



Serum 25-hydroxyvitamin D, vitamin D supplement and asthma control: The HUNT study

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ABSTRACT

Few studies have investigated the association between serum 25-hydroxyvitamin D (25[OH]D), vitamin D supplement and asthma control among adults. We aimed to examine whether low levels of serum 25(OH)D or not taking vitamin D supplement were associated with an increased risk of poorly controlled asthma among Norwegian adults with asthma.

We used a definition of asthma control adapted from the Global Initiative for Asthma. We first examined cross-sectional associations between serum 25(OH)D ($n = 806$) or vitamin D supplement ($n = 1179$) and poorly controlled asthma. Next, among those with well controlled asthma at baseline, we examined prospective associations between serum 25(OH)D ($n = 147$) or vitamin D supplement ($n = 208$) and poorly controlled asthma at follow-up, approximately 11 years later. We estimated risk ratios (RR) and 95% confidence intervals (CI) with Poisson regression.

The adjusted RR for poorly controlled asthma was 1.00 (95% CI, 0.89–1.13) for adults with serum 25(OH)D < 50 nmol/L in cross-sectional and 1.50 (95% CI, 0.46–4.95) in prospective analyses. The adjusted RR for poorly controlled asthma was 1.17 (95% CI 1.00–1.37) for non-users of vitamin D supplement in cross-sectional and 1.66 (95% CI 0.49–5.67) in prospective analyses.

Our study did not show strong evidence that among adults with asthma, having a low serum 25(OH)D or being a non-user of vitamin D supplement was associated with an increased risk of poorly controlled asthma. Some point estimates indicated an increased risk, however our estimates were generally imprecise and further evidence is needed.

1. Introduction

Asthma affects about 334 million people worldwide and represents approximately 1% of the total global disease burden [1,2]. There are also substantial social and economic burdens from asthma and its care [3]. There is no cure for asthma, nor any effective means yet to prevent asthma. Therefore asthma control is the primary goal of asthma management. Among patients assessed by primary health care physicians in Canada, however, a substantial proportion have uncontrolled asthma (59%) [4]. Even among patients receiving specialist care, almost 50% do not achieve a sufficient level of control [5]. This is unfortunate

because people with well controlled asthma can live relatively burden free compared to those with poorly controlled asthma. While much research has focused on achieving asthma control with medication, fewer studies have focused on identifying potential modifiable risk factors such as low vitamin D level, particularly among the adult population.

Low vitamin D status has become a significant public health concern in northern countries [6]. As most vitamin D in humans is created from precursors in the skin after direct exposure to sunlight, people living in northern countries such as Norway are particularly vulnerable to weak sun exposure in the winter season and reduced skin synthesis of vitamin

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D. In Norway, up to 40% of the general population may be deficient in vitamin D (with deficiency defined as 25-hydroxyvitamin D [25(OH)D] < 50 nmol/L) [7]. Furthermore, a recent systematic review and meta-analysis suggested that vitamin D could prevent asthma attacks or improve control of asthma symptoms [8], additionally vitamin D may be a marker of asthma severity [9]. These findings suggest a possible role of vitamin D in asthma control.

With only a few studies conducted in children [10–13], and three in adults [14–16], it is difficult to draw a conclusion on the association between vitamin D and asthma control. Additionally, the previous studies in adults have been limited in size and duration. Therefore our aim was to examine whether low levels of serum 25(OH)D or not taking vitamin D supplement were associated with an increased risk of poorly controlled asthma in adults with asthma.

2. Methods

We followed individuals with asthma that participated in The Nord-Trøndelag Health Study (HUNT), a population-based cohort study. The study was carried out at three time points over approximately 20 years (HUNT1 [1984–1986], HUNT2 [1995–1997] and HUNT3 [2006–2008]). A detailed description of the HUNT study can be found elsewhere [17]. Only HUNT2 and HUNT3 include questions about asthma.

