 229 mL (SE 87, *P* trend <.01). However, subjects

Table 3. Mean Difference (SE) in FEV_1 and FVC by Serum 25(OH)D Quartile[a]

	25(OH)D Quartile[b]					
	Q1 (n = 2520)	Q2 (n = 2525)	Q3 (n = 2523)	Q4 (n = 2526)	*P* Value[c]	*P* for Trend
FEV_1, mL						
Model 1	0	20 (16)	47 (16)[f]	51 (17)[f]	<.01	<.001
Model 2	0	14 (17)	48 (16)[d]	45 (18)[f]	<.01	<.005
Model 3	0	13 (17)	46 (16)[f]	48 (18)[e]	<.01	<.005
Model 4	0	19 (16)	32 (16)[d]	38 (16)[d]	.106	<.05
FVC, mL						
Model 1	0	16 (19)	47 (19)[d]	58 (20)[f]	<.05	<.005
Model 2	0	13 (20)	49 (16)[d]	54 (21)[e]	<.05	<.005
Model 3	0	11 (19)	46 (19)[d]	54 (20)[e]	<.05	<.005
Model 4	0	13 (19)	43 (19)[d]	51 (20)[d]	<.05	<.005

[a] Model 1 was adjusted for age, sex, height, and season; model 2 as model 1, with additional adjustment for smoking and exercise; model 3 as model 2, with additional adjustment for BMI, occupation, and region; model 4 as model 3, with additional adjustment for asthma, airway obstruction, and pulmonary TB.

[b] Quartile 1 (Q1) <15.3, Q2 15.3 to <19.6, Q3 19.6 to <24.9, Q4 ≥24.9 for men; Q1 <12.8, Q2 12.8 to <16.5, Q3 16.5 to <21.4, Q4 ≥21.4 for women.

[c] *P* values are associated with analysis of covariance.

[d–f] For comparison with lowest vitamin D quartile: [d] $P < .05$; [e] $P < .01$; [f] $P < .005$.

Table 4. Mean Difference (SE) in FEV_1 by Serum 25(OH)D Quartile According to Respiratory Diseases[a]

	n	25(OH)D Quartile[b]					
		Q1	Q2	Q3	Q4	*P* Value[c]	*P* for Trend
Asthma							
Yes	335	0	94 (100)	152 (105)	66 (121)	.431	.476
No	9747	0	14 (17)	41 (17)[d]	48 (18)[e]	<.05	<.005
Airway obstruction							
Yes	1060	0	84 (57)	129 (57)[d]	65 (66)	.142	.269
No	9036	0	11 (16)	26 (16)	36 (17)[d]	.173	<.05
Pulmonary TB							
Yes	556	0	86 (69)	139 (72)	229 (87)[e]	.055	<.01
No	9526	0	7 (17)	35 (16)[d]	35 (17)[d]	.062	<.05

[a] FEV_1 was adjusted for age, sex, height, season, smoking and exercise, BMI, occupation, and region. Asthma was defined by physician diagnosis history of asthma. Airway obstruction was defined by FEV_1/FVC of less than 70%. Pulmonary TB was defined by physician diagnosis history of pulmonary TB.

[b] Quartile 1 (Q1) <15.3, Q2 15.3 to <19.6, Q3 19.6 to <24.9, Q4 ≥24.9 for men; Q1 <12.8, Q2 12.8 to <16.5, Q3 16.5 to <21.4, Q4 ≥21.4 for women.

[c] *P* values are associated with analysis of covariance.

[d,e] For comparison with lowest vitamin D quartile: [d] $P < .05$; [e] $P < .01$.

with an asthma history or who had obstructive lung function did not exhibit significant correlation between 25(OH)D and pulmonary function. Participants without respiratory diseases persistently showed a positive association for 25(OH)D with both FEV_1 and FVC. The differences of FVC between top and bottom quartiles in 25(OH)D were insignificant among subjects with a history of pulmonary diseases, even for those with a history of TB (Table 5). As shown in Figure 1, FEV_1 (A) and FVC (B) steeply increased until 5 to 10 ng/mL of 25(OH)D and slowed when 25(OH)D over 20.0 to 25.0 ng/mL.

