Vitamin D and lung function decline in adults with asthma: The HUNT Study

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ABSTRACT

We investigated whether low 25-hydroxyvitamin D (25(OH)D) levels were associated with more lung function decline in adults with asthma and whether this association was modified by smoking status or inhaled corticosteroid (ICS) use. We analyzed 395 adults with asthma from the Nord-Trøndelag Health Study (1995-2008), Norway. Plasma 25(OH)D and lung function were measured at baseline, and lung function measurements were repeated at follow-up, approximately 11 years. Linear regression was used to estimate changes in lung function decline. Participants with low 25(OH)D (<50 nmol/L) had more decline in lung function measurements for FEV_1 (388 ml), FVC (298 ml) and FEV_1/FVC ratio (3.7 %) over the follow-up, compared to those with high 25(OH)D (≥50 nmol/L) who declined 314 ml, 246 ml and 3.0 %, respectively (p-values=0.08, 0.30 and 0.23, respectively). The associations were stronger in never smokers and non-ICS users. In never smokers, low 25(OH)D levels were associated with more decline in FEV_1 (445 vs. 222 ml) (p-value=0.01). In non-ICS users, low 25(OH)D levels were associated with more decline in FEV_1 (467 vs. 320 ml) (p-values=0.02). Low serum 25 (OH)D levels were weakly associated with more lung function decline in adults with asthma, stronger associations were observed in never smokers and non-ICS users.

Key words: 25-hydroxyvitamin D, vitamin D, asthma, lung function, spirometry

Word count: 201

Abbreviations: 25(OH)D, 25-hydroxyvitamin D, HUNT, Nord-Trøndelag Health; ICS, inhaled corticosteroid, FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

The effects of vitamin D supplementation in the prevention and treatment of rickets and osteomalacia are well established but its influence on non-bone diseases is far more elusive (1). Within respiratory epidemiology, investigators speculate that vitamin D may affect both immune cells and airway smooth muscle which may have a direct effect on lung function, and indeed some studies have found that low vitamin D status may be associated with impaired lung function, airway hyperresponsiveness and other markers of asthma severity (2-5). While most studies have been conducted in the general population (2, 3, 6-9), fewer studies have investigated the association between vitamin D status and lung function in adults with asthma (4, 10-14).

In adults with asthma, mixed results have been observed in cross-sectional studies (4, 11-14) and one most recent randomized trial did not find an association between vitamin D supplementation for 28 weeks and change in lung function (10). Given the inconsistencies between these studies, further studies are needed, particularly using a prospective cohort or interventional design with follow-up for several years.

Studies in the general population have observed that the association between low vitamin D status and lung function decline may differ by smoking status (3, 8, 9, 15) , with the hypothesized association being stronger in smokers. However, in adults with asthma, only one cross-sectional study has investigated this issue, and the association did not vary by smoking status (11). Another subgroup of interest is people with asthma who are not treated with inhaled corticosteroids (ICS); they also may be more responsive to the putative beneficial effects of vitamin D (4).

In a previous cross-sectional study conducted in the Nord-Trøndelag Health Study (HUNT), Larose et al. investigated the association of vitamin D status and lung function in 760 adults with asthma (12). We now have the opportunity to investigate the association between vitamin D

status and lung function decline after an average 11 years of follow-up. We analyzed these unique data from the HUNT Study to investigate 1) the association between vitamin D status and lung function decline in adults with asthma; and 2) whether this association was modified by smoking status or ICS use.