We defined two different analysis samples as serum 25(OH)D was only measured in a sample of participants, as defined in prior reports [18,19]. The question on use of vitamin D supplement was asked to women between the age of 20 and 70 years (Fig. 1). Additionally,

participants without ever asthma, missing information on asthma control, or 55 years or older at HUNT2 were excluded from both analyses. The age restriction was included to reduce the possibility of COPD being misclassified as asthma. Taken together, we included 806 adults who reported ever asthma in the cross-sectional analyses of serum 25(OH)D and 1179 women who reported ever asthma in the cross-sectional analyses of vitamin D supplement. Additionally, asthma patients with serum 25(OH)D measurements were those who reported ever asthma in both HUNT2 and HUNT3, and also reported wheezing during the last 12 months in HUNT2, as per the requirements of the previous studies [18,19].

We next examined the prospective association of serum 25(OH)D and use of vitamin D supplement among those with well controlled asthma in HUNT2 that had follow-up information on asthma control, approximately 11 years later in HUNT3. These analyses included 147 and 208 participants with asthma, respectively.

2.1. Serum 25(OH)D

Blood samples were taken at HUNT2 and sampling followed a strict quality protocol [17]. Serum was separated and immediately cooled and stored the same day or within two to three days (due to weekends and public holidays) 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 range of 10–375 nmol/L. The intra-assay coefficient of variation and the inter-assay coefficient of variation of our samples were low, 4% and 8%, respectively. We categorized serum 25(OH)D as < 50, 50–74.9 and ≥ 75 nmol/L, and as per 25 nmol/L decrease based on previous literature [20–23].

2.2. Vitamin D supplement use

In HUNT2, women between the age of 20–70 years of age were asked “Do you usually use some of the following dietary supplements: Vitamin D”. We defined women answering yes to this question as users of vitamin D supplement. The question on Vitamin D supplementation was designed to indicate which individuals used vitamin D tablets (vitamin D only), but some of those who used cod liver oil (a common dietary supplement used across Norway) may have answered “yes” to this question.

2.3. Covariates

Information on covariates was collected during the health examination and from the questionnaires. This included age, body mass index (BMI), sex (male, female), smoking status (never, current, former), education (≤ 10 , 11–13, ≥ 14 years, unknown), economic difficulties (yes, no, unknown), use of inhaled corticosteroids during the last 6 months (yes, no, unknown), season of blood sample (Winter [December–February], Spring [March–May], Summer [June–August], Autumn [September–November]) and current allergic rhinitis (yes, no, unknown). Economic difficulty included participants that had difficulty meeting the cost of food, transport, and/or housing. For all covariates the unknown category includes missing.

2.4. Asthma control

In HUNT2 and HUNT3, participants that reported asthma or other respiratory symptoms were requested to partake in the HUNT Lung study. This survey included questions on asthma symptoms which we used to define asthma control. Our definition was adapted from the Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention [3]. Please see the supplementary material for a more detailed explanation (Supplementary Table 1). In

