Serum 25-hydroxyvitamin D levels and incident asthma in adults – The HUNT Study

Xiao-Mei Mai

Arnulf Langhammer

Carlos A. Camargo Jr

Yue Chen

Author of correspondence:

Xiao-Mei Mai, PhD, Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, 7491 Trondheim, Norway; Tel: +47 735 98879; E-mail: xiao-mei.mai@ntnu.no

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Abbreviations used:

AOR: Adjusted odds ratio; **CI:** Confidence interval; **COPD:** chronic obstructive pulmonary disease; **HUNT:** Nord-Trøndelag Health Study; **25(OH)D:** 25-hydroxyvitamin D; **OR:** Odds ratio

Abstract

The impact of low vitamin D status on asthma development is unclear. We investigated the relation between baseline serum 25-hydroxyvitamin D [25(OH)D] level and incident asthma in adults, including possible effect-modification by allergy status, using allergic rhinitis as a proxy measure. A cohort of 25,616 adults aged 19-55 years participated in 2 surveys of Nord-Trøndelag Health Study (HUNT 2, 1995-97 and HUNT 3, 2006-08) in Norway. Of this, a nested case-control study included 584 new-onset asthma cases and 1,958 non-asthma controls whose baseline serum 25(OH)D levels were measured. After adjustment for potential asthma risk factors, baseline serum 25(OH)D <50 nmol/L was not significantly associated with asthma in either women (adjusted odds ratio [AOR] = 0.94; 95% confidence interval [CI]: 0.67, 1.32) or men (AOR = 1.47, 95% CI: 0.93, 2.32). In men, allergic rhinitis modified the association with the AOR being 0.87 (95% CI: 0.36, 2.06) among men with allergic rhinitis and 2.32 (95% CI: 1.06, 5.10) among men without allergic rhinitis. Serum 25(OH)D level was not associated with incident asthma in women, regardless of allergy status. Low vitamin D status was not significantly associated with incident asthma in most adults, but may have increased risk among men without allergy.

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Keywords: allergic rhinitis, allergy, incident asthma, prospective study, nested case-control study, serum 25(OH)D, vitamin D

The relationship between vitamin D status and asthma development is highly controversial; Wjst claims that asthma is caused by vitamin D supplementation (1), while Litonjua and Weiss assert that asthma is caused by vitamin D deficiency (2). Previous studies of vitamin D intake have yielded conflicting results (3-8), possibly due to the studies' reliance on questionnaire data on vitamin D in diet and supplements without incorporating skin synthesis of vitamin D after sun exposure. Measurement of serum 25-hydroxyvitamin D [25(OH)D] integrates all sources of vitamin D and is the best available approach to determine the body vitamin D status (9).

Although high serum 25(OH)D levels were recently found to be associated with a reduced risk of asthma-related symptoms, such as wheeze (10), this may be explained by reduced respiratory infections alone (10-13). The impact of 25(OH)D on the development of actual asthma is unclear. To date, there are few prospective studies on serum 25(OH)D levels and incident asthma and they have yielded mixed findings, and focused primarily on children (10, 14-16). A recent cross-sectional study observed a significant association between lower serum 25(OH)D level and a higher risk of ever asthma diagnosis among non-atopic but not atopic individuals (17). In the present study, we evaluated the association between baseline serum 25(OH)D levels and incident asthma among adults in the Nord-Trøndelag Health Study (HUNT) in Norway. We also explored possible effect-modification by allergy status.

MATERIALS AND METHODS

Study design

HUNT is the largest and most comprehensive population health survey in Norway (18). The adult part of the HUNT invited all inhabitants aged 19 years or older in the county of Nord-Trøndelag in the 3 separate surveys: HUNT 1 (1984-86), HUNT 2 (1995-97) and HUNT 3 (2006-08). In the current study, we used data from HUNT 2 and HUNT 3. Briefly, HUNT 2 invited about 93,000 adults in 1995-97, and 65,215 subjects participated (response rate: 70%). Among them, 57% (n = 37,059) took part in HUNT 3 in 2006-08. We established a cohort population that included all subjects who participated in both HUNT 2 and HUNT 3 and were less than 65 years of age in HUNT 3 (n = 25,616) (**Figure 1**). The age limit was set to decrease the possibility of misclassification of asthma and chronic obstructive pulmonary disease (COPD).