METHODS

Study population

The HUNT Study is a population based study comprised of three surveys conducted in 1984-86 (HUNT1), 1995-97(HUNT2) and 2006-08(HUNT3) in the county of Nord-Trøndelag, Norway. Adults aged 20 years or older in the population of Nord-Trøndelag (n=93,898 in 1997) were invited to participate in each of the surveys (16). Our study utilized those participating in HUNT2 (n=65,237) and HUNT3 (n=50,807) as information on asthma was not collected in HUNT1 (n=77,212)(16). Of the survey participants, 37,071 participated in both HUNT2 and HUNT3, of which 548 reported asthma and were under the age of 55 in HUNT2. For the present analysis, we will refer to HUNT2 as "baseline" and HUNT3 as "follow-up". Asthma was defined as those answering "yes" to three questions – 1) "Do you have or have you had asthma?" at baseline, 2) "Have you had attacks of wheezing or breathlessness during the last 12 months?" at baseline, and 3) "Do you have or have you had asthma?" at follow-up – and "no" to a fourth question: "Have you had or do you have any of the following: chronic bronchitis, emphysema or chronic obstructive pulmonary disease " at follow-up. Additionally, to exclude others with chronic obstructive pulmonary disease, participants with a forced expiratory volume in 1 second (FEV_1) / forced vital capacity (FVC) ratio <70% at baseline were excluded. A further 153 participants

were excluded because they did not have measurements of vitamin D status at baseline or lung function measures either at baseline or at follow-up, leaving 395 participants in our analysis cohort. In the subgroup analyses by smoking status (n=387), an additional 8 participants were excluded because of missing information on smoking status. All 395 subjects had information on ICS use.

Vitamin D status

The best estimates of vitamin D status are provided by measuring serum 25-hydroxyvitamin D (25(OH)D). Blood samples were collected at baseline and stored at -70° C until serum 25(OH)D levels were measured. Serum 25(OH)D was measured using the DiaSorin LIAISON 25-OH Vitamin D TOTAL assay (DiaSorin, Saluggia, Italy), a fully automated antibody-based chemiluminescence assay with a detection rang of 10-375 nmol/L. In our measurements, the intra-assay coefficient of variation was 4% and the inter-assay coefficient of variation was 8%. We categorized low serum 25(OH)D as <50 nmol/L and high serum 25(OH)D as ≥50 nmol/L based on the Institute of Medicine report and previous literature (12, 15, 17-19).

Covariables

At baseline, key information on participants was recorded including age, sex, height, weight, smoking status (current, former, never, unknown), years of education (<10, ≥10 years, unknown), number of hours of physical activity (number of hours of light exercise per week; <1, ≥1 hour, unknown), socio-economic status (received social benefit or reported economic difficulties, unknown), use of asthma medication (ever, never), ICS use (ever user, non-user) and season of blood sample (Winter [December-February], Spring [March-May], Summer [June-August], Autumn [September-November]). Height and weight were measured at a clinical examination by

trained health professionals and body mass index was calculated as weight (in kilograms) divided by height squared (in meters). Ever users of asthma medication responded "yes" to "Do you use or have you used asthma medication?".

Current smokers responded "yes" to "Do you smoke - cigarettes daily?". Former smokers respond "no" to "Do you smoke – cigarettes daily?" but did not indicate that they never smoked daily. Never smokers respond "no" to "Do you smoke –cigarettes daily?" and "yes" to "Never smoked daily".

ICS users answered "yes" to "Have you ever regularly used medicines like becotide, flutide, pulmicort or viarox?" or "Have you used medicines named becotide, flutide, pulmicort or viarox regularly in the last half year" or responded to at least one medication in the following question "If you have used ICS in the last 6 months, what did you use – becotide/viarox, flutide, flunitec, or pulmicort" or the participant responded on the question for ICS dosage last week "What is the average daily dosage that you used last week?".

Lung function decline

Lung function measurements were recorded at baseline and follow-up by trained health professionals in accordance with the 1994 American Thoracic Society recommendations (20). At baseline, FEV_1 and FVC were measured with three MasterScope spirometers, version 4.15 (Erich Jaeger GmbH, Wuerzburg, Germany) and at follow-up with an updated version of the same equipment (version 5.1). Further information on the measurements and quality control of these measures can be found elsewhere (21, 22). Three measures of lung function decline were calculated; 1) decline in FEV_1 (FEV_1 at baseline minus FEV_1 at follow-up), 2) decline in FVC

(FVC at baseline minus FVC at follow-up) and 3) decline in FEV_1/FVC (calculated as FEV_1/FVC at baseline minus FEV_1/FVC at follow-up).