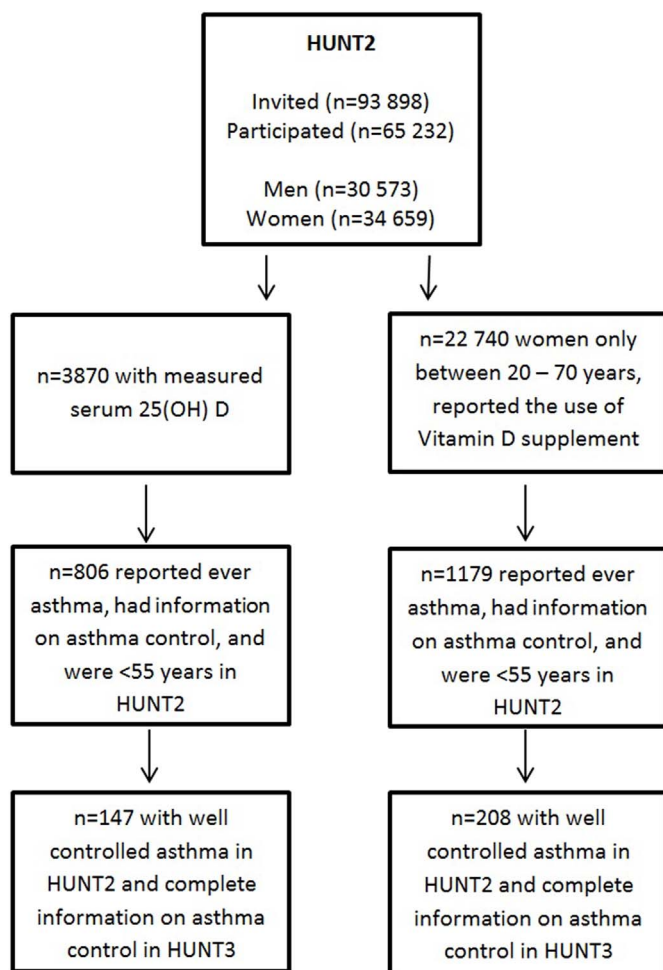


Fig. 1. Flow chart of the analysis samples, The Nord-Trøndelag Health Study, Norway.

HUNT2 and HUNT3, responses to four questions corresponding to four symptoms of asthma control, 1) daytime symptoms, 2) night awakenings, 3) the need for reliever medication, and 4) activity limitations, were used to define well controlled (No symptoms) and poorly controlled (1–4 symptoms).

2.5. Statistical analysis

We investigated the cross-sectional and prospective associations between serum 25(OH)D or use of vitamin D supplement and level of asthma control. In both analyses, the group with the highest level of serum 25(OH)D (≥ 75 nmol/L) or users of vitamin D was the reference category. To test for linear trend we treated the serum 25(OH)D categories as an ordinal variable. Additionally, we analysed serum 25(OH)D per 25 nmol/L decrease as a continuous variable. We estimated risk ratios (RR) and 95% confidence intervals (CI) using a modified Poisson regression with a robust error variances procedure due to the tendency of logistic regression to overestimate risk when the outcome is common [24].

To control for potential confounding factors we adjusted for age, BMI, sex, smoking status, education, economic difficulties, use of inhaled corticosteroids during the last 6 months, season of blood sample and current allergic rhinitis in multivariate models. We included these potential confounders based on prior knowledge and previous studies of the association between the potential confounders and serum 25(OH)D, vitamin D supplement and asthma control. In the analyses of vitamin D supplement we did not adjust for sex because only women were included.

Statistical analyses were performed using R Version 3.2.2 for Windows [25].

3. Ethics

The project was approved by the Regional Committee for Ethics in Medical Research. All participants signed informed consent for participation and the use of data in research.

4. Results

Table 1 presents the characteristics of the two analytic cohorts. The mean age was slightly higher and proportion of those with economic difficulty was lower in the serum 25(OH)D sample than the vitamin D supplement sample. However, both samples had a similar mean BMI and the proportions of those who were non-smokers, completed ≥ 14 years of education, used inhaled corticosteroids during the last 6 months and had current allergic rhinitis, were also similar.

The baseline characteristics of the samples according to serum 25(OH)D levels or use of vitamin D supplement can be found in the online supplement (Online supplement, Table 2).

Table 2 presents the RRs for poorly controlled asthma among three groups of serum 25(OH)D using those with serum 25(OH)D ≥ 75 nmol/L as the reference group. In the crude models, those with the lowest levels of serum 25(OH)D had a RR for poorly controlled asthma of 1.03 (95% CI, 0.93–1.16). This association was similar after adjustment for potential confounding factors (adjusted RR 1.00, 95% CI 0.89–1.13).

Table 3 presents the RR for poorly controlled asthma in HUNT3 amongst those with well controlled asthma at HUNT2. The group with serum 25(OH)D between 50 and 74.9 nmol/L at HUNT2 tended to have the highest RR for poorly controlled asthma in HUNT3 (crude RR 2.01, 95% CI 0.71–5.66). The association was attenuated after adjustment for potential confounders (adjusted RR 1.51, 95% CI 0.52–4.41). The RR for the group with the lowest serum 25(OH)D levels was also elevated (adjusted RR 1.50, 95% CI 0.46–4.95).