The cohort population answered the same questions regarding wheeze and asthma in HUNT 2 and HUNT 3, i.e. “Have you had attacks of wheezing or breathlessness during the last 12 months” and “Do you have or have you had asthma?” Subjects who reported no wheeze or asthma in HUNT 2 but reported asthma in HUNT 3 were regarded as incident asthma cases.

To study the association between baseline serum 25(OH)D level and incident asthma, a nested case-control study was carried out including all incident asthma cases (n = 600) during an average 11-year follow up and a number of non-asthma controls (n = 2,013). The non-asthma control group was taken from a 10% random sample of the cohort population (n = 2,584) after excluding those who had wheeze or asthma in either HUNT 2 or HUNT 3 (Figure 1). This 10% random sample was originally chosen for other research purposes in the HUNT study. The size of the random sample was decided upon economic and logistic reasons. We

estimated before conducting the study that a sample size of 600 cases and 2,000 controls would allow us to detect an approximate 20% increase in asthma risk associated with low serum 25(OH)D concentration at the $\alpha = 0.05$ and $1-\beta = 0.85$ levels, with no consideration of potential effect modification. Among the sampled cases and controls, there were 584 incident asthma cases and 1,958 non-asthma controls whose blood specimens collected in HUNT 2 were available and sufficient for the measurement of 25(OH)D levels (Figure 1). Season for blood sampling varied among the subjects.

Serum 25(OH)D levels

Baseline serum 25(OH)D levels were measured by using LIAISON® 25-OH Vitamin D TOTAL (DiaSorin, Saluggia, Italy), a fully automated antibody-based chemiluminescence assay. The detection range of the assay is 10 to 375 nmol/L. The assay has an intra-assay coefficient of variation of 4% and an inter-assay coefficient of variation of 8%.

Other variables

Allergy status was considered as a potential important effect modifier. Allergic rhinitis was used as a proxy measure for allergy status. Allergic rhinitis (yes/no/missing) was classified according to responses to a question in the HUNT 3 questionnaire, “Do you or have you had allergic rhinitis or hay fever?” Other important variables – such as age, smoking habits, family history of asthma, education, physical activity, socioeconomic status and season for blood sampling – were collected in HUNT 2. These baseline covariates were categorized as: age (19-29, 30-39, 40-49, and 50-55 years), daily smoker (yes/no), family history of asthma (yes/no), years of education (<10, 10-12, and ≥13 years), average hours of light physical activity per week (<1, 1-2, and ≥3 hours), social benefit recipient (yes/no), economic difficulties (yes/no), and season for blood sampling (December to May vs. June to

November). Family history of asthma was denoted as current or ever asthma in any of the family members (mother, father, brother and/or sister). Social benefit recipients were those who reported receiving any of the public welfare benefits, such as sick pay/rehabilitation/retraining/unemployment/transitional benefits, disability/retirement/widow's pension, family income supplement, and/or other benefits. Subjects who had economic difficulties were identified by their affirmative answer to the question, "During the last year, has it at any time been difficult to meet the costs of food, transportation, housing and such?" People with missing information on smoking, family history of asthma, education, physical activity, and socioeconomic status were grouped into an "unknown" category for each variable and included in the analyses; multiple imputation of the missing data was performed as a sensitivity analysis with similar analytic results (not presented). Body weight and height in HUNT 2 were measured by health professionals. Body mass index was calculated as body weight in kilograms divided by square of height in meters (kg/m^2), and was grouped into <25.0, 25.0-29.9, and ≥30.0 kg/m^2 categories according to the recommendations of the World Health Organization (19).

Statistical analysis

The statistical analyses were performed in women and men separately to allow identification of asthma risk factors that may be specific to one sex only based on a priori assumption (20). Baseline characteristics were compared between incident asthma cases and non-asthma controls: un-paired t-tests were used for continuous variables; Chi-square tests were used for categorical variables. Baseline serum 25(OH)D levels were treated as continuous values and also classified into 3 groups: <50.0, 50.0-74.9, and ≥75.0 nmol/L (equivalent to <20.0, 20.0-29.9, and ≥30.0 ng/ml), which are widely used cut-off points in scientific literature (10, 21, 22). The association between 25(OH)D and incident asthma was examined by using logistic

