Infant Vitamin D Supplementation and Allergic Conditions in Adulthood

Northern Finland Birth Cohort 1966

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ABSTRACT: **Allergen-induced secretion of Th2-type cytokines and IgE production have recently been reported to be increased in mice treated with $1,25(OH)_2D$, the active form of vitamin D. Our objective was to investigate whether vitamin D supplementation in infancy is associated with the risk of atopy, allergic rhinitis, and asthma. The Northern Finland Birth Cohort consists of all individuals in the two most northern provinces of Finland who were due to be born in 1966. Data on vitamin D supplementation during the first year of life was obtained in 1967. Current asthma and allergic rhinitis were reported at age 31 years (n = 7,648), and atopy determined by skin-prick test in a sub-sample still living in northern Finland or the Helsinki area (n = 5,007). The prevalence of atopy and allergic rhinitis at age 31 years was higher in participants who had received vitamin D supplementation regularly during the first year compared to others (OR 1.46, 95% CI 1.4–2.0, and OR 1.66, 95% CI 1.1–1.6, respectively). A similar association was observed for asthma (OR 1.35, 95% CI 0.99–1.8). These associations persisted after adjustment for a wide range of behavioral and social factors (adjusted: OR 1.33 for all, P = 0.01 for atopy, P = 0.001 for allergic rhinitis, and P = 0.08 for asthma). We observed an association between vitamin D supplementation in infancy and an increased risk of atopy and allergic rhinitis later in life. Further study is required to**

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determine whether these observations reflect long-term effects on immune regulation or differences in unmeasured determinants of vitamin D supplementation.

KEYWORDS: **vitamin D; allergy; allergic rhinitis; asthma; atopy; infant supplementation; hygiene hypothesis**

INTRODUCTION

Findings from a recent animal experiment suggest that administration of $1,25(OH)_2D$ to mice increases allergen-induced T cell proliferation, IL-4 and IL-13 cytokine levels, and serum IgE production.[1] Vitamin D is known to be important for immune regulation, and there is some evidence that it may induce a shift in the balance between Th1- and Th2-type cytokines toward Th2 domination.[1,2] Reduced secretion of Th1-type cytokines IL-2 and INF-γ[1–6] and an increase in Th2-type IL-4[2,7,8] have been observed in several experiments after treatment with $1,25(OH)_2D$. In addition to concurrent effects on cytokine secretion, there is experimental evidence and epidemiological data that suggest that vitamin D deficiency or intake early in life may affect the risk of immune-mediated diseases, such as type 1 diabetes.[9–11] Compared to allergies, type 1 diabetes has been suggested to present the opposite end of immune deviation; allergies are characterized by a Th2 skew in immune responses, while in type 1 diabetes Th1-type responses dominate.[12] The mechanisms underlying long-term associations between vitamin D supplementation/status and diabetes risk are not fully established, but downregulation of the Th1-type immune response pattern would provide one possible explanation.[13] Early life influences are also believed to be important for the development of allergies and asthma.[14–16] If vitamin D has long-term effects on Th1/Th2 polarization, then infant supplementation could be expected to affect susceptibility to allergies later in life.

Despite differences in the etiology of type 1 diabetes and allergies, risk of both types of conditions has been suggested to be increased by reduction in immune tolerance after excessive hygiene during critical periods of development.[12,17] There is evidence that compliance to vitamin supplementation recommendations is affected by social and behavioral factors,[11,18] which in turn may be associated with the domestic standards of hygiene, and could influence the associations between vitamin D supplementation and subsequent disease risk.

A link between vitamin D and allergy risk has been hypothesized;[19] to date, however, there have been no earlier studies that have investigated this association in humans. We have previously reported a reduced risk of type 1 diabetes after vitamin D supplementation in infancy in the Northern Finland Birth Cohort 1966 (NFBC 1966).[11] We now hypothesize that infant vitamin D supplementation increases the risk of allergies or asthma in adulthood and test this in the same cohort.