Table 4 shows the RR for poorly controlled asthma in HUNT2 for non-users of vitamin D supplement compared to users. The crude RR for poorly controlled asthma was 1.18 (95% CI 0.99–1.39). The RR

Table 1

Baseline characteristics of the study participants in the serum 25(OH)D sample and the vitamin D supplement sample (only women), The Nord-Trøndelag Health Study, Norway.

Baseline characteristic	Serum 25(OH)D sample (n = 806)		Vitamin D supplement sample (n = 1179)	
	mean	SD	mean	SD
Age	39.1	9.2	37.9	10.1
BMI	26.9	4.8	26.6	5.2
	n	%	n	%
Sex				
Women	463	57.4	1179	100.0
Men	343	42.6	–	–
Smoking status				
Never	310	38.5	454	38.5
Former	249	30.9	296	25.1
Current	247	30.6	429	36.4
Education				
≤ 10 years	161	20.0	246	20.9
11–13 years	445	55.2	618	52.4
≥ 14 years	188	23.3	298	25.3
Unknown	12	1.5	17	1.4
Economic difficulties				
No	390	48.4	642	54.5
Yes	313	38.8	527	44.7
Unknown	103	12.8	10	0.8
ICS last 6 months				
No	534	66.3	892	75.7
Yes	268	33.3	281	23.8
Unknown	4	0.5	6	0.5
Season of blood sample				
Autumn	298	37.0	394	33.4
Spring	185	23.0	292	24.8
Summer	100	12.4	153	13.0
Winter	223	27.7	340	28.8
Current allergic rhinitis				
No	214	26.6	413	35.0
Yes	463	57.4	699	59.3
Unknown	129	16.0	67	5.7

Abbreviations: 25(OH)D: serum 25-hydroxyvitamin D, BMI: body mass index, ICS: inhaled corticosteroids, SD: standard deviation.

Table 2

The cross-sectional association between serum 25(OH)D and poorly controlled asthma in HUNT2, The Nord-Trøndelag Health Study, Norway (n = 806).

Serum 25(OH)D	Crude				Adjusted ^a	
	n	cases	RR	95% CI	RR	95% CI
≥ 75	164	119	Ref.		Ref.	
50–74.9	289	199	0.95	0.84–1.07	0.95	0.84–1.07
< 50	353	265	1.03	0.93–1.16	1.00	0.89–1.13
P for trend			0.34		0.84	
Per 25 nmol/L decrease	806	583	1.02	0.98–1.07	1.01	0.96–1.06

Abbreviations: 25(OH)D: serum 25-hydroxyvitamin D, CI: confidence interval, RR: risk ratio, Ref.: reference.

^a Adjusted for age, body mass index, sex, smoking status, education, economic difficulties, ICS use last 6 months, season of blood sample and current allergic rhinitis.

remained the same after adjustment for potential confounders (adjusted RR 1.17, 95% CI 1.00–1.37).

Table 5 shows the RRs for poorly controlled asthma in HUNT3 for non-users of vitamin D supplement compared to users, among those with well controlled asthma in HUNT2. The crude RR for poorly controlled asthma was 1.45 (95% CI 0.46–4.54). The association increased after adjustment (adjusted RR 1.66, 95% CI 0.49–5.67).

Table 3

The prospective association between serum 25(OH)D and poorly controlled asthma in HUNT3, among those with well controlled asthma in HUNT2, The Nord-Trøndelag Health Study, Norway (n = 147).

Serum 25(OH)D			Crude		Adjusted ^a	
	n	cases	RR	95% CI	RR	95% CI
≥ 75 nmol/L	34	4	Ref.		Ref.	
50–74.9 nmol/L	55	13	2.01	0.71–5.66	1.51	0.52–4.41
< 50 nmol/L	58	11	1.61	0.56–4.67	1.50	0.46–4.95
P for trend			0.48		0.56	
Per 25 nmol/L decrease	147	28	1.01	0.69–1.48	1.02	0.63–1.66

Abbreviations: 25(OH)D: serum 25-hydroxyvitamin D, CI: confidence interval, RR: risk ratio, Ref.: reference.