Statistical methods

Statistical analyses were performed in the total cohort as well as in subgroups stratified by smoking status or ICS use. Baseline characteristics of the participants are presented for those with serum 25(OH)D levels <50 or ≥50 nmol/L in the total cohort (Table 1). Linear regression was used to estimate the association between serum 25(OH)D and lung function decline (Tables 2-4). We investigated serum 25(OH)D as both a continuous and categorical variable. The difference in lung function decline between serum 25(OH)D <50 and ≥50 nmol/L and 95% confidence intervals (CI) were presented. Additionally, the means of lung function decline were presented. Models were adjusted for age, sex, height, body mass index, smoking status, education, physical activity, socio-economic status, use of asthma medication, ICS use and season of blood sample. Adjustments for these variables were based on *a priori* hypotheses concerning their relationship to 25(OH)D and lung function. Subgroup analyses were conducted by both smoking status and ICS use. In the subgroup analysis by smoking, the estimates did not differ between current and former smokers so these two groups were combined in the final analysis. Tests for interaction were performed as likelihood ratio tests in linear regression models. All statistical analyses were performed using STATA version 13.1 (StataCorp, College Station, Texas).

Ethics

This study was approved by the Regional Committee for Medical Research Ethics, Norway and all participants gave informed written consent.

RESULTS

In the total cohort (n=395), serum (OH)D levels ranged from 10.7nmol/L to 163 nmol/L. The median and mean levels were 55.6 nmol/L and 58.4 nmol/L, respectively. 41% of the participants had a serum 25(OH)D <50 nmol/L. The mean rates of lung function decline in our study were 31 ml per year (standard deviation [SD] 35ml) for FEV_1 and 24 ml per year (SD 41ml) for FVC. Table 1 presents the baseline characteristics of the analysis cohort. Participants with serum 25(OH)D <50 nmol/L were more likely to be current smokers, less educated, less physically active, have a lower socioeconomic status, use ICS and have their blood samples taken in winter or spring than participants with serum 25(OH)D ≥50 nmol/L.

Table 2 presents the association between serum 25(OH)D and lung function decline in the total cohort. Those with serum 25(OH)D <50 nmol/L had more decline in lung function for FEV_1 (adjusted mean decline 388 ml), FVC (adjusted mean decline 298 ml) and FEV_1/FVC ratio (adjusted mean decline 3.7 %) over the 11-year follow-up period, than those with serum 25(OH)D ≥50 nmol/L (adjusted mean decline FEV_1 314 ml, FVC 246 ml and FEV_1/FVC ratio 3.0%; p-values=0.08, 0.30 and 0.23, respectively).

Table 3 presents the primary analyses stratified by smoking status. Among never smokers, having serum 25(OH)D <50 nmol/L was associated with more decline in FEV_1 and FVC compared to having serum 25(OH)D ≥50 nmol/L (adjusted mean decline 445 ml vs. 222 ml, and 347 ml vs. 128 ml, respectively) (p-values=0.01 and 0.01, respectively). In never smokers, we also observed more decline in the FEV_1/FVC ratio in those with serum 25(OH)D <50 nmol/L than ≥50 nmol/L with an adjusted mean decline of 4.2 vs. 2.8%, respectively (p-value=0.12). By contrast, no clear associations were observed in ever smokers. The p-value for interaction between serum 25(OH)D, and smoking status was 0.08 for decline in FEV_1 and 0.14 for decline in FVC.