regression analyses, and odds ratios (OR) and 95% confidence intervals (CI) were calculated. Multivariable logistic regression models included age, daily smoking, family history of asthma, education, physical activity, social benefit, economic difficulties and body mass index categories at baseline as potential risk factors for asthma. All these covariates were coded as categorical variables including the "unknown" group. The analyses were further stratified by allergic rhinitis (yes/no/missing). Since there were a number of subjects with missing information on allergic rhinitis (n = 269 for women and n = 277 for men), we performed 2 sensitivity analyses in women and men respectively by placing the "missing" group with subjects who either did or did not report having allergic rhinitis. To examine the potential misclassification for reported asthma, we repeated the analysis by excluding those who reported having doctor-diagnosed COPD, and by using a stricter asthma definition that required reported asthma in combination with using inhaled corticosteroids alone or combined with long-acting beta2-agonists during the last year (in Norway, asthma diagnosis was always confirmed by a doctor when adult patients were prescribed asthma medication). We also used a stricter definition for allergic rhinitis: i.e. reported having allergic rhinitis and/or hay fever in combination with an affirmative response to a question on allergy condition (symptoms from lung, nose or eyes when exposed to pets, pollen or dust) in a subsequent interview; the stricter definition for no allergic rhinitis was negative answers to both questions; subjects who met only 1 criterion were not included in the analysis. Statistical significance was set at 2-tailed $P < 0.05$, except for $P_{interaction}$ where $P < 0.10$ was used. All statistical analyses were performed with STATA, release 12.0 (College Station, Texas, USA) (23).

Ethics

The study was approved by the Regional Committee for Medical Research Ethics. All participants gave their informed consent.

RESULTS

Table 1 shows the differences in baseline characteristics between incident asthma cases and non-asthma controls. Asthma cases compared with controls had a higher mean value of body mass index but a lower mean value of serum 25(OH)D in both women and men. Asthma cases were more likely to have a family history of asthma, less years of education and lower socioeconomic status than controls. However, there were no differences in age, physical activity or season for blood sampling between cases and controls. Among women only, asthma cases were more likely to be smokers than the non-asthma controls.

For baseline serum 25(OH)D levels, 45% of the asthma cases vs. 37% of the controls had a level below 50.0 nmol/L in women, and in men they were 47% and 41%, respectively (**Table 2**). The unadjusted analysis for women revealed a non-significant increase in asthma risk with the 25(OH)D level <50.0 nmol/L compared with the ≥75.0 nmol/L group (OR = 1.31, 95% CI: 0.96, 1.78) but a statistically significant trend with 25(OH)D levels (P = 0.03). Among men, a significantly increased risk of asthma was associated with the 25(OH)D level of 50.0-74.9 nmol/L (OR = 1.63, 95% CI: 1.04, 2.53) and <50 nmol/L (OR = 1.75, 95% CI: 1.14, 2.68) when compared with the ≥75.0 nmol/L group.

After adjustment for potential risk factors for asthma, the adjusted OR (AOR) for serum 25(OH)D <50 nmol/L compared with serum 25(OH)D ≥75 nmol/L was not statistically significant in either women or men (**Table 3)**. Allergic rhinitis modified the association between serum 25(OH)D level and asthma in men; there was no association among men with allergic rhinitis (AOR = 0.87, 95%CI: 0.36, 2.06), but a significant association among men without allergic rhinitis (AOR = 2.32, 95%CI: 1.06, 5.10). Among men with no allergic

rhinitis, each 25 nmol/L reduction in 25(OH)D level was significantly associated with an AOR being 1.49 (95% CI: 1.09, 2.04) for incident asthma (*P* for interaction of 25(OH)D level * allergy = 0.07, Table 3). The results were similar after additional adjustment for season of blood collection (data not shown). Serum 25(OH)D level was not significantly associated with asthma in women, with or without allergic rhinitis, after adjustment for the same covariates (Table 3).

When men with missing information on allergic rhinitis were combined with those without allergic rhinitis, incident asthma was still significantly associated with 25(OH)D <50 nmol/L relative to a level ≥75 nmol/L in men (AOR = 1.92, 95% CI: 1.06, 3.47), while no significant association remained in men with allergic rhinitis and missing group combined (**Table 4**). In women the results remained null when merging the missing group with those with or without allergic rhinitis (data not shown).

