Original Contribution

Serum 25-Hydroxyvitamin D Levels and Incident Asthma in Adults

The HUNT Study

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The impact of low vitamin D status on asthma development is unclear. The authors investigated the relation between the 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 Norwegian adults aged 19–55 years participated in 2 surveys of the Nord-Trøndelag Health Study known as HUNT 2 (1995–1997) and HUNT 3 (2006–2008). Of this cohort, a nested case-control study included 584 new-onset asthma cases and 1,958 nonasthma controls whose baseline serum 25(OH)D levels were measured. After adjustment for potential asthma risk factors, the baseline serum level of 25(OH)D (<50 nmol/L) was not significantly associated with asthma in either women (adjusted odds ratio = 0.94, 95% confidence interval (CI): 0.67, 1.32) or men (adjusted odds ratio = 1.47, 95% CI: 0.93, 2.32). In men, allergic rhinitis modified the association with the adjusted odds ratio 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. The 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 it may have increased risk among men without allergy.

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

Abbreviations: 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.

The relation between vitamin D status and asthma development is highly controversial: Wjst and Dold (1) claim that asthma is caused by vitamin D supplementation, while Litonjua and Weiss (2) assert that asthma is caused by vitamin D deficiency. Previous studies of vitamin D intake have yielded conflicting results (3–8), possibly because of 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 a lower serum 25(OH)D level and a higher risk of ever asthma diagnosis among nonatopic but not atopic individuals (17). In the present study, we evaluated the association between baseline serum 25(OH)D levels and incident asthma among Norwegian adults in the Nord-Trøndelag Health Study (HUNT). 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 HUNT invited all inhabitants aged 19 years or older in the county of Nord-Trøndelag to participate in 3 separate surveys: HUNT 1 (1984–1986), HUNT 2 (1995–1997), and HUNT 3 (2006–2008). In the current study, we used data from HUNT 2 and HUNT 3. Briefly, HUNT 2 invited about 93,000 adults in 1995–1997, and 65,215 subjects participated (response rate: 70%). Among them, 57% (n = 37,059) took part in HUNT 3 in 2006–2008. 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, that is, “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 the baseline serum 25(OH)D level and incident asthma, we carried out a nested case-control study including all incident asthma cases (n = 600) during an average 11-year follow-up and a number of nonasthma controls (n = 2,013). The nonasthma 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 by 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 a low serum 25(OH)D concentration at the α = 0.05 and 1 − β = 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 nonasthma controls whose blood specimens collected in HUNT 2 were available and sufficient for the measurement of 25(OH)D levels (Figure 1). The 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 10–375 nmol/L. The assay has an intraassay coefficient of variation of 4% and an interassay coefficient of variation of 8%.

Other variables

Allergy status was considered as a potentially 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 have or have you had allergic rhinitis or hay fever?” Other important variables—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 analytical
results (not presented). Body weight and height in HUNT 2 were measured by health professionals. Body mass index was calculated (weight (kg)/height (m)^2) and 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 on the basis of a priori assumption (20). Baseline characteristics were compared between incident asthma cases and nonasthma controls. Unpaired t tests were used for continuous variables; χ^2 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 cutoff points in the scientific literature (10, 21, 22). The association between 25(OH)D and incident asthma was examined by using logistic regression analyses, and odds ratios and 95% confidence intervals 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). Because 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 physician-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 β₂-agonists during the last year (in Norway, asthma diagnosis was always confirmed by a physician when adult patients were prescribed asthma medication). We also used a stricter definition for allergic rhinitis, that is, 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, software (StataCorp LP, College Station, Texas) (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 nonasthma 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 were the nonasthma controls.

For baseline serum 25(OH)D levels, 45% of the asthma cases versus 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 nonsignificant increase in asthma risk with the 25(OH)D level of <50.0 nmol/L compared with the ≥75.0 nmol/L group (odds ratio (OR) = 1.31, 95% confidence interval (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 odds ratio for a serum 25(OH)D level of <50 nmol/L compared with a serum 25(OH)D level of ≥75 nmol/L was not statistically significant in either women or men (Table 3). Allergic rhinitis modified the association between the serum 25(OH)D level and asthma in men: There was no association among men with allergic rhinitis (adjusted odds ratio (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 serum 25(OH)D level was significantly associated with an adjusted odds ratio of 1.49 (95% CI: 1.09, 2.04) for incident asthma (P_{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). The 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 <50 nmol/L of 25(OH)D 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 the 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 physician-diagnosed COPD were excluded, the association of <50 nmol/L of 25(OH)D 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 adjusted odds ratio of 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 Table 1.