Discussion

We found a robust positive association between serum 25(OH)D level and lung function in Korean adults. This association was independent of age, sex, BMI, lifestyle (smoking and regular exercise), occupation, residence, season, and some respiratory diseases. This relationship was also shown in 2 cross-sectional population studies in the United States and United Kingdom (3, 4); top and bottom quartile differences in 25(OH)D increased 48 mL in FEV_1, less than that reported in the United Kingdom (93 mL) and United States (126 mL) studies. These small differences in the Korean population have not been fully explained, but it may be partially because average levels of 25(OH)D in the Korean population (18.7 ng/mL) were strictly lower than the United Kingdom (21.0 ng/mL) and United States (31.0 ng/mL) results.

In the present study, subjects with a history of pulmonary TB had lower 25(OH)D than those without a pulmonary TB background. Furthermore, in subjects with a

Table 5. Mean Difference (SE) in FVC by Serum 25(OH)D Quartile According to Respiratory Diseases[a]

	n	25(OH)D Quartile[b]					
		Q1	Q2	Q3	Q4	*P* Value[c]	*P* for Trend
Asthma							
Yes	335	0	10 (91)	39 (97)	78 (108)	.64	.619
No	9747	0	15 (20)	46 (19)[d]	59 (21)[e]	<.05	<.005
Airway obstruction							
Yes	1060	0	26 (68)	119 (69)	27 (71)	.254	.467
No	9036	0	11 (20)	38 (20)	53 (21)[d]	<.05	<.01
Pulmonary TB							
Yes	556	0	45 (74)	124 (82)	109 (83)	.396	.118
No	9526	0	8 (20)	37 (20)	47 (21)[d]	.065	<.05

[a] FVC, forced vital capacity, adjusted for age, sex, height, season, smoking and exercise, body mass index, occupation, and region. Asthma was defined by physician diagnosis history of asthma. Airway obstruction was defined by FEV_1/FVC of less than 70%. Pulmonary TB was defined by physician diagnosis history of pulmonary TB.

[b] Quartile 1 (Q1) <15.3, Q2 15.3 to <19.6, Q3 19.6 to <24.9, Q4 ≥24.9 for men; Q1 <12.8, Q2 12.8 to <16.5, Q3 16.5 to <21.4, Q4 ≥21.4 for women.

[c] *P* values are associated with analysis of covariance.

[d,e] For comparison with lowest vitamin D quartile: [d] $P < .05$; [e] $P < .005$.

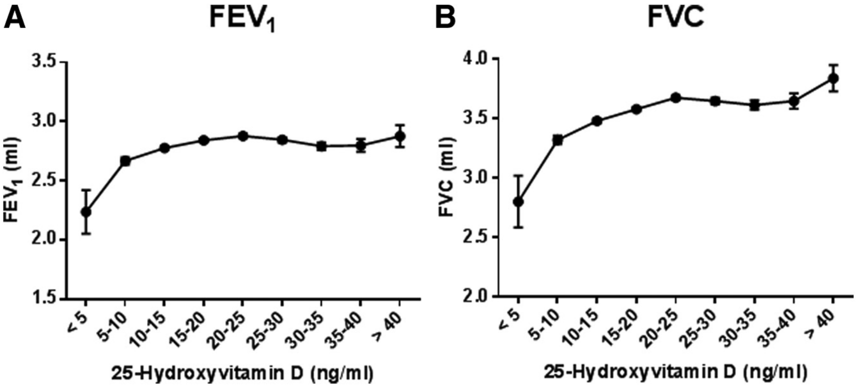

Figure 1. Relationship between serum 25(OH)D and lung function in Korean adults. FEV1 (A) and FVC (B) increased steeply until 5 to 10 ng/mL of 25(OH)D and slowed when 25(OH)D over 20.0 to 25.0 ng/mL.