Table 4 presented the primary analyses stratified by ICS use. We found that in non-ICS users, serum 25(OH)D <50 nmol/L was associated with more decline in FEV_1 and FVC compared to non-ICS users with serum 25(OH)D ≥50 nmol/L (adjusted mean decline 467 ml vs. 320 ml and 392 ml vs. 207 ml, respectively), (p-values=0.02 and 0.01, respectively). No clear associations were observed for the FEV_1/FVC ratio. The p-value for interaction between serum 25(OH)D and ICS status was 0.14 for FEV_1 decline and 0.03 for FVC decline.

DISCUSSION

In this prospective cohort study, we observed a weak association between low serum 25(OH)D levels and more lung function decline in adults with asthma, although this apparent difference was not statistically significant. The association was stronger among never smokers and non-ICS users, and null in their counterparts (i.e., ever smokers and ICS users). These subgroup findings suggest that the association between high serum 25(OH)D levels and lung function may be more complex than previously appreciated.

The mean rates of lung function decline in our study were comparable to other previously reported rates of decline in adults with asthma (23, 24). For example, in a 15-year follow-up study of 1,095 adults with asthma, Lange et al. found the mean decline in FEV_1 was 38 ml per year (23). Additionally, in a study which included 713 adults with asthma, similar rates of decline were observed for both FEV_1 and FVC (24). Rates of lung function decline are generally higher in smokers, and the slight differences in these rates and our rates (38 vs. 31ml) may be attributed to differences in such a characteristic (25% current smokers in our study versus 68-74% current smokers in the study by Lange et al.).

To the best of our knowledge, we present the first analysis of the association between serum 25(OH)D and lung function decline over a long time period in adults with asthma. For study design reasons alone, the current data go well beyond several cross-sectional studies on the association between vitamin D status and lung function in adults with asthma. Four of these cross-sectional studies found that serum 25(OH)D levels were associated with impaired lung function (4, 11, 13, 14) and one did not find a clear association (12). These studies generally only adjusted for a limited number of confounders (such as age, sex and body mass index) and the temporality of the association could not be assessed. In contrast, the current study adjusted for many additional potential confounding factors, including physical activity, smoking status, socio-economic status and asthma medication use. Recently, one randomized clinical trial was published investigating the association between vitamin D treatment and asthma treatment failures in 408 adults with asthma (10). In this 28-week trial, vitamin D supplementation (100,000 IU once, then 4,000 IU daily) did not reduce the rate of first treatment failure (10). First treatment failure included impaired lung function, additional use of medication, emergency department or hospitalization for asthma, participant lack of satisfaction with treatment and physician clinical judgment (10). In a secondary analysis, treatment with vitamin D was found to have no significant association with lung function improvement (change in FEV_1). However in an exploratory analysis of participants who achieved a 25(OH)D level of ≥75 nmol/L, there was a reduction in the overall rate of treatment failures and exacerbations (10).

Our study extends on these previous findings by investigating serum 25(OH)D and lung function decline over a much longer time frame (approximately 11 years). If serum 25(OH)D has a subtle influence on lung function, one might expect to capture the association only by studying such a long time period. While we only observed a weak association between serum 25(OH)D and lung

function decline in the total cohort, we did observe stronger associations in never smokers and non-ICS users. In the general population, several prospective studies have found a stronger association in smokers compared to non-smokers (3, 8, 9, 15) . In adults with asthma, only one other study has investigated this subgroup (11). This cross-sectional study, which included 435 Chinese adults, did not find that the 25(OH)D-lung function association differed between smokers and non-smokers (11). In contrast to previous studies, we found, in Norwegian adults with asthma, the strongest association between serum 25(OH)D and change in lung function among never smokers, where those with high serum 25(OH)D had the least decline in lung function. Regarding the association between serum 25(OH)D, lung function decline and ICS use, we found a stronger association in non-users. This finding is consistent with a previous study from Sutherland et al., which found that low vitamin D status was associated with impaired lung function (FEV_1) and the association was strongest in those who were not on ICS (4). We speculate that if there were beneficial effects of higher vitamin D status on lung function in asthma patients, this effect would be less important clinically because never smokers and non-ICS users are more likely to have smaller decline in lung function, milder asthma, or milder airway inflammation. In addition, we did not observe a clear association between serum 25(OH)D and FEV_1/FVC ratio, in particular in the analysis stratified by ICS. It is possible that those who were not on ICS have the mildest form of disease, and are less likely to suffer from significant airway obstruction.