METHODS

NFBC 1966 consists of all births in the two most northern provinces of Finland, which continued after the 24th week of pregnancy and where the expected date of delivery was in 1966 (12,058 live-births, coverage 96%).[11] Women were first con-

tacted during pregnancy, and their offspring followed up at ages 1, 14, and 31 years. Data on sociodemographic, behavioral, and other background factors were collected by a structured questionnaire administered to the women visiting prenatal clinics in the 24th to 28th week of gestation. For 9.7% of the mothers, the questionnaire was completed later on in pregnancy, and in a few cases after the delivery. A questionnaire on the outcome of the delivery and on the newborn infant was filled in by the midwives in the maternity hospitals.[20] Of the children alive, 91% participated in the one-year follow-up study (n = 10,821).[21] Data obtained during the children's visits to the child health centers were supplemented with information obtained during an examination performed by public health nurses and general practitioners. In 1997 (age 31) the questionnaire, which included questions on allergic rhinitis and asthma, was sent to all individuals with a known address (n = 11,541). Seventy-five percent of them (n = 8,690) returned the questionnaire with an informed consent. Clinical examination including skin-prick test was performed in a subsample of participants living in northern Finland or the Helsinki area (of the 8,463 eligible participants, 6,007 participated).[22] Atopy was determined by sensitivity to cat, birch, timothy grass, or house dust mite (reaction ≥ 3 mm). Individuals with reaction to negative control (n = 12) or who had some indication that the test was not successful (n = 40) were excluded. Participants were classified as having allergic rhinitis if they reported allergic cold (related to contact with animals or pollen, e.g., hay fever) during the past 12 months. Current asthma was classified as asthma with wheezing during the past 12 months or by current use of asthma medication. An additional questionnaire including questions about family history of allergy and asthma (in mother, father, or siblings) was administered to cohort members participating in the clinical examination. After excluding refusals and those with missing data in the outcomes, 5,007 participants were available for analyses on atopy, and 7,648 for studies on allergic rhinitis and asthma.

Frequency of vitamin D supplementation during the first year of life was reported by the mother as regular, irregular, or none.[11] Information on rickets suspected by healthcare personnel during the first year was obtained from the child's health records. The daily dose of vitamin D was calculated on the basis of concentration of vitamin D in the product used and the reported dosage (categorized as <50 μg, 50 μg, or >50 μg). Eighty-four children received cod liver oil and were classified as having received the recommended 50-μg dose. Information was available on whether a child had received an increased dose of vitamin D at some point during the first year of life.

Social class at the time of birth (1966) was based on the prestige of the father's occupation if the mother was married, or of her own occupation, if single, widowed, or divorced. Mothers were classified into smokers and nonsmokers on the basis of their reported smoking at the beginning of the third month of pregnancy. Desirability of the pregnancy (wanted/preferred later/unwanted), the mother's frame of mind during pregnancy (as usual/depressed/very depressed), and the mother's interest in following health education or programs on domestic and child issues (regularly or often/sometimes/rarely or never) were asked in the questionnaire for the first survey filled in during the 24 to 28th week of gestation. Birth order was based on the mother's parity, including stillbirths.

The Ethics Committee of the Faculty of Medicine at the University of Oulu approved the study. Permission to collect outcome data using national registers was given by the Ministry of Social Welfare and Health.

