Serum 25-hydroxyvitamin D levels and lung function in adults with asthma: the HUNT Study

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ABSTRACT The association between vitamin D status and lung function in adults with asthma remains unclear.

We studied this cross-sectional association and possible modification by sex and allergic rhinitis in 760 adults (aged 19–55 years) with self-reported asthma in the Nord-Trøndelag Health Study. Serum 25-hydroxyvitamin D (25(OH)D) level <50 nmol·L^{-1} was considered deficient. Lung function measurements included forced expiratory volume in 1 s (FEV_1) % predicted, forced vital capacity (FVC) % predicted and FEV_1/FVC ratio. Multiple linear regression models were used to estimate adjusted regression coefficients (β) and 95% confidence intervals.

44% of asthma adults had serum 25(OH)D levels <50 nmol·L^{-1}. Its associations with lung function measures seemed to be modified by sex and allergic rhinitis ($p<0.03$ for three-way interaction term). Overall, a serum 25(OH)D level <50 nmol·L^{-1} was not associated with lung function measurements in subjects with allergic rhinitis in this asthma cohort. In men with asthma but without allergic rhinitis, however, a serum 25(OH)D level <50 nmol·L^{-1} was significantly associated with lower FEV_1/FVC ratio (β=−8.60%; 95% CI: −16.95%– −0.25%).

Low serum 25(OH)D level was not associated with airway obstruction in most asthma adults with the exception of men with asthma but without allergic rhinitis.

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Introduction

Successful treatment and prevention of rickets during the first half of the 20th century led to universal acceptance that optimal vitamin D status is required for good bone health in children and adults [1]. Recently, the relationships between vitamin D status and various non-skeletal health outcomes including respiratory disorders [2], cardiovascular disease [3], cancer [4], and all-cause mortality [5], have been addressed. Vitamin D deficiency (defined as 25-hydroxyvitamin D (25(OH)D) <50 nmol·L^{-1}) is prevalent worldwide [6, 7]. The global burden of obstructive airway diseases, such as asthma, is high [8].

In our previous study, we observed an association between vitamin D deficiency and incident asthma in adults, particularly in men without allergy status [9]. In addition, several studies have shown an association between vitamin D deficiency and lower lung function in general adult populations [10–14], among which, two studies suggested a potentially stronger association in men compared to women [11, 14]. Most of these previous studies found a significant association between serum 25(OH)D at the <50 nmol·L^{-1} level and lower forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), but not the FEV_1/FVC ratio in the general population. To date, there are few published studies on vitamin D status and lung function in adults with asthma. A recent cross-sectional study of Chinese adults with asthma showed significantly lower FEV_1 % predicted and a significantly lower FEV_1/FVC ratio in participants who were vitamin D deficient (<50 nmol·L^{-1}) [15].

In addition to our previous finding of an association between low serum 25(OH)D and incident asthma in men without allergy, a cross-sectional study using data from the National Health and Nutrition Examination Survey (NHANES 2005–2006) reported an association between lower serum 25(OH)D levels and greater odds of asthma diagnosis in non-atopic individuals [16]. These previous findings suggest that vitamin D status may influence asthma *via* a non-allergic rather than allergic pathway. However, the biological pathway by which vitamin D may influence lung function parameters in asthma patients remains unclear.

In this current cross-sectional study we aimed to assess the association between serum 25(OH)D and lung function in adults with asthma. We also aimed to examine possible interactions by sex and allergy status. We hypothesised that low serum 25(OH)D levels would be associated with lower lung function, and that this association would most likely be present in men with asthma but without allergy status.

Materials and methods

Study design

This is a cross-sectional study using the second survey of the Nord-Trøndelag Health Study (HUNT2). HUNT is a large population health survey of Norwegian inhabitants at latitude 64° North [17]. Three adult surveys have been conducted to date: HUNT1 to HUNT3 (1984–1986 to 2006–2008). The study population consisted of Norwegian adults aged 19 years or older, with socio-demographic characteristics considered generally representative of Norway [18].