We can only speculate on the pathophysiology underlying the association between serum 25(OH)D and lung function as the mechanisms are far from established. Vitamin D receptors have been found in almost all immune cells and it is likely that vitamin D may play a role in both airway inflammation and airway remodeling (25). Vitamin D may influence airway remodeling

by affecting airway smooth muscle growth and contractility, fibroblast proliferation, extracelluar matrix proteins and matrix metalloproteinase production (25). In a murine model of airways in chronic asthma, vitamin D treatment with ovalbumin challenge reduced inflammation and structural changes (26). In asthma, extensive airway remodeling can occur including abnormally thickened epithelium with mucus gland hypertrophy, altered fibrosis composition, and greatly increased airway smooth muscle mass and this might have a direct effect on lung function (25). For example, in people with asthma, thickening of the basement membrane has been negatively associated with FEV_1 (27).

A strength of the current study is that serum 25(OH)D was measured at baseline and we were able to analyze lung function decline after the time of blood sampling. This longitudinal design may provide us with an insight in to the temporality of the association between serum 25(OH)D and lung function decline that cannot be observed in cross-sectional studies. Our study also included a reasonably large number of participants and serum 25(OH)D, lung function and anthropometric data were measured by trained health professionals. Additionally, we had information on the participants' health and lifestyle which allowed us to control for a range of potential confounders.

Despite such strengths, our study had several limitations. Because of the longitudinal design, it is possible that selection bias may have occurred as entry into our study required that participants were able to attend the follow-up. However, in a study of non-responders to the HUNT Study, generally participants did not report differently from non-participants in terms of unhealthy lifestyle factors (i.e. body mass index and smoking status) or asthma status, which argues against major selection bias in the current study(28). Additionally, participants in our analysis required complete data on serum 25(OH)D and lung function. However, when we compared our analysis

cohort to those with missing data no substantial differences were found (Web Table 1). Additionally, our study excluded participants with chronic obstructive pulmonary disease using pre-bronchodilator measurements, and some of the most severe asthma cases may have been excluded. This may have influenced our results, however, when we included those who met this criteria but did not have a history of smoking, the results were similar to the total cohort (adjusted difference in decline for FEV1 [69 vs. 74ml], FVC [38 vs. 52ml], FEV_1/FVC [0.9 vs. 0.7%]), (Web Tables 2-4).

Unfortunately this study only included one measurement of serum 25(OH)D at baseline and this may have weakened our ability to study the association. Repeated measures of 25(OH)D throughout the follow-up period would give better estimates of the long-term association. However, it has been found that although seasonal variation of vitamin D exists, there is no large variation in urinary calcium excretion, suggesting that at least the seasonal fluctuations in serum levels might not be physiologically relevant (5). Still it is possible that seasonal variation may cause misclassification bias in the categories of vitamin D (<50 nmol/L and ≥50 nmol/L). Therefore we performed analyses stratified by season and generally the direction of our results remained unchanged (Web Tables 5-7). Furthermore, a study investigating the reproducibility of serum 25(OH)D measurements over time has suggested that a baseline measurement of serum 25(OH)D provides a reasonably representative measure for prospective studies (29). Additionally it is important to note that vitamin D levels vary depending on the season of blood sample more in northern populations than in southern populations, which should be considered when comparing our findings to other populations. Our outcome, lung function, may also be prone to measurement error. Measures of lung function may vary due to the hour or season the measurements were taken, the attention to the protocol by the medical staff or the effort of the

participant. However, we have no reason to believe that measurement error would vary by serum 25(OH)D status and thereby bias the results.