STATISTICAL ANALYSIS

Odds ratios (OR) with 95% confidence intervals from logistic regression analyses were used to compare prevalence of allergy and asthma between the exposure groups. Those receiving no supplementation were combined with irregularly supplemented cohort members because of the small number of individuals who did not receive any vitamin D supplementation ($n = 9$ for analyses on atopy, $n = 20$ for allergic rhinitis/asthma). In the fully adjusted models, individuals with missing data in the covariates were assigned into a separate category; however, results were similar after omitting those with incomplete data from the analyses. Because information on family history of asthma and on family history of allergy was available only for the subsample who participated in the clinical examination, their effects were assessed in separate models. Selection bias was investigated in relation to social class in 1966, gender, and vitamin D supplementation. Those who attended clinical examination ($n = 6{,}007$) were compared with those who were not invited or were invited but did not attend ($n = 2{,}456 + 3{,}174 = 5{,}630$). Women (52 vs. 46%) and farmers' children were overrepresented (21 vs. 16%), while offspring to fathers from unskilled backgrounds were somewhat underpresented (27 vs. 21%) among attendees compared to the remainder alive at 31 years. Cohort members who attended the examination were equally likely to have received vitamin D supplementation according to the recommendations, compared to others who had not (84 vs. 83%, $P = 0.13$). The statistical analyses were carried out using STATA (version 8).[23]

RESULTS

Of the participants with information on frequency of vitamin D supplementation, 31% ($n = 1{,}536$) had at least one positive skin-prick test, 28% ($n = 2{,}172$) had allergic rhinitis, and 7% ($n = 517$) had asthma. Of the participants who reported allergic rhinitis during the past 12 months, 58% also had a positive reaction in the skin-prick test (vs. 20% in those who did not have allergic rhinitis).

Compliance to vitamin D supplementation recommendations (i.e., child received 50 µg regularly) was associated with several social and behavioral characteristics of the mother, with significant trends observed for the child's birth order, maternal age, education, social class, interest in health education, frame of mind during pregnancy, and desirability of pregnancy ($P < 0.001$ for all comparisons). Cohort members with family history of asthma were less likely to receive supplementation according to recommendations ($P = 0.02$), while there was no difference by family history of allergy. Many of the same characteristics that were predictive of worse compliance to vitamin D recommendations were associated with reduced risk of allergies. Significant associations with atopy and allergic rhinitis ($P < 0.05$) were observed for sex, birth order, maternal education, mother's frame of mind, and desirability of pregnancy (TABLE 1). Atopy was also associated with maternal age and interest in health education ($P \leq 0.01$). Asthma was less affected by these characteristics and an association was apparent only with social class ($P = 0.02$). As expected, family history of allergy and asthma was associated with all three outcomes ($P < 0.001$ for all comparisons). Maternal smoking during pregnancy was not associated with com-

TABLE 1. Allergic diseases at age 31 and infant vitamin D supplementation by family history, and social and maternal characteristics in 1966

	Number of participants with information on atopy/allergic rhinitis and asthma[a]	Vitamin D supplementation recommended 50 µg/day[b] Number (%)	Suspected rickets Cases (%)	Atopy Cases (%)	Allergic rhinitis Cases (%)	Asthma Cases (%)
Total	5007/7648	6350 (83)	143 (1.9)	1536 (31)	2172 (28)	517 (6.8)
Boys	2482/3631	2986 (83)	80 (2.2)	837 (34)	964 (27)	230 (6.3)
Girls	2525/4017	3364 (84)	63 (1.6)	699 (28)	1208 (30)	287 (7.1)
Birth order of child						
1	1554/2423	2154 (89)	37 (1.5)	546 (35)	720 (30)	152 (6.3)
2–3	1986/3074	2587 (85)	51 (1.7)	647 (33)	903 (29)	218 (7.1)
>3	1458/2141	1599 (75)	53 (2.6)	342 (23)	547 (26)	147 (6.9)
Unknown	9/10	10 (100)	0 (0)	1 (11)	2 (20)	0 (0)
Age of mother (years)						
<20	300/481	420 (87)	5 (1.0)	87 (29)	127 (26)	25 (5.2)
20–29	2770/4354	3688 (85)	67 (1.5)	908 (33)	1244 (29)	299 (6.9)
>29	1937/2813	2242 (80)	71 (2.5)	541 (28)	801 (28)	193 (6.9)
Education of mother						
None/basic	3335/4983	4041 (82)	101 (2.0)	958 (29)	1336 (27)	329 (6.6)
More than basic	1598/2562	2227 (87)	41 (1.6)	557 (35)	803 (31)	181 (7.1)
Unknown	74/103	82 (80)	1 (1.0)	21 (28)	33 (32)	7 (6.8)