The target population for HUNT2 (1995–1997) consisted of approximately 93 000 Norwegian adults living in Nord-Trøndelag County. The participation rate was 70% (n=65 237) [17] from which we established an asthma cohort of adults aged 19–55 years who provided an affirmative response to both of the following two questions: "Have you had attacks of wheezing or breathlessness during the last 12 months?" and "Do you have or have you had asthma?". The asthma cohort also confirmed their asthma status in HUNT3 with an affirmative response to the question: "Do you or have you had asthma?" (n=898). The current study was based on 760 asthma cases with complete data on both exposure (serum 25(OH)D) and outcome (lung function); 40 subjects were excluded due to missing data on 25(OH)D and 98 subjects were excluded due to missing data on lung function.

Serum 25(OH)D measurements

Blood samples were collected in HUNT2 and stored at −70°C for later use. Serum 25(OH)D levels were measured using LIASON 25-OH Vitamin D TOTAL (DiaSorin, Saluggia, Italy); a fully automated antibody-based chemiluminescence assay with detection range of 10–375 nmol·L^{-1}, intra-assay coefficient of variation (CV) of 4% and inter-assay CV of 8%. Serum 25(OH)D levels are considered the best marker for body vitamin D status [19] and were categorised according to widely used and accepted cut-off points (<50 nmol·L^{-1}, 50–74.9 nmol·L^{-1} or ⩾75 nmol·L^{-1}) [7]. Serum 25(OH)D levels were also analysed as a continuous independent variable.

Lung function measures

Two MasterScope Jaeger v.5.1 spirometers were used to measure lung function by trained professionals at screening stations. Instrument quality control included twice daily calibration. Biological control was conducted once daily *via* staff lung function assessment. Participants were made to sit upright and use a

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nose-clip [20]. Recommendations and criteria from the American Thoracic Society (ATS) were followed and applied [21]. Participants were required to give three–five acceptable and reproducible trials during which expiration continued for ⩾6 s. The best trial was determined by identification of the flow/volume curve using the highest sum of FEV_1 and FVC. The acceptability and reproducibility of results were reviewed by expert technicians. In the HUNT surveys, the highest sum of FEV_1 and FVC and the best FEV_1/FVC ratio were used. Predicted reference values were derived from the prediction equations of spirometry based on the same HUNT population [20], and these predicted values were used to calculate FEV_1 % pred. and FVC % pred.

Other variables

Sex and allergy status were considered potentially important modifiers of the association between serum 25(OH)D and lung function. Allergic rhinitis was used as a proxy for allergy status (yes, no or unknown) based on participant response to the question: "Do you have or have you had allergic rhinitis or hay fever?". Other important variables including body mass index (BMI), socio-economic status (education, receipt of social benefit and economic difficulties), season of blood sample collection, lifestyle factors (physical activity and smoking status) and asthma medication or corticosteroid use, were collected in HUNT2. Body weight and height were measured in HUNT2 by trained professionals whilst participants wore light clothing. BMI was calculated and included in the analysis as a continuous variable. The other covariates were categorised as years of education (<10, ⩾10 or unknown), receipt of social benefits (yes, no or unknown), economic difficulties in the past year (yes, no or unknown), season of blood sample collection (December–May or June–November), number of hours of light physical activity per week (<1, ⩾1 or unknown), smoking status (never, former, current or unknown), ever use of asthma medication (yes, no or unknown) and regular use of inhaled corticosteroids in the last 6 months (yes or no).