^a Adjusted for age, body mass index, sex, smoking status, education, economic difficulties, ICS use last 6 months, season of blood sample and current allergic rhinitis.

Table 4

The cross-sectional association between vitamin D supplement and poorly controlled asthma in HUNT2, The Nord-Trøndelag Health Study, Norway (n = 1179, women only).

Vitamin D supplement use			Crude		Adjusted ^a	
	n	cases	RR	95% CI	RR	95% CI
Yes	176	83	Ref.		Ref.	
No	1003	557	1.18	0.99–1.39	1.17	1.00–1.37

Abbreviations: CI: confidence interval, RR: risk ratio, Ref.: reference.

^a Adjusted for age, body mass index, smoking status, education, economic difficulties, ICS use last 6 months, season of blood sample and current allergic rhinitis.

Table 5

The prospective association between vitamin D supplement and poorly controlled asthma in HUNT3, among those with well controlled asthma in HUNT2, The Nord-Trøndelag Health Study, Norway (n = 208, women only).

Vitamin D supplement use			Crude		Adjusted ^a	
	n	cases	RR	95% CI	RR	95% CI
Yes	33	3	Ref.		Ref.	
No	175	23	1.45	0.46–4.54	1.66	0.49–5.67

Abbreviations: CI: confidence interval, RR: odds ratio, Ref.: reference.

^a Adjusted for age, body mass index, smoking status, education, economic difficulties, ICS use last 6 months, season of blood sample and current allergic rhinitis.

5. Discussion

5.1. Main findings

In this Norwegian population-based study of adults with asthma, we did not observe strong evidence that low serum 25(OH)D or non-users of vitamin D supplement were associated with higher risk of poorly controlled asthma. Despite some point estimates being elevated, our estimates were too imprecise to conclude with any level of confidence that serum 25(OH)D or non-users of vitamin D supplement was associated with higher risk of poorly controlled asthma.

5.2. Previous studies

Very few epidemiological studies on serum 25(OH)D and asthma control have been conducted, with most studies in children [10–13,26], and one in adults [14]. In the study of adults, Korn et al. cross-sectionally examined 280 adults with asthma. Inconsistent with our findings, the study found that serum 25 (OH)D concentrations were higher among those with better asthma control: controlled 29.5 ± 12.5 ng/ml, partly controlled 25.9 ± 10.8 ng/ml, and uncontrolled 24.2 ± 11.8 ng/ml [14]. However this study could not assign

temporality; was conducted in a large referral center and may not be representative of patients with asthma from the general population; and did not adjust for potentially confounding factors such as smoking. Among the studies in children, all found that increased serum 25 (OH)D concentrations were associated with better asthma control (defined by GINA or the Asthma Control Test) [10–13,26].

Regarding vitamin D supplement, several randomized control trials have been conducted [8,15,16,27,28], including two in adults [15,16]. In the study by Castro et al., 408 adults with asthma and low vitamin D levels were randomized to oral vitamin D₃ or placebo [16]. Consistent with our finding, treatment with vitamin D₃ did not improve asthma control. However in a most recent systematic review and meta-analysis of randomized trials of both children and adults, people given vitamin D supplement experienced fewer asthma exacerbations requiring systemic corticosteroids (incidence rate ratio 0.64, 95% CI 0.46–0.90) and hospitalizations due to acute attacks (odds ratio 0.39, 95% CI 0.19–0.78) [8]. Specifically for asthma control however, the study found no effect of vitamin D on asthma control test scores (mean difference -0.08 , 95% CI -0.70 – 0.54).