Baseline Characteristics in Incident Asthma Cases Versus Nonasthma Controls in Women and Men, a Nested Case-Control Study, the HUNT Study, 1995–1997 to 2006–2008

<table>
<thead>
<tr>
<th></th>
<th>Women Cases (n=376)</th>
<th>Controls (n=1,073)</th>
<th>P Value</th>
<th>Men Cases (n=208)</th>
<th>Controls (n=885)</th>
<th>P Value</th>
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<tr>
<td></td>
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<td>No.</td>
<td>%</td>
<td>Mean (SD)</td>
<td>No.</td>
<td>%</td>
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<tr>
<td>Age in HUNT 2, years(^a)</td>
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<td>39.7 (8.5)</td>
<td>0.21</td>
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<td>40.0 (8.9)</td>
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<td>Body mass index(^a,b)</td>
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<td>25.3 (3.9)</td>
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<td>27.0 (3.7)</td>
<td>26.2 (3.2)</td>
<td>&lt;0.001</td>
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<td>25(OH)D, nmol/L(^a)</td>
<td>56.7 (23.7)</td>
<td>59.5 (23.1)</td>
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<td>54.8 (20.8)</td>
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<td>50</td>
<td>24</td>
<td>193 22</td>
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<td>53</td>
<td>721 67</td>
<td>147</td>
<td>71</td>
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<td>7</td>
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<td></td>
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</tr>
<tr>
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<td>47</td>
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<td>110 12</td>
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<td>128</td>
<td>62</td>
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<td>Education, years(^c)</td>
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<tr>
<td>&lt;10</td>
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<td>26</td>
<td>217 20</td>
<td>47</td>
<td>23</td>
<td>147 17</td>
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<tr>
<td>≥10</td>
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<td>159</td>
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<td>1</td>
<td>7 1</td>
<td>2</td>
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<td>29</td>
<td>14</td>
<td>117 13</td>
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<tr>
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<td>49</td>
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<td>138</td>
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<td>39</td>
<td>19</td>
<td>172 19</td>
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<td>66</td>
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<tr>
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<td>116 11</td>
<td>33</td>
<td>16</td>
<td>126 14</td>
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<td>45</td>
<td>470 44</td>
<td>84</td>
<td>40</td>
<td>386 44</td>
</tr>
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</table>

Abbreviations: HUNT, Nord-Trøndelag Health Study; 25(OH)D, 25-hydroxyvitamin D; SD, standard deviation.
\(^a\) Unpaired t tests were used for comparisons between cases and controls for continuous variables.
\(^b\) Body mass index: weight (kg)/height (m)\(^2\).
\(^c\) \(\chi^2\) tests were used for categorical variables not including the “unknown” categories.
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 nonsignificant 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 the 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 immunoglobulin E and specific immunoglobulin E to aerallergens, 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, the large loss of follow-up in the United Kingdom 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 that found an association between low serum 25(OH)D levels and asthma in nonatopic subjects only (17). If the association is causal, the contribution of low vitamin D status to asthma development is more likely via nonallergic 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 that it has many different forms or phenotypes (24–26). Immunologic mechanisms and risk factors for allergic and nonallergic asthma can be quite different, with allergic asthma characterized by eosinophilic inflammation dependent on T helper 2 cells, while nonallergic 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 nonallergic 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 a low level of 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 nonallergic asthma in men and women with distinct phenotypes predisposed to different origins. Although it is most unlikely, we cannot completely rule out that the nonallergic “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 nonasthma controls were selected. Furthermore, we performed sensitivity analyses to make sure that missing information on allergic rhinitis had no important impact on our main results.

We acknowledge that the study has several potential limitations. First, there remains the possibility for asthma to be misclassified, although reported asthma is the most common approach in epidemiologic studies (12, 31). However, analyses that excluded subjects with COPD and that used a stricter asthma definition (by requiring the use of inhaled corticosteroids to become a case) yielded stronger associations between the serum 25(OH)D level and asthma among men without allergic rhinitis. Second, 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 over time in adults (correlation coefficients: 0.80 for 1-year follow-up and 0.52 for a 14-year follow-up period) (32). Third, 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 immunoglobulin E 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 the 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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All authors contributed equally to the work.

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Conflict of interest: none declared.

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