Statistical analysis

The statistical analyses were performed separately in women (n=446) and men (n=314), and further stratified by allergic rhinitis based on our prior hypothesis and a significant three-way interaction of categorical serum 25(OH)D with sex and allergic rhinitis on lung function parameters ($p<0.03$). Baseline characteristics were compared between women and men (table 1). Linear-regression analysis was used to estimate the association between serum 25(OH)D level and lung function measures (FEV_1 % pred., FVC % pred. and FEV_1/FVC ratio) (tables 2–4). Analyses were conducted using serum 25(OH)D as a categorical (<50 nmol·L^{-1}, 50–74.9 nmol·L^{-1} or ⩾75 nmol·L^{-1}), or continuous independent variable. Crude and adjusted regression coefficients (β) and 95% confidence intervals (CI) were estimated. Multiple linear regression models included BMI, education, receipt of social benefits, economic difficulties in the last year, season of blood sample collection, physical activity, smoking status, ever use of asthma medication and regular use of inhaled corticosteroids in the last 6 months as important covariates. Missing data on education, social benefits, economic difficulties, physical activity, smoking status and ever asthma medication, were categorised as "unknown" and included in the multiple linear-regression analysis; multiple imputations of missing data on the above covariates and missing on allergic rhinitis were performed. To minimise possible misclassification of reported asthma, we excluded those who reported having chronic obstructive pulmonary disease (COPD), chronic bronchitis or emphysema and repeated the analyses. All statistical analyses were performed using Stata, version 12.1 (StataCorp, College Station, TX, USA).

Ethics

This study received ethics approval from the Regional Committee for Medical Research Ethics. All study participants gave informed written consent.

Results

A comparison between participants in the analysis group (n=760) and those excluded due to missing information on either exposure or outcome (n=138) showed that the analysis group had higher serum 25 (OH)D levels, a higher proportion of never smokers, were less likely to report regular use of inhaled corticosteroids, and had better lung function (online Appendix 1).

Table 1 shows the characteristics of the study sample by sex. Overall, 44% of study participants had serum 25(OH)D level <50 nmol·L^{-1} with no substantial difference between sexes. The mean level of serum 25 (OH)D in all adults with asthma was 57 nmol·L^{-1}. Women with asthma were more likely than men with asthma to receive social benefits, be physically active, use asthma medication and have allergic rhinitis. Women and men were similar in age, BMI, education, season of blood sample collection and smoking

TABLE 1 Baseline characteristics in an adult asthma cohort, the HUNT Study, 1995–1997

	Women n=446	Men n=314	p-value[#]
Age years	37.35±0.44	38.54±0.51	0.08
25(OH)D level nmol·L^{-1}	56.87±1.12	57.28±1.28	0.81
<50.0	195 (43.72)	138 (43.95)	0.95
⩾50.0	251 (56.28)	176 (56.05)	
Body mass index kg·m^{-2}	26.86±0.26	26.80±0.22	0.86
Education years			0.23
<10	84 (18.83)	70 (22.29)	
⩾10	354 (79.37)	242 (77.07)	
Unknown	8 (1.79)	2 (0.64)	
Social benefit recipient			<0.001
Yes	166 (37.22)	62 (19.75)	
No	201 (45.07)	175 (55.73)	
Unknown	79 (17.71)	77 (24.52)	
Economic difficulties			0.94
Yes	179 (40.13)	117 (37.26)	
No	207 (46.41)	137 (43.63)	
Unknown	60 (13.45)	60 (19.11)	
Season			0.73
December–May	223 (50.00)	161 (51.27)	
June–November	223 (50.00)	153 (48.73)	
Physical activity h·week^{-1}			0.003
<1	99 (22.20)	95 (30.25)	
⩾1	310 (69.51)	180 (57.32)	
Unknown	37 (8.30)	39 (12.42)	
Smoking status			0.08
Never	161 (36.10)	123 (39.17)	
Current	154 (34.53)	84 (26.75)	
Former	118 (26.46)	96 (30.57)	
Unknown	13 (2.91)	11 (3.50)	
Asthma medication (ever)			0.002
Yes	424 (95.07)	279 (88.85)	
No	22 (4.93)	34 (10.83)	
Unknown	0	1 (0.32)	
Inhaled corticosteroids (last 6 months)			0.06
Yes	170 (38.12)	99 (31.53)	
No	276 (61.88)	215 (68.47)	
Allergic rhinitis (ever)			0.03
Yes	270 (60.54)	172 (54.78)	
No	85 (19.06)	81 (25.80)	
Unknown	91 (20.40)	61 (19.43)	
FEV_1 % predicted	90.38±0.74	88.06±0.94	0.05
FVC % predicted	95.77±0.59	95.58±0.75	0.84
FEV_1/FVC ratio %	78.40±0.39	75.01±0.53	<0.001