history of TB, the difference between 25(OH)D top and bottom quartiles increased 229 mL in FEV_1, which was significantly larger than quartile differences in subjects without a pulmonary TB history. Among participants with a history of TB, only 1.5% of them were taking anti-TB medication. Therefore, it should be unlikely that serum 25(OH)D level was influenced by the administration of treatment regimen on TB. These results suggest that the susceptibility of pulmonary TB might be related to vitamin D deficiency and also that vitamin D therapy may be beneficial for lung function in this population. Although there has been some evidence to the contrary, a recent meta-analysis demonstrated that participants with TB had significantly lower serum 25(OH)D (9). The precise mechanism for this phenomenon remains unknown, but it has been suggested that vitamin D accelerates recovery from infection by enhancing innate immunity via up-regulation of antimicrobial peptides (21). Another possible mechanism is that 1α,25-dihydroxyvitamin D_3 down-regulates expression and secretion of matrix metalloproteinase enzymes implicated in degradation of pulmonary extracellular matrix in TB patients (22).

In fact, vitamin D therapies improved TB outcomes, characterized by increased in vitro activity against *Mycobacterium bovis* (23), sputum conversion, and radiological improvement (24) or solution of the inflammatory response during TB treatment (11). Another prospective study suggests that vitamin D deficiency predisposes to active TB. Among healthy TB contact within the family, extreme vitamin D deficiency (<7 ng/mL) at baseline was associated with increased risk of active TB progression over the subsequent 4 years of follow-up (25). Comparing highest tertile (>13 ng/mL) with the lowest tertile (<7 ng/mL), relative risk of active TB progression was 5 times as much; moreover, there were no active TB progressions in 25(OH)D >13 ng/mL. These results suggest relatively modest elevations of serum 25(OH)D might be effective for the prevention of TB.

South Korea's TB control remains at developing country levels, and vitamin D deficiency is similar to the age distribution for new cases of TB, following a bimodal distribution with the first peak occurring in the patient's 20s (17, 26). The present study suggests that vitamin D therapy might be beneficial as a preventive or adjunctive for TB therapy in Korean patients.

Many studies have revealed that vitamin D deficiency increases the risk of severe asthma exacerbation by dampening the inflammatory immune response (27, 28). However, the present study indicates that the difference in FEV_1 between the top and bottom quartiles of serum 25(OH)D was insignificant for both subjects with obstructive lung function and those with an asthma history. Other cross-sectional studies also reported similar results in subjects with chronic bronchitis or emphysema in relation to serum 25(OH)D concentrations (3). However, a prospective cohort study revealed that bronchiectasis patients with vitamin D deficiency (<10 ng/mL) suffered more frequent exacerbation and greater percentage of FEV_1 decline over a 3-year period (29). Another cohort study of elderly men reported that vitamin D sufficiency (vitamin D ≥20 ng/mL) appeared to have a protective effect on lung function, and the rate of lung function declined in smokers over a 20-year time span, modifying the smoking effects over this period (30). Trials with high-dose vitamin D supplementation in severe COPD patients did not reduce the incidence of exacerbations, but in participants with severe vitamin D deficiency at baseline (<10 ng/mL), vitamin D supplementation showed a significant reduction in exacerbations of 43% over 1 year (13). Additional trials demonstrated that vitamin D supplement does not reduce the incidence of upper respiratory tract infection in healthy adults who have sufficient levels of 25(OH)D (mean baseline level was 29 ng/mL) (14). One of the possible causes of these inconsistent findings could be the fact that the required vitamin D level for respiratory health is relatively lower than current recommendations based on skeletal outcome. There is no consensus about optimal serum 25(OH)D levels for nonskeletal health. The Institute of Medicine suggested a level of 20 ng/mL as adequate to prevent adverse skeletal health (31). The National Osteoporosis Foundation, International Osteoporosis Foundation, and American Geriatrics Society suggest that a minimum level of 30 ng/mL is necessary (32). In the present study, even as improved lung function trends were maintained, the increment of pulmonary function was noticeably slowed when 25(OH)D exceeded 16.5 to 24.9 ng/mL.