5.3. Mechanisms

While no mechanism has been established, several studies strongly suggest that vitamin D could play a role in the pathophysiology of asthma. Vitamin D receptors can be found on a number of tissues and immune cells in the airways, and it has been shown that respiratory epithelial cells express 1 α -hydroxylase and are able to locally activate vitamin D [29]. Vitamin D can influence immune cells which may regulate inflammation and immunomodulation. It has been described that human CD4⁺ T-regulatory cells excrete higher levels of IL-10 in the presence of vitamin D and this may enhance glucocorticoid responses [30]. The anti-viral properties of vitamin D may also play a role in reducing asthma morbidity. Vitamin D increases antimicrobial peptide production and decreases NF- κ B response to respiratory syncytial virus [31]. This might reduce inflammation and the severity of respiratory viral infections and consequently improve asthma control.

5.4. Strengths and limitations

Our study adds to previous research by investigating both serum 25(OH)D and vitamin D supplement in a large sample of adults with asthma. It examined both cross-sectional and prospective associations, adjusted for a comprehensive number of possible confounding factors, and studied a representative sample of the general population with asthma.

Our study had several limitations. The diagnosis of asthma was self-reported from a questionnaire. However, previous studies suggest that the validity and reliability of self-reported asthma are acceptable [32–35]. Besides this, asthma patients with serum 25(OH)D measurements were those who reported ever asthma in both HUNT2 and HUNT3, and also reported wheezing during the last 12 months in HUNT2 [18,19]. These selection criteria would have reduced potential misclassification in our study.

Our definition of asthma control was adapted from the GINA guidelines, but we did not have the exact same questions as defined in the guidelines.

Vitamin D supplement was defined from a questionnaire on vitamin D supplement use, and we did not have information on dosage or frequency of use. This has limited our investigation and therefore interpretation of these results. Secondly, our investigation on vitamin D supplement use only included women and these findings may not reflect the association in men. Thirdly, those with poor health may be more likely to take vitamin D supplements and this would weaken any association. Finally, the question on vitamin D supplement aimed to find out which individuals used vitamin D tablets (vitamin D only), but some of those who used cod liver oil (which contained high levels of

vitamin A at the time of HUNT2, as well as normal dosage of vitamin D) may have answered “yes” to this question. The high level of vitamin A could have reduced the effect of vitamin D by binding to the same receptors [36].

Observational studies inherently limit causal inference. While we had information on a comprehensive number of potential confounding factors, not all participants had complete information on all covariates and this may have biased our results. Additionally, the category of economic difficulty is subjectively indicated, and information on objective measures such as income would help reduce confounding. There is also a possibility of residual confounding by unknown factors. However, any unknown confounder would largely bias our results only if it was strongly associated with both serum 25(OH)D or vitamin D supplement and asthma control and unrelated to the covariates included in our models. Reverse causality may also bias the cross-sectional analyses.

Finally, despite using all available data from this cohort, the sample size and power of our study was limited, and this was evident by the lack of precision of our estimates, and therefore a chance finding was likely. This was particularly evident for both of the prospective analyses where a very limited number of adults with well controlled asthma were included.

6. Conclusions

Our study did not show strong evidence that among adults with asthma, having a low serum 25(OH)D or being a non-user of vitamin D supplement was associated with an increased risk of poorly controlled asthma. Some point estimates indicated an increased risk, however our estimates were imprecise and further evidence from larger studies is needed.

Contribution

BMB and XM conceived and designed the study. AL and BMB acquired the samples and analysed the data. All authors interpreted the data. All authors wrote and revised the manuscript. BMB is accountable for the accuracy and integrity of all parts of the work.

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Conflicts of interest

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2018.01.017>.

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Supplementary tables

Serum 25-hydroxyvitamin D, Vitamin D Supplement and Asthma Control: The HUNT Study

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Supplementary Table 1. The GINA assessment of asthma control and corresponding questions in HUNT2 and HUNT3