Data are presented as mean±sd or n (%), unless otherwise stated. HUNT: Nord-Trøndelag Health Study; 25(OH)D: 25-hydroxyvitamin D; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: A t-test was performed to analyse the difference between women and men for continuous variables and a Chi-squared test was applied for categorical variables (missing data were excluded).

status. Men with asthma had lower FEV_1 % pred. and FEV_1/FVC ratio compared with women with asthma, whereas FVC% pred. showed no difference between sexes.

The three-way interaction term (categorical 25(OH)D × sex × allergic rhinitis) was significant for the FEV_1/FVC ratio (p=0.023) and FEV_1 (p=0.017) models. After stratification by sex (table 2), the adjusted regression coefficients for women with asthma revealed non-significant associations between serum 25 (OH)D as a categorical or continuous variable and all three lung function measures. However, men with asthma and with serum 25(OH)D level <50 nmol·L^{-1} showed a significantly lower FEV_1/FVC ratio (β=-4.31%, 95% CI: -7.25%– -1.38%) and FEV_1 % pred. (β=−8.44%, 95% CI: -13.78%– -3.11%) compared with the ⩾75 nmol·L^{-1} group (table 2). Men with asthma also showed a lower FEV_1/FVC ratio and FEV_1 % pred. for each 25 nmol·L^{-1} reduction of 25(OH)D, but we found no substantial associations between serum 25(OH)D and FVC % pred. in men with asthma.

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TABLE 2 Crude and adjusted regression coefficients (β) for the associations between serum 25(OH)D and lung function measures in an adult asthma cohort, the HUNT Study, 1995–1997

25(OH)D nmol·L^{-1}	FEV$_1$ % pred		FVC % pred		FEV$_1$/FVC ratio %	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Women[#]						
⩾75.0	0.00	0.00	0.00	0.00	0.00	0.00
50.0–74.9	−1.92 (−5.91–2.06)	−1.25 (−5.27–2.77)	−0.89 (−4.08–2.30)	−0.10 (−3.36–3.16)	−1.35 (−3.46–0.76)	−0.82 (−2.89–1.25)
<50.0	−4.46 (−8.29–0.64)	−2.16 (−6.22–1.90)	−2.44 (−5.50–0.62)	−0.30 (−3.59–2.99)	−1.88 (−3.91–0.14)	−1.41 (−3.49–0.67)
Each 25-nmol·L^{-1} reduction	−1.51 (−3.04–0.02)	−0.69 (−2.32–0.95)	−0.81 (−2.03–0.42)	0.02 (−1.30–1.35)	−0.62 (−1.43–0.19)	−0.53 (−1.37–0.31)
Men[¶]						
⩾75.0	0.00	0.00	0.00	0.00	0.00	0.00
50.0–74.9	−5.66 (−10.66–0.66)	−6.31 (−11.39–1.24)	−3.48 (−7.50–0.54)	−3.48 (−7.61–0.66)	−1.96 (−4.78–0.88)	−2.39 (−5.18–0.39)
<50.0	−7.78 (−12.58–2.98)	−8.44 (−13.78–3.11)	−4.30 (−8.16–0.45)	−4.17 (−8.52–0.17)	−3.34 (−6.06–0.63)	−4.31 (−7.25–1.38)
Each 25-nmol·L^{-1} reduction	−2.76 (−4.77–0.75)	−3.05 (−5.31–0.79)	−1.20 (−2.81–0.42)	−1.21 (−3.05–0.62)	−1.39 (−2.53–0.26)	−1.73 (−2.96–0.49)

Data are presented as β (95% CI). [#]: n=446; [¶]: n=314. 25(OH)D: 25-hydroxyvitamin D; FEV$_1$: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. Multiple linear regression models adjusted for body mass index, education, social benefits, economic difficulties, season, physical activity, smoking status, asthma medication, inhaled corticosteroid. Multiple linear regression models for FEV$_1$/FVC ratio were also adjusted for age and height.