TABLE 1. (*continued*) Allergic diseases at age 31 and infant vitamin D supplementation by family history, and social and maternal characteristics in 1966

	Number of participants with information on atopy/allergic rhinitis and asthma[a]	Vitamin D supplementation recommended 50 μg/day[b] Number (%)	Suspected rickets Cases (%)	Atopy Cases (%)	Allergic rhinitis Cases (%)	Asthma Cases (%)
Social class[c]						
Professional	1162/1828	1596 (88)	28 (1.5)	452 (39)	595 (33)	135 (7.4)
Skilled	1659/2528	2204 (88)	31 (1.2)	563 (34)	737 (29)	192 (7.6)
Unskilled	1060/1667	1343 (81)	31 (1.9)	292 (28)	449 (27)	104 (6.2)
Farmer	1071/1538	1132 (74)	47 (3.1)	211 (20)	367 (24)	83 (5.3)
Unknown	55/87	75 (86)	6 (6.9)	18 (33)	24 (28)	4 (4.6)
Mother follows health education[d]						
Regularly/often	2119/3248	2793 (86)	52 (1.6)	698 (33)	951 (29)	226 (7.0)
Sometimes	2269/3448	2818 (82)	69 (2.0)	663 (29)	957 (28)	234 (6.8)
Rarely/never	543/832	651 (79)	20 (2.4)	153 (28)	233 (28)	54 (6.5)
Unknown	76/120	88 (74)	2 (1.7)	22 (29)	31 (26)	3 (2.5)
Mother's frame of mind during pregnancy						
As usual	4275/6506	5479 (85)	124 (1.9)	1342 (31)	1888 (29)	439 (6.8)
Derpressed	545/841	644 (78)	15 (1.8)	146 (27)	217 (26)	56 (6.7)
Very depressed	93/152	113 (75)	3 (2.0)	22 (24)	34 (22)	14 (9.2)
Unknown	94/149	114 (77)	1 (0.7)	26 (28)	33 (22)	8 (5.4)
Pregnancy wanted by mother						
Now	3147/4825	4171 (87)	88 (1.8)	1033 (33)	1441 (30)	329 (6.8)
Later	1180/1795	1463 (82)	25 (1.4)	326 (28)	466 (26)	117 (6.5)
Unwanted	581/878	602 (70)	29 (3.3)	151 (26)	222 (25)	61 (7.0)
Unknown	99/150	114 (77)	1 (0.7)	26 (26)	43 (29)	10 (6.7)

TABLE 1. (*continued*) Allergic diseases at age 31 and infant vitamin D supplementation by family history, and social and maternal characteristics in 1966

	Number of participants with information on atopy/allergic rhinitis and asthma[a]	Vitamin D supplementation recommended 50 µg/day[b] Number (%)	Suspected rickets Cases (%)	Atopy Cases (%)	Allergic rhinitis Cases (%)	Asthma Cases (%)
Family history of allergy						
No	2275/2392	2025 (84)	50 (2.1)	560 (25)	501 (21)	89 (3.7)
Yes	2067/2245	1905 (84)	33 (1.5)	775 (37)	843 (38)	232 (10.3)
Unknown	655/3011	4652 (83)	133 (2.4)	201 (30)	828 (28)	196 (6.5)
Family history of asthma						
No	3321/3538	3023 (84)	65 (1.8)	978 (29)	918 (26)	167 (4.7)
Yes	1226/1310	1072 (82)	21 (1.6)	425 (35)	467 (36)	169 (12.9)
Unknown	133/2800	4487 (83)	130 (2.4)	133 (29)	787 (28)	181 (6.5)

[a]Information on atopy available from the subsample invited to the clinical examination; data on allergic rhinitis and asthma obtained from questionnaire survey addressed to the whole cohort.