The present study does have several limitations. First, because this study is cross-sectional, we cannot rule out reverse causality as an explanation for the observed associations. Second, the prevalence of asthma and pulmonary TB could incorporate misclassification bias because they were based on participants' reports of their physicians' diagnosis. However, the Korean national TB surveillance system has been ongoing since 1965, and it is likely that physician diagnosis appraisal is fairly accurate compared with other countries. Regardless, our findings require confirmation by other studies where the diagnosis of asthma and TB are based on objective criteria rather than self-reported physician diagnosis. Third, the overall low 25(OH)D participant level constrains our ability to adequately estimate optimal 25(OH)D levels for lung function. Fourth, data on sun exposure and dietary or supplementary vitamin D intake were not available.

Our study represents the first to determine the relationship between lung function and vitamin D based on a national representative population in Korea. Although 59.6% of our present study participants recorded 25(OH)D levels below 20 ng/mL, vitamin D status continues to have a positive relationship with lung function. In particular, this relationship is prominent in subjects susceptible to pulmonary TB. Considering that the prevalence of TB in Korea has remained high in comparison with those of other the Organization for Economic Cooperation and Development countries (26), this study suggests a practical role of vitamin D in the clinical field of TB. Additional research is needed to determine the required vitamin D level for respiratory health and protective roles of vitamin D in other respiratory diseases.

Acknowledgments

Address all correspondence and requests for reprints to: Churl-Min Kim, MD, PhD, Department of Family Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 137-701, Korea. E-mail: musofm@catholic.ac.kr.

The study concept and design were prepared by C.-J.C., M.S., W.-S.C., S.-A.Y., and C.-M.K. T.L., Y.-J.C., K.-S.K., and C.-J.C., performed the statistical analyses and interpretation of data. C.-M.K., M.S., and C.-J.C. drafted the manuscript. Completion of the first draft into final manuscript version was done by C.-J.C. All authors have read the draft versions and approved the final version of the manuscript.

Disclosure Summary: The authors have nothing to declare.