After further stratification by allergic rhinitis, neither categorical nor continuous serum 25(OH)D levels were significantly associated with lung function measures in women with asthma, and with or without allergic rhinitis (table 3). We did not observe a significant association of serum 25(OH)D <50 nmol·L^{-1} with FEV$_1$/FVC ratio among men with asthma and with allergic rhinitis, but a substantial association was observed among men with asthma but without allergic rhinitis (adjusted β=−8.60%, CI: −16.95% to −0.25% for 25(OH)D as a categorical variable) (table 4).

When participants with reported COPD, chronic bronchitis or emphysema were excluded, the association between categorical serum 25(OH)D and lung function measures in women with asthma and with or without allergic rhinitis remained null. The association between categorical serum 25(OH)D and FEV$_1$/FVC ratio was still more obvious in men with asthma but without allergic rhinitis (online Appendix 2).

Multiple imputations of missing data on allergic rhinitis and other adjusted covariates were performed, and similar analytical results were obtained (data not presented).

TABLE 3 Crude and adjusted regression coefficients (β) for the associations between serum 25(OH)D and lung function measures stratified by allergic rhinitis in an adult asthma cohort, the HUNT Study, 1995–1997 (women only)

25(OH)D nmol·L^{-1}	FEV$_1$ % pred		FVC % pred		FEV$_1$/FVC ratio %	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Allergic rhinitis yes[#]						
⩾75.0	0.00	0.00	0.00	0.00	0.00	0.00
50.0–74.9	0.87 (−3.85–5.59)	0.63 (−4.16–5.42)	0.96 (−3.07–5.00)	1.29 (−2.87–5.45)	−0.16 (−2.62–2.31)	−0.32 (−2.73–2.09)
<50.0	−1.26 (−5.90–3.38)	1.01 (−3.80–5.82)	−1.98 (−5.95–1.98)	−0.11 (−4.29–4.06)	0.32 (−2.10–2.75)	0.83 (−1.57–3.24)
Each 25-nmol·L^{-1} reduction	−0.60 (−2.50–1.31)	0.47 (−1.53–2.47)	−0.80 (−2.43–0.84)	0.10 (−1.64–1.83)	0.07 (−0.93–1.06)	0.24 (−0.76–1.24)
Allergic rhinitis no[¶]						
⩾75.0	0.00	0.00	0.00	0.00	0.00	0.00
50.0–74.9	−6.41 (−17.13–4.32)	−5.64 (−17.09–5.80)	−4.36 (−12.07–3.35)	−2.99 (−11.27–5.28)	−3.21 (−9.61–3.19)	−1.95 (−8.25–4.36)
<50.0	−6.19 (−15.73–3.34)	−0.96 (−12.33–10.41)	−1.88 (−8.73–4.97)	1.64 (−6.58–9.86)	−4.29 (−9.98–1.41)	−1.67 (−7.85–4.51)
Each 25-nmol·L^{-1} reduction	−2.02 (−5.62–1.58)	0.17 (−3.96–4.31)	−0.55 (−3.15–2.05)	0.72 (−2.27–3.72)	−1.40 (−3.55–0.75)	−0.12 (−2.36–2.11)

Data are presented as β (95% CI). [#]: n=270; [¶]: n=85. 25(OH)D: 25-hydroxyvitamin D; FEV$_1$: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. Multiple linear regression models adjusted for body mass index, education, social benefits, economic difficulties, season, physical activity, smoking status, asthma medication, inhaled corticosteroid. Multiple linear regression models for FEV$_1$/FVC ratio were also adjusted for age and height.