[b]Information on dose was missing for 41 participants.

[c]Social class based on father's occupation if known, otherwise mother's.

[d]Based on the question, "Is the mother interested in following articles/programs on children, health care, or domestic issues in newspapers/magazines or on television or radio?"

TABLE 2. Prevalence of allergy and asthma at age 31 by the use of vitamin D supplements and suspected rickets in infancy

	Number of participants with information on atopy/allergic rhinitis and asthma[a]	Atopy Cases (%)	Allergic rhinitis Cases (%)	Asthma Cases (%)
Use of vitamin D				
None	9/20	3 (33)	3 (15)	0 (0)
Irregularly	576/880	129 (22)	198 (22)	47 (5.2)
Regularly	4422/6748	1407 (32)	1974 (29)	470 (7.0)
Dose of Vitamin D[b]				
<2000 IU	29/55	9 (31)	13 (24)	1 (1.8)
2000 IU	4174/6350	1340 (32)	1847 (29)	444 (7.0)
>2000 IU	197 /317	49 (25)	102 (32)	23 (7.3)
Suspected rickets				
No	4921/7505	1518 (31)	2141 (29)	509 (6.8)
Yes	86/143	18 (21)	31 (22)	8 (5.6)

[a]Information on atopy available from the subsample invited to the clinical examination; data on allergic rhinitis and asthma obtained from questionnaire survey addressed to the whole cohort.

[b]Restricted to children receiving vitamin D supplementation regularly.

pliance to supplementation recommendations or with prevalence of allergies and asthma (data not presented).

Prevalence of allergic conditions was greater in participants who had received vitamin D supplementation regularly compared to those who had received it irregularly or not at all ($P < 0.001$ for atopy and allergic rhinitis, $P = 0.05$ for asthma, TABLE 2). Dose of vitamin D was not significantly associated with the prevalence of allergies ($P \geq 0.10$ for all). There was a borderline association between rickets and the risk of atopy and allergic rhinitis ($P = 0.05$ and $P = 0.07$), but no association with asthma ($P = 0.56$). Adjustment for the social and behavioral factors attenuated, but did not fully explain, the associations between use of vitamin D and the risk of atopy or allergic rhinitis (TABLE 3). Adjustment for family history of allergies or asthma did not have marked influence on the observed associations (data not shown). The dose of vitamin D (among children receiving supplementation regularly) was not significantly associated with any of the outcomes, although there were some suggestions for increases in the occurrence of allergic rhinitis and asthma at higher doses (TABLE 3). The association between suspected rickets and risk of atopy, allergic rhinitis, or asthma was not significant after adjustment for social and behavioral risk factors.

DISCUSSION

Our findings from the population-based NFBC 1966 are the first to suggest that supplementation with vitamin D in infancy may increase the risk of allergic condi-

TABLE 3. Risk of allergy and asthma at age 31 by the use of vitamin D supplements and suspected rickets in infancy

	Atopy		Allergic rhinitis		Asthma	
	OR (95% CI)[a]	Adjusted OR (95% CI)[b]	OR (95% CI)[a]	Adjusted OR (95% CI)[b]	OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Use of vitamin D						
None/irregularly	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Regularly	1.66 (1.35–2.04)	1.33 (1.07–1.64)	1.46 (1.24–1.72)	1.33 (1.12–1.58)	1.35 (0.99–1.84)	1.33 (0.97–1.82)
Dose of vitamin D[c]						
<2000 IU	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
2000 IU	1.06 (0.48–2.34)	1.02 (0.46–2.29)	1.33 (0.71–2.49)	1.34 (0.71–2.53)	4.08 (0.56–30)	3.83 (0.53–27)
>2000 IU	0.72 (0.30–1.70)	0.77 (0.32–1.84)	1.54 (0.79–3.00)	1.70 (0.87–3.36)	4.27 (0.56–32)	3.98 (0.52–30)
Suspected rickets						
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Yes	0.58 (0.34–0.96)	0.61 (0.35–1.05)	0.70 (0.47–1.05)	0.73 (0.49–1.11)	0.82 (0.40–1.69)	0.80 (0.38–1.67)

[a]Adjusted for sex.