References

1. **Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA.** Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2011;155:827–838.
2. **Holick MF.** Vitamin D deficiency. *N Engl J Med*. 2007;357:266–281.
3. **Black PN, Scragg R.** Relationship between serum 25-hydroxyvitamin D and pulmonary function in the third national health and nutrition examination survey. *Chest*. 2005;128:3792–3798.
4. **Berry DJ, Hesketh K, Power C, Hyppnen E.** Vitamin D status has a linear association with seasonal infections and lung function in British adults. *Br J Nutr*. 2011;106:1433–1440.
5. **Shaheen SO, Jameson KA, Robinson SM, et al.** Relationship of vitamin D status to adult lung function and COPD. *Thorax*. 2011;66:692–698.
6. **Ginde A, Mansbach JM, Camargo CA.** Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med*. 2009;169:384–390.
7. **Litonjua A.** Vitamin D deficiency as a risk factor for childhood allergic disease and asthma. *Curr Opin Allergy Clin Immunol*. 2012;12:179–185.
8. **Janssens W, Bouillon R, Claes B, et al.** Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. *Thorax*. 2010;65:215–220.
9. **Nnoaham KE, Clarke A.** Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. *Int J Epidemiol*. 2008;37:113–119.
10. **Schwalfenberg GK.** A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. *Mol Nutr Food Res*. 2011;55:96–108.
11. **Coussens AK, Wilkinson RJ, Hanifa Y, et al.** Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment. *Proc Natl Acad Sci U S A*. 2012;109:15449–15454.
12. **Dimeloe S, Richards DF, Urry ZL, et al.** 1α,25-Dihydroxyvitamin D3 promotes CD200 expression by human peripheral and airway-resident T cells. *Thorax*. 2012;67:574–581.
13. **Lehouck A, Mathieu C, Carremans C, et al.** High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med*. 2012;156:105–114.
14. **Murdoch DR, Slow S, Chambers ST, et al.** Effect of vitamin D3 supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial. *JAMA*. 2012;308:1333–1339.
15. **van Schoor NM, Lips P.** Worldwide vitamin D status. *Best Pract Res Clin Endocrinol Metab*. 2011;25:671–680.
16. **Mithal A, Wahl DA, Bonjour JP, et al.** Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int*. 2009;20:1807–1820.
17. **Choi HS, Oh HJ, Choi WH, et al.** Vitamin D insufficiency in Korea—a greater threat to younger generation: the Korea National Health and Nutrition Examination Survey (KNHANES) 2008. *J Clin Endocrinol Metab*. 2011;96:643–651.
18. **Kim S, Lim J, Kye S, Joung H.** Association between vitamin D status and metabolic syndrome risk among Korean population: based on the Korean National Health and Nutrition Examination Survey IV-2, 2008. *Diabetes Res Clin Pract*. 2012;96:230–236.
19. **Park S, Lee B.** Vitamin D deficiency is an independent risk factor for cardiovascular disease in Koreans aged ≥50 years: results from the Korean National Health and Nutrition Examination Survey. *Nutr Res Pract*. 2012;6:162–168.
20. **Miller MR, Hankinson J, Brusasco V, et al.** Standardisation of spirometry. *Eur Respir J*. 2005;26:319–338.
21. **De Smet K, Contreras R.** Human antimicrobial peptides: defensins, cathelicidins and histatins. *Biotechnol Lett*. 2005;27:1337–1347.
22. **Coussens A, Timms PM, Boucher BJ, et al.** 1α,25-Dihydroxyvita-

min D_3 inhibits matrix metalloproteinases induced by *Mycobacterium tuberculosis* infection. *Immunology*. 2009;127:539–548.
23. **Martineau AR, Wilkinson RJ, Wilkinson KA, et al.** A single dose of vitamin D enhances immunity to mycobacteria. *Am J Respir Crit Care Med*. 2007;176:208–213.
24. **Nursyam EW, Amin Z, Rumende CM.** The effect of vitamin D as supplementary treatment in patients with moderately advanced pulmonary tuberculous lesion. *Acta Med Indones*. 2006;38:3–5.
25. **Talat N, Perry S, Parsonnet J, Dawood G, Hussain R.** Vitamin D deficiency and tuberculosis progression. *Emerg Infect Dis*. 2010; 16:853–855.
26. **Park Y, Hong S, Boo Y, et al.** The national status of tuberculosis using nationwide medical records survey of patients with tuberculosis in Korea. *Tuberc Respir Dis (Seoul)*. 2012;73:48–55.
27. **Freishtat RJ, Iqbal SF, Pillai DK, et al.** High prevalence of vitamin D deficiency among inner-city African American youth with asthma in Washington, DC. *J Pediatr*. 2010;156:948–952.
28. **Brehm JM, Celedon JC, Soto-Quiros ME, et al.** Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med*. 2009;179:765–771.
29. **Chalmers JD, McHugh BJ, Docherty C, Govan JR, Hill AT.** Vitamin-D deficiency is associated with chronic bacterial colonisation and disease severity in bronchiectasis. *Thorax*. 2013;68:39–47.
30. **Lange NE, Sparrow D, Vokonas P, Litonjua AA.** Vitamin D deficiency, smoking, and lung function in the normative aging study. *Am J Respir Crit Care Med*. 2012;186:616–621.
31. **Rosen CJ, Abrams SA, Aloia JF, et al.** IOM committee members respond to Endocrine Society vitamin D guideline. *J Clin Endocrinol Metab*. 2012;97:1146–1152.
32. **Holick MF, Binkley NC, Bischoff Ferrari HA, et al.** Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1911–1930.