When participants with doctor-diagnosed COPD were excluded, the association of 25(OH)D <50 nmol/L with incident asthma was strengthened in men without allergic rhinitis (AOR = 3.68, 95% CI: 1.25, 10.85). Using medical treatments as indirect validation of asthma diagnosis, we found that each 25 nmol/L reduction in 25(OH)D level was significantly associated with an AOR being 2.78 (95% CI: 1.03, 4.55) for reported asthma in combination with inhaled corticosteroid use in men without allergic rhinitis. These sensitivity analyses continued to show no significant association between 25(OH)D and asthma among men with allergic rhinitis and among women with or without allergic rhinitis.

In men without allergic rhinitis by the stricter definition (i.e. men who reported no allergic rhinitis or hay fever in the questionnaire and who also confirmed their lack of allergy in the

subsequent interview, n = 427), each 25 nmol/L reduction in 25(OH)D level was significantly associated with an increased risk of asthma (AOR = 1.75 , 95% CI: 1.12, 2.70), but the associations remained non-significant in men with allergic rhinitis (n = 100) and in women with (n = 199) or without (n = 547) allergic rhinitis using the stricter definition.

DISCUSSION

Our study is one of the first large prospective studies evaluating the association between serum 25(OH)D levels and incident asthma in adults. We observed no significant association between serum 25(OH)D levels and incident asthma among women, nor among men with allergic rhinitis. However, we did find a significant inverse association between serum 25(OH)D level and risk of incident asthma among men without allergic rhinitis.

Previous prospective studies were mostly conducted in children and the findings were inconsistent (10, 14-16). A birth cohort study from New Zealand demonstrated that 25(OH)D in cord blood was inversely associated with the risk of respiratory infection and wheeze, but not with asthma by the age of 5 years (10). Another birth cohort study conducted in Tucson, Arizona, observed that both low and high levels of cord blood 25(OH)D levels were associated with increased levels of total IgE and specific IgE to aeroallergens, but not with allergic rhinitis or asthma at 5 years of age (16). A United Kingdom study actually found an increased risk of asthma in children whose mothers had higher 25(OH)D concentrations during pregnancy (14). However, large loss of follow-up in the UK study poses concerns; among the original cohort with available maternal 25(OH)D levels, only 38% of the children were followed up to 9 years of age. By contrast, in a recent publication children (particularly boys) with inadequate vitamin D at 6 years of age were at an increased risk of developing bronchial hyperresponsiveness and asthma at 14 years of age (15).

Our finding of a significant inverse association in men without allergic rhinitis is in line with the earlier mentioned cross-sectional study which found an association between low serum 25(OH)D levels and asthma in non-atopic subjects only (17). If the association is causal, the

contribution of low vitamin D status on asthma development is more likely via non-allergic than allergic pathways. There is growing appreciation that asthma is a complex trait caused by multiple environmental factors in combination with more than 100 major and minor susceptibility genes and has many different forms or phenotypes (24-26). Immunological mechanisms and risk factors for allergic and non-allergic asthma can be quite different, with allergic asthma characterized by eosinophilic inflammation dependent on T helper 2 cells, while non-allergic asthma has neutrophilic inflammation independent of T helper 2 cells (26). Allergen exposure is the predominant risk factor for allergic asthma, while the risk factors for non-allergic asthma are diverse, such as environmental factors associated with air pollutants and occupation, viral infection, stress, obesity and many unknown factors (26). Nevertheless, the reasons for an association of low 25(OH)D with asthma only in men without allergic rhinitis (but not in women without allergic rhinitis) are not obvious. This sex difference might also reflect the heterogeneity of non-allergic asthma in men and women with distinct phenotypes predisposed to different origins. Although it is most unlikely, we cannot completely rule out that the non-allergic "asthma" was simply recurrent respiratory infections. Vitamin D deficiency is shown to be associated with impaired innate immunity, reduced antimicrobial peptide cathelicidin (27, 28) and increased susceptibility to respiratory infections (10, 11, 13). The sex-specificity could be explained, in part, by the greater vulnerability to infections in males than females (29, 30).

Our nested case-control study design links serum 25(OH)D levels at baseline with newly developed asthma during the follow-up with a clear directionality for the association of interest. Selection bias would be less likely when population-based incident asthma cases and non-asthma controls were selected. Furthermore, we performed sensitivity analyses to make sure that missing on allergic rhinitis had no important impact on our main results.