[b]Adjusted for sex, birth order, maternal education and age, social class in 1958, if mother follows health education, mother's state of mind, and desirability of pregnancy.

[c]Analyses restricted to children receiving vitamin D supplementation regularly.

tions in later life. The observed association between vitamin D supplementation and risk of allergic diseases is in line with a recent report on increased allergen-induced secretion of Th2-type cytokines (IL-4 and IL-13) and IgE production in mice treated with $1,25(OH)_2D$.[1] Together with our earlier observation on the beneficial effects of vitamin D on autoimmune diabetes,[11] these observations may suggest that vitamin D intake in infancy has long-term effects on immune regulation, possibly by inducing a shift toward a Th2-dominated immune response pattern. An alternative explanation for our findings could be provided by better hygiene in mothers who supplemented their children according to the recommendations, compared to others who did not. However, although there was a clear attenuation in the association between vitamin D supplementation and the risk of allergic conditions, these associations persisted after adjustment for the wide-range of social and behavioral indicators. In accordance with the contemporary dose recommendations, the majority of the infants in the NFBC 1966 received 2000 IU vitamin D per day, which is five times more than is currently recommended in Finland[24] and ten times greater compared to current U.S. recommendations.[25] In addition, the dose of $1,25(OH)_2D$ in the previous animal experiment was very high.[1,26] Therefore, these data do not suggest that vitamin D in the currently recommended levels would influence allergy risk.

Spanning an area from about 300 km on either side of the Arctic Circle, NFBC 1966 has a particularly interesting population for studies on vitamin D. The average daylight in the area is only 2 h per day in December, and even though it increases up to an average of 23 h per day in June, during the major part of the year cutaneous vitamin D synthesis is low compared to more southern areas. The limited exposure to sunlight allows us to have a good estimate on the total vitamin D intake from the first year of life. Breast milk contains only small amounts of vitamin D, and infant formulas were not fortified with the vitamin in the 1960s in Finland; therefore, lack of information on infant feeding is not likely to have affected our estimates of vitamin D intake. However, we had no information on vitamin D supplementation after the first year. According to contemporary recommendations, vitamin D supplementation was recommended to all children up to two years of age,[27] which may suggest that systematic supplementation in many cases was restricted to the first two years of life.

The main outcomes in our study were the presence of allergies and asthma during the past 12 months (at age 31 years). Therefore, cases in our study include individuals who had already developed the disease in childhood, as well as those with a late-onset condition. Although the exact age at allergy onset was unknown, we had some (unspecific) information on allergies and asthma from age 14 years. The observed association between frequency of vitamin D supplementation and allergy risk was repeated in the group of participants reporting these conditions already by age 14 (OR 1.33 for allergy/oversensitivity and 1.52 for asthma), and also in adult-onset cases reporting current symptoms but without any indication from the earlier survey (1.60 for atopy, 1.39 for allergic rhinitis, and 1.44 for asthma). However, because the information from age 14 is based on an open question that enquired about all chronic conditions, restricting the maximum number of conditions to two for any individual, the true prevalence of allergies and asthma at age 14 is underestimated; thus, these data need to be interpreted cautiously.

To conclude, our findings suggest an association between large-dose vitamin D supplementation in infancy and an increased risk of atopy, allergic rhinitis, and

asthma later in life. Further study is required to determine whether these observations could imply that vitamin D supplementation in infancy may have long-term effects on immune regulation, or if they reflect some unmeasured determinants of vitamin D supplementation.

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