TABLE 4 Crude and adjusted regression coefficients (β) for the associations between serum 25(OH)D and lung function measures stratified by allergic rhinitis in an adult asthma cohort, the HUNT Study, 1995–1997 (men only)

25(OH)D nmol·L^{-1}	FEV$_1$ % pred		FVC % pred		FEV$_1$/FVC ratio %	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Allergic rhinitis yes[#]						
⩾75.0	0.00	0.00	0.00	0.00	0.00	0.00
50.0–74.9	−5.46 (-11.44–0.52)	−5.38 (-11.69–0.94)	−4.30 (-9.42–0.81)	−4.14 (-9.51–1.22)	−1.21 (-4.72–2.30)	−1.11 (-4.80–2.57)
<50.0	−8.82 (-14.67– −2.97)	−7.67 (-14.84– −0.50)	−6.02 (-11.02– -1.01)	−4.46 (-10.56–1.63)	−2.92 (-6.36–0.52)	−3.23 (-7.44–0.97)
Each 25-nmol·L^{-1} reduction	−3.76 (-6.10– −1.42)	−3.40 (-6.31– −0.48)	−2.36 (-4.37– −0.34)	−1.98 (-4.47–0.50)	−1.37 (-2.75–0.01)	−1.34 (-3.05–0.37)
Allergic rhinitis no[¶]						
⩾75.0	0.00	0.00	0.00	0.00	0.00	0.00
50.0–74.9	−5.58 (-18.62–7.46)	−10.43 (-25.10–4.23)	−1.63 (-11.25–7.99)	−2.00 (-13.45–9.44)	−2.12 (-9.46–5.23)	−6.18 (-14.01–1.67)
<50.0	−11.85 (-24.15–0.46)	−17.56 (−33.20– −1.93)	−6.57 (−15.65–2.50)	−7.91 (-20.11–4.29)	−4.69 (-11.62–2.24)	−8.60 (-16.95– -0.25)
Each 25-nmol·L^{-1} reduction	−3.46 (-8.80–1.89)	−5.28 (-11.86–1.31)	−1.44 (-5.38–2.51)	−1.37 (-6.49–3.75)	−1.79 (-4.77–1.19)	−3.06 (-6.58–0.45)

Data are presented as β (95% CI). [#]: n=172; [¶]: n=81. 25(OH)D: 25-hydroxyvitamin D; FEV$_1$: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. Multiple linear regression models adjusted for body mass index, education, social benefits, economic difficulties, season, physical activity, smoking status, asthma medication and inhaled corticosteroid. Multiple linear regression models for FEV$_1$/FVC ratio were also adjusted for age and height.

Discussion

We found that 44% of adults with asthma had deficient serum 25(OH)D levels (<50 nmol·L^{-1}), which was slightly higher than the prevalence of vitamin D deficiency (40%) in the general HUNT population [22]. We observed no association between serum 25(OH)D and lung function among women with asthma and with or without allergy status. However, we did find a significant association in a subgroup of men. In men with asthma but without allergic rhinitis, low serum 25(OH)D level was associated with a considerably reduced FEV1/FVC ratio.

Studies on vitamin D status and lung function in asthma populations are scarce. A cross-sectional study of Puerto Rican children with asthma (n=287) reported a significant association between vitamin D insufficiency (<75 nmol·L^{-1}) and lower FEV1/FVC ratio [23]. A cross-sectional study of 54 US adults with persistent asthma observed an association between reduced continuous serum 25(OH)D and impaired FEV1 after adjustment for age, sex and BMI [24]. To be noted, this study did not evaluate other lung function measures except for FEV1. A Chinese study of 435 adults with asthma found a significant association between vitamin D deficiency (<50 nmol·L^{-1}) and low values for FEV1/FVC ratio and FEV1 [15]. However, this study did not report sex-specific results.