Although we controlled for a large range of confounding factors it is possible that residual confounding may explain some of our findings. For example, BMI may be a poor measure of obesity. However when we further adjusted for waist circumference we generally observed slightly stronger results than in our original analyses (data not shown). Furthermore, unknown factor/s can cause residual confounding but the unknown factor/s must not be related to any other variables already controlled for in our model. Finally, it is possible that participants with poor lung function at baseline were less likely to conduct outside activities and this might lower their exposure to sunlight and therefore lower serum 25(OH) D status. Poor lung function at baseline might also exacerbate lung function decline. However, when we controlled for lung function (FEV_1) at baseline, it did not substantially alter our estimates from the original estimates in the total cohort (adjusted difference in decline for FEV1 [69 vs. 74ml], FVC [46 vs. 52ml], FEV_1/FVC [0.7 vs. 0.7%]), (Web Tables 8-10).

In summary, among a well-characterized cohort of 395 adults with asthma, low 25(OH)D level was weakly associated with more lung function decline over approximately 11 years of follow-up. However, in never smokers and non-ICS users the associations were stronger. Further research is needed to confirm whether elevated serum 25(OH)D levels provide any beneficial effect on lung function change in adults with asthma and whether there is substantial variation in the association by smoking status and ICS usage.

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Table 1. Baseline Characteristics of the Analysis Cohort, Nord–Trøndelag Health Study, Norway (1995-1997).

Baseline characteristic	25(OH)D <50 (nmol/L) (n=162)			25(OH)D ≥50 (nmol/L) (n=233)	
	No.	%	Mean (SD)	No. (%)	Mean (SD)
Age (years)			38 (9)		38 (9)
Sex					
Women	97 (60)			129 (55)	
Men	65 (40)			104 (45)	
Height			171 (10)		172 (9)
Body mass index (kg/m^2)			28 (5)		26 (5)
Smoking					
Never	62 (38)			102 (43.8)	
Current	53 (33)			47 (20.2)	
Former	42 (26)			81 (34.8)	
Unknown	5 (3)			3 (1.3)	
Education (years)					
<10	35 (22)			38 (16)	
≥10	126 (78)			193 (83)	
Unknown	1 (1)			2 (1)	
Physical activity (hrs/wk)					
<1	41 (25)			51 (21.9)	
≥1	106 (65)			158 (68)	
Unknown	15 (9)			24 (10)	
Socioeconomic status					
High	52 (32)			97 (42)	
Low	91 (56)			102 (44)	
Unknown	19 (12)			34 (15)	
Asthma medication (ever)					
No	15 (9)			21 (9)	
Yes	147 (91)			212 (91)	
Inhaled corticosteroids (ever)					
No	80 (49)			140 (60)	
Yes	82 (51)			93 (40)	
Season of blood sample					
Winter	79 (49)			37 (16)	
Spring	47 (29)			53 (23)	
Summer	9 (6)			33 (14)	
Autumn	27 (17)			110 (47)	
25 (OH)D (nmol/L)			36 ± 10		74 ± 20
FEV_1 (L)			3.5 ± 0.8		3.6 ± 0.8
FVC (L)			4.4 ± 1.1		4.5 ± 1.0
FEV_1/FVC (%)			80.3 ± 5.5		80.1± 5.3

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 2. Serum 25-Hydroxyvitamin D at Baseline in Relation to Lung Function Decline in Adults with Asthma in the Nord–Trøndelag Health Study, Norway, 1995-2008.