We acknowledge that the study has several potential limitations. Firstly, there remains possibility for asthma to be misclassified although reported-asthma is the most common approach in epidemiological studies (12, 31). However, analyses that excluded subjects with COPD and that used a stricter asthma definition (by requiring use of inhaled corticosteroids to become case) yielded stronger associations between serum 25(OH)D level and asthma among men without allergic rhinitis. Secondly, there is a debate on the validity of a single measurement of serum 25(OH)D for body vitamin D status. A previous Norwegian study showed a high correlation and small variation of 25(OH)D levels overtime in adults (correlation coefficients: 0.80 for 1-year follow-up and 0.52 for a 14-year follow-up period) (32). Thirdly, allergic rhinitis was considered as a proxy measure for allergy status. There is an indication that such a definition has a modest sensitivity and a high specificity compared with measurement of allergen-specific IgE levels (33, 34). Objective measures for allergy status are called for in future studies. However, sensitivity analyses using stricter definitions for allergic rhinitis and no allergic rhinitis yielded similar results. Finally, we acknowledge that the impact of vitamin D deficiency on asthma is relatively small if truly causal. Although we measured 25(OH)D levels in a large sample of cases and controls, it is still possible that the study lacks the statistical power to detect small associations in some of the subsets after stratification by sex and allergic rhinitis.

In conclusion, we found no association between serum 25(OH)D level and risk of incident asthma among women and among men with allergic rhinitis. By contrast, we found a significant inverse association of 25(OH)D with incident asthma in men without allergic rhinitis. The growing appreciation of asthma heterogeneity (24-26) suggests that this subgroup finding merits further investigation. The novel finding might open new preventive

and therapeutic perspectives for asthma among men without allergy.

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Author affiliations:

Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway (Xiao-Mei Mai, and Arnulf Langhammer)

Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA (Carlos A. Camargo, Jr.)

Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada (Yue Chen)

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Figure legend

Figure 1. Flow chart of the study population, a nested case-control study, the HUNT study, 1995-97 to 2006-08

Abbreviations: HUNT, Nord-Trøndelag Health Study; 25(OH)D, 25-hydroxyvitamin D.

Table 1. Baseline Characteristics in Incident Asthma Cases vs. Non-asthma Controls in Women and Men, a Nested Case-Control Study, the HUNT Study, 1995-97 to 2006-08

	Women							**Men**						
	Cases n = 376			Controls n = 1,073				Cases n = 208			Controls n = 885			
	Mean (SD)	n	%	Mean (SD)	n	%	*P* value	Mean (SD)	n	%	Mean (SD)	n	%	*P* value
Age in HUNT 2 (years)[a]	39.1 (9.1)			39.7 (8.5)			0.21	40.3 (8.8)			40.0 (8.9)			0.72
BMI (kg/m^2)[a]	26.4 (4.5)			25.3 (3.9)			<0.001	27.0 (3.7)			26.2 (3.2)			<0.001
25(OH)D (nmol/L)[a]	56.7 (23.7)			59.5 (23.1)			0.05	54.8 (20.8)			58.9 (23.5)			0.02
Daily smoker[b]							<0.001							0.48
yes		152	40		286	27			50	24		193	22	
no		199	53		721	67			147	71		646	73	
unknown		25	7		66	6			11	5		46	5	
Family history of asthma[b]							<0.001							<0.001
yes		99	26		163	15			47	23		110	12	
no		207	55		830	77			128	62		715	81	
unknown		70	19		80	7			33	16		60	7	
Education (years)[b]							0.03							0.04
<10		96	26		217	20			47	23		147	17	
≥10		276	73		849	79			159	76		731	83	
unknown		4	1		7	1			2	1		7	1	
Physical activity (hours/week)[b]							0.18							0.88
<1		86	23		208	19			50	24		219	25	
≥1		253	67		746	70			129	62		549	62	
unknown		37	10		119	11			29	14		117	13	
Social benefit recipient[b]							<0.001							0.07
yes		130	35		230	21			31	15		92	10	
no		184	49		681	63			138	66		621	70	
unknown		62	16		162	15			39	19		172	19	
Economic difficulties[b]							<0.001							0.04
yes		147	39		288	27			66	32		226	26	
no		182	48		669	62			109	52		533	60	
unknown		47	13		116	11			33	16		126	14	
Season for blood sampling[b]							0.64							0.40
Dec.-May		206	55		603	56			124	60		499	56	
Jun.-Nov.		170	45		470	44			84	40		386	44	

Abbreviations: BMI, body mass index; HUNT, Nord-Trøndelag Health Study; 25(OH)D, 25-hydroxyvitamin D; SD, standard deviation.