GINA asthma control symptoms	HUNT2	HUNT3
1) Daytime symptoms		
In the past 4 weeks, has the patient had: Daytime asthma symptoms more than twice/week?	Have you at any time in the last 12 months been short of breath when resting during the day?(Yes/No)	Think about the past 7 days: How many days have you had symptoms of your lung disease?
Controlled = ≤ 2 times/week	Controlled = No	Controlled = ≤ 2 times/week
2) Night awakenings		
In the past 4 weeks, has the patient had: Any night waking due to asthma?	Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?(Yes/No)	Think about the past 7 days: How many of the last 7 nights have you been affected/woken by your breathing problems (including coughing)?
Controlled = 0 times/4 weeks	Controlled = No	0 times/week
3) Reliever medication need		
In the past 4 weeks, has the patient had: Reliever needed for symptoms* more than twice/week?	If you currently use asthma medicines, have you used beta2 agonists in the last month?(Never, once or less often a week, many times a week, daily)	How many days in the past week have you taken any symptom relieving medicine?
Controlled = ≤ 2 times/week*	Controlled = $\leq$ once or less often a week	Controlled = ≤ 2 times/week
4) Activity limitations		
In the past 4 weeks, has the patient had: Any activity limitation due to asthma?	How much do your respiratory problems (dyspnea) affect your daily activities? (Not at all, a little, much, very much)	Think about the past 7 days: How many of the last 7 days have breathing problems interfered with your normal activities (sports, school, work, housework, etc.)?
Controlled = 0 times/4 weeks	Controlled = $\leq$ a little	Controlled = 0 times/week

* Excluded reliever medication taken before exercise

Supplementary Table 2. Baseline characteristics of the samples according to serum 25(OH)D levels or use of vitamin D supplement.

Baseline characteristic		Serum 25(OH)D sample (n=806)						Vitamin D supplement sample (n=1179)			
Serum 25(OH)D		≥75 nmol/L (n=164)		50-74.9 nmol/L (n=298)		<50 nmol/L (n=353)		Users (n=176)		Non-users (n=1003)	
		mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Age		38.1	9.7	40.0	8.8	38.9	9.4	40.5	10.1	37.4	10.0
BMI		25.2	3.8	26.7	4.4	27.9	5.2	26.1	4.6	26.7	5.3
		n	%	n	%	n	%	n	%	n	%
Sex	Women	99	60.4	160	55.4	204	57.8	176	100.0	1003	100.0
	Men	65	39.6	129	44.6	149	42.2	-	-	-	-
Smoking status	Never	78	47.6	110	38.1	122	34.6	72	40.9	382	38.1
	Former	58	35.4	93	32.2	98	27.8	46	26.1	250	24.9
	Current	28	17.1	86	29.8	133	37.7	58	33.0	371	37.0
Education	≤ 10 years	27	16.5	53	18.3	81	23.0	28	15.9	218	21.7
	11-13 years	86	52.4	162	56.1	197	55.8	86	48.9	532	53.0
	≥14 years	50	30.5	71	24.6	67	19.0	58	33.0	240	23.9
	Unknown	1	0.6	3	1.0	8	2.3	4	2.3	13	1.3
Economic difficulties	No	95	57.9	137	47.4	158	44.8	103	58.5	539	53.7
	Yes	48	29.3	114	39.5	151	42.8	70	39.8	457	45.6
	Unknown	21	12.8	38	13.2	44	12.5	3	1.7	7	0.7
ICS last 6 months	No	109	66.5	206	71.3	219	62.0	134	76.1	758	75.6
	Yes	55	33.5	80	27.7	133	37.7	40	22.7	241	24.0
	Unknown	0	0.0	3	1.0	1	0.3	2	1.1	4	0.4
Season of blood sample	Autumn	67	40.9	140	48.4	91	25.8	51	29.0	343	34.2
	Spring	41	25.0	60	20.8	84	23.8	46	26.1	246	24.5
	Summer	37	22.6	39	13.5	24	6.8	25	14.2	128	12.8
	Winter	19	11.6	50	17.3	154	43.6	54	30.7	286	28.5
Current allergic rhinitis	No	47	28.7	69	23.9	98	27.7	54	30.7	359	35.8
	Yes	93	56.7	176	60.9	194	55.0	110	62.5	589	58.7
	Unknown	24	14.6	44	15.2	61	17.3	12	6.8	55	5.5

Abbreviations: BMI: body mass index, ICS: inhaled corticosteroids, SD: standard deviation