25 (OH)D (nmol/L)	**N**	**FEV_1 (ml)**			**FVC (ml)**			**FEV_1/FVC (%)**		
		Difference in decline[a]	95% CI	Mean decline[a]	Difference in decline[a]	95% CI	Mean decline[a]	Difference in decline[a]	95% CI	Mean decline[a]
Total	395									
≥ 50	233	Ref.		314	Ref.		246	Ref.		3.0
< 50	162	74	-9, 158	388	52	-46, 149	298	0.7	-0.5, 1.9	3.7
Per 25 unit decrease	395	21	-19, 62		29	-20, 76		0.1	-0.6, 0.6	

Abbreviations: 25(OH) D, 25-hydroxyvitamin D; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

[a] Adjusted age, sex, height, body mass index, smoking status (never, current, former, unknown), education (<10years, ≥10 years, unknown), physical activity (<1hr week, ≥1hr week, unknown), socioeconomic status (high, low, unknown), use of asthma medication ever (yes, no), use of inhaled corticosteroids ever (yes, no), season of blood sample (winter, spring, summer, autumn).

Table 3. Serum 25-Hydroxyvitamin D at Baseline in Relation to Lung Function Decline in Adults with Asthma in the Nord–Trøndelag Health Study, Norway (1995-2008), Stratified by Smoking Status.

25 (OH)D (nmol/L)	**N**	**FEV_1 (ml)**			**FVC (ml)**			**FEV_1/FVC (%)**		
		Difference in decline[a]	95% CI	Mean decline[a]	Difference in decline[a]	95% CI	Mean decline[a]	Difference in decline[a]	95% CI	Mean decline[a]
Ever smokers	223									
≥ 50	128	Ref.		379	Ref.		325	Ref.		3.1
< 50	95	10	-95, 114	389	-24	-148, 101	302	0.6	-1.1, 2.2	3.7
Per 25 unit decrease	233	13	-37, 63		8	-52, 67		0.2	-0.6, 1.0	
Never smokers	164									
≥ 50	102	Ref.		222	Ref.		129	Ref.		2.8
< 50	62	223	82, 365	445	218	57, 378	347	1.4	-0.4, 3.2	4.2
Per 25 unit decrease	164	72	1, 144		91	11, 171		0.1	-0.8, 1.1	

Abbreviations: 25(OH) D, 25-hydroxyvitamin D; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

[a]Adjusted age, sex, height, body mass index, education (<10years, ≥10 years or unknown), physical activity (<1hr week, ≥1hr week or unknown), socioeconomic status (high, low or unknown), use of asthma medication ever (yes or no), use of inhaled corticosteroids ever (yes or no), season of blood sample (winter, spring, summer or autumn).

Table 4. Serum 25-Hydroxyvitamin D at Baseline in Relation to Lung Function Decline in Adults with Asthma in the Nord–Trøndelag Health Study, Norway (1995-2008), Stratified by Use of Inhaled Corticosteroids (ICS).

25 (OH)D (nmol/L)	**N**	**FEV_1 (ml)**			**FVC (ml)**			**FEV_1/FVC (%)**		
		Difference in decline[a]	95% CI	Mean decline[a]	Difference in decline[a]	95% CI	Mean decline[a]	Difference in decline[a]	95% CI	Mean decline[a]
ICS	175									
≥ 50	93	Ref.		316	Ref.		302	Ref.		2.1
< 50	82	-18	-136, 101	299	-93	-226, 40	209	1.3	-0.4, 3.1	3.4
Per 25 unit decrease		11	-44, 67		-17	-83, 50		0.4	-0.4, 1.2	
No ICS	220									
≥ 50	140	Ref.		320	Ref.		207	Ref.		3.8
< 50	80	147	24, 269	467	185	40, 329	392	-0.2	-1.9, 1.5	3.6
Per 25 unit decrease	220	28	-35, 90		98	20, 176		-0.4	-1.3, 0.5	

Abbreviations: 25(OH) D, 25-hydroxyvitamin D; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, Inhaled corticosteroids.

[a]Adjusted age, sex, height, body mass index, smoking status (never, current, former or unknown), education (<10years, ≥10 years or unknown), physical activity (<1hr week, ≥1hr week or unknown), socioeconomic status (high, low or unknown), use of asthma medication ever (yes or no), season of blood sample (winter, spring, summer or autumn).