[a]Un-paired t-tests were used for comparisons between cases and controls for continuous variables and [b]Chi-square tests for categorical variables not including the “unknown” categories.

Table 2. Baseline Serum 25(OH)D Level in Categories in Incident Asthma Cases vs. Non-asthma Controls in Women and Men, a Nested Case-Control Study, the HUNT Study, 1995-97 to 2006-08

	Women						**Men**					
	Cases n = 376		Controls n = 1,073				Cases n = 208		Controls n = 885			
25(OH)D (nmol/L)	n	%	n	%	Crude OR	95% CI	n	%	n	%	Crude OR	95% CI
≥75.0	81	22	247	23	1.00	Referent	33	16	214	24	1.00	Referent
50.0-74.9	125	33	430	40	0.89	0.64, 1.22	77	37	307	35	1.63	1.04, 2.53
<50.0	170	45	396	37	1.31	0.96, 1.78	98	47	364	41	1.75	1.14, 2.68
P for trend[a]					0.03						0.02	

Abbreviations: CI, confidence interval; HUNT, Nord-Trøndelag Health Study; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio.

[a]*P* for trend was tested by treating 25(OH)D categories as an ordinal variable.

Table 3. Adjusted[a] Odds Ratios and 95% Confidence Intervals for Incident Asthma Associated With Baseline Serum 25(OH)D Levels in Women and Men in Un-stratified or Stratified Subgroups by Allergic Rhinitis, a Nested Case-Control Study, the HUNT Study, 1995-97 to 2006-08

	Un-stratified		Stratified by allergic rhinitis					
Women	n = 1449		No (n = 796)		Yes (n = 384)		Missing (n = 269)	
25(OH)D (nmol/L)	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI
≥75.0	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
50.0-74.9	0.80	0.57, 1.13	0.95	0.55, 1.64	0.76	0.42, 1.39	0.70	0.28, 1.74
<50.0	0.94	0.67, 1.32	0.91	0.52, 1.60	1.31	0.71, 2.39	0.65	0.26, 1.62
Each 25 nmol/L reduction	0.97	0.85, 1.12	0.93	0.74, 1.15	1.15	0.88, 1.49	0.81	0.56, 1.19
P for interaction[b]			0.27					
Men	n = 1093		No (n = 620)		Yes (n = 196)		Missing (n = 277)	
25(OH)D (nmol/L)	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI
≥75.0	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
50.0-74.9	1.50	0.95, 2.38	1.84	0.83, 4.08	1.31	0.54, 3.15	2.18	0.80, 5.99
<50.0	1.47	0.93, 2.32	2.32	1.06, 5.10	0.87	0.36, 2.06	1.95	0.73, 5.21
Each 25 nmol/L reduction	1.14	0.94, 1.37	1.49	1.09, 2.04	0.92	0.63, 1.33	1.09	0.75, 1.59
P for interaction[b]			0.07					

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HUNT, Nord-Trøndelag Health Study; 25(OH)D, 25-hydroxyvitamin D.

[a]Multivariable logistic regression model included age (19-29, 30-39, 40-49, and 50-55 years), daily smoking (yes, no, and unknown), family history of asthma (yes, no, and unknown), education (<10, 10-12, ≥13 years, and unknown), physical activity (<1, 1-2, ≥3 hours per week, and unknown), social benefit (yes, no, and unknown), economic difficulties (yes, no, unknown) and body mass index (<25.0, 25.0-29.9, and ≥30.0 kg/m^2) at baseline.

[b]*P* for interaction of 25(OH)D values * allergic rhinitis was calculated using likelihood ratio test.