Regarding a sex difference, a most recent report in children provided consistent results of an association between low plasma 25(OH)D levels and low FEV1 and FEV1/FVC ratio in boys with asthma [25]. A study of 3359 Canadian adults observed an association between vitamin D deficiency (<50 nmol·L^{-1}) and lung function (FEV1 and FVC but not FEV1/FVC ratio) in men [14]. In the Longitudinal Aging Study Amsterdam, a strong association between serum 25(OH)D and peak expiratory flow rate was observed in older men but not in older women [11]. Although both adult studies were performed in a general population, these findings do provide some support to our sex-specific finding in adults with asthma. Our observation in asthmatic men but not women does not seem to be explained by type 2 error in women (false-negative finding) due to a comparable number of women (n=446) and men (n=314) in our analyses. It may be explained by lower lung function in asthmatic men compared with asthmatic women (table 1). Women with asthma in our study were more likely than men with asthma to report use of asthma medication, which may indicate greater compliance with recommended treatment for asthma and thus better lung function. However, a previous Canadian study indicated that sex may modify the association between asthma and lung function, *i.e.* the association of asthma with lower lung function was stronger in men than in women [26]. Even though the explanation seems plausible, a sex-specific association of serum 25(OH)D with lung function in adults with asthma warrants further investigation and confirmation.

Our finding of an association between low serum 25(OH)D level and reduced FEV1/FVC ratio in men with asthma but without allergic rhinitis is consistent with our earlier study in which an association between low serum 25(OH)D and incident asthma was demonstrated only among men with no allergy status [9]. In support of our previous finding, Keet *et al.* [16] found an association between low serum

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25(OH)D levels and ever asthma in non-atopic subjects. According to a recent genome-wide association study composed of Euro-American subjects with asthma, T-helper type 1 non-allergic pathway genes are associated with lung function in asthmatic subjects [27]. Lower serum 25(OH)D levels have also been associated with thicker airway smooth muscle (ASM) mass in children with severe asthma [28]. Serum 25 (OH)D levels modulate the contraction, inflammation and remodelling of ASM function [29] which may be a possible mechanism for airway obstruction in asthma subjects. Taken together, our current data extends our previous findings to generate the hypothesis that low serum 25(OH)D levels associated with airway obstruction may influence asthma *via* a non-allergic pathway, not only on asthma onset but also on asthma severity and control, particularly in men.

Our study is one of a few to investigate the relationship between serum 25(OH)D and lung function in adults with asthma, and the first to explore the potential modification of this association by sex and allergy status. Our study has several strengths, including a large sample of adults with asthma who contributed complete data on both serum 25(OH)D and lung function measures. Serum 25(OH)D, spirometric and anthropometric data were objectively measured by trained health professionals. Blood samples were collected across all four seasons with a large variation in serum 25(OH)D levels. We were able to control for a range of potential confounding factors in an adult asthma cohort of participants who reported current asthma (wheeze plus ever asthma) in HUNT2 and who further confirmed their asthma status in HUNT3. Multiple imputations of missing data and a sensitivity analysis which excluded potential COPD participants were conducted to strengthen our results.

We acknowledge several limitations to this study including the use of single serum 25(OH)D measurements which may have contributed to measurement error. However, results from a recent prospective study in the US suggested high intra-individual reproducibility over time [30]. We excluded 15% of asthma cases due to missing data on exposure and/or outcomes which may lead to selection bias. Nevertheless, persons included in the analysis cohort seemed to have better serum 25(OH)D levels and better lung function which may have resulted in an underestimation of the association (online Appendix 1). Residual confounding may exist due to lack of more complete and/or precise information on doses of, and adherence to asthma medication or regular use of inhaled corticosteroids. Due to the cross-sectional design of this study, it was not possible to infer causality.

In conclusion, we found no association between serum 25(OH)D and lung function in most adults with asthma, with the exception of men with asthma but without allergic rhinitis. The observed interactions by sex and allergy status warrant further investigation and replication. Previous longitudinal work has looked at serum 25(OH)D and lung function decline in continuous smoking COPD patients [31], a prospective study on serum 25(OH)D and lung function changes in an asthma cohort or a general adult population, would be of high interest.

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