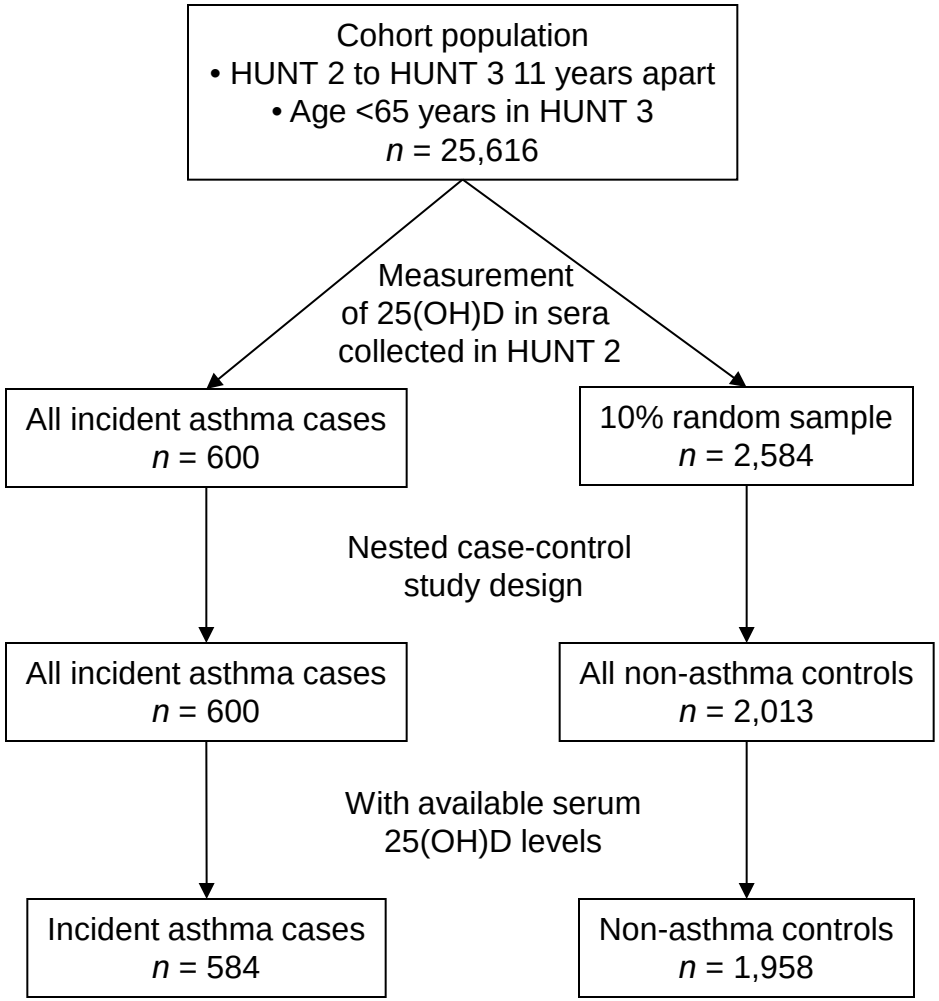
Table 4. Adjusted[a] Odds Ratios and 95% Confidence Intervals for Incident Asthma With Baseline Serum 25(OH)D Levels in Men: Sensitivity Analyses by Placing Subjects Without or With Allergic Rhinitis With Missing, a Nested Case-Control Study, the HUNT Study, 1995-97 to 2006-08

	Without allergic rhinitis + Missing n = 897		With allergic rhinitis + Missing n = 473	
25(OH)D (nmol/L)	AOR	95% CI	AOR	95% CI
≥75.0	1.00	Referent	1.00	Referent
50.0-74.9	1.79	0.98, 3.27	1.52	0.83, 2.81
<50.0	1.92	1.06, 3.47	1.13	0.61, 2.06
Each 25 nmol/L reduction	1.25	0.98, 1.56	0.90	0.75, 1.09

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HUNT, Nord-Trøndelag Health Study; 25(OH)D, 25-hydroxyvitamin D.

[a]Multivariable logistic regression model included age (19-29, 30-39, 40-49, and 50-55 years), daily smoking (yes, no, and unknown), family history of asthma (yes, no, and unknown), education (<10, 10-12, ≥13 years, and unknown), physical activity (<1, 1-2, ≥3 hours per week, and unknown), social benefit (yes, no, and unknown), economic difficulties (yes, no, unknown) and body mass index (<25.0, 25.0-29.9, and ≥30.0 kg/m^2) at baseline.

Figure 1


Cohort population
• HUNT 2 to HUNT 3 11 years apart
• Age <65 years in HUNT 3
n = 25,616
Measurement
of 25(OH)D in sera
collected in HUNT 2
All incident asthma cases
n = 600
10% random sample
n = 2,584
Nested case-control
study design
All incident asthma cases
n = 600
All non-asthma controls
n = 2,013
With available serum
25(OH)D levels
Incident asthma cases
n = 584
Non-asthma controls
n = 1,958