High-Dose Vitamin D Supplementation Does Not Prevent Allergic Sensitization of Infants

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Objective To investigate the effect of vitamin D supplementation dose on allergic sensitization and allergic diseases in infants, and to evaluate whether vitamin D status in pregnancy and at birth are associated with infant allergy outcomes.

Study design Altogether, 975 infants participated in a randomized, controlled trial of daily vitamin D supplementation of 10 μg (400 IU) or 30 μg (1200 IU) from the age of 2 weeks. At 12 months of age, food and aeroallergen IgE antibodies were measured, and the occurrence of allergic diseases and wheezing were evaluated.

Results We found no differences between the vitamin D supplementation groups in food (OR, 0.98; 95% CI, 0.66-1.46) or aeroallergen sensitization at 12 months (OR, 0.76; 95% CI,0.34-1.71). Allergic diseases or wheezing did not differ between groups, except for milk allergy which occurred more often in infants administered 30 μg vitamin D compared with the 10 μg dose (OR, 2.23; 95% CI, 1.00-4.96). Infants with high cord blood 25-hydroxyvitamin D (≥100 nmol/L) had a higher risk of food allergen sensitization compared with those with lower 25(OH)D concentration (75-99.9 nmol/L; OR, 2.00; 95% CI, 1.19-3.39).

Conclusions High-dose vitamin D supplementation did not prevent allergic sensitization, allergic diseases, or wheezing during the first year of life. In contrast, we observed an increased risk of milk allergy in infants randomized to higher vitamin D supplementation, and an increased risk of allergic sensitization in infants with high cord blood vitamin D status, indicating a possible adverse effect of high concentrations of vitamin D. *(J Pediatr 2019;209:139-45)*.

Observational studies demonstrate a link between vitamin D status at birth and the development of allergic diseases. The results are, however, inconsistent. In a Taiwanese birth cohort, maternal vitamin D status was inversely related to allergic sensitization and atopic diseases in the offspring, whereas another study reported positive association of maternal and cord blood 25-hydroxyvitamin (25(OH)D) levels with children's risk for food allergy and allergic sensitization during the first 2 years of life.[1,2] A longitudinal follow-up study of children from birth to age 5 years found persistent vitamin D deficiency in childhood to be associated with eosinophilia and allergic sensitization.[3]

Similarly, some studies have reported vitamin D deficiency during pregnancy or in early childhood to be a risk factor for wheezing and later development of asthma,[4,5] whereas others have found no association.[6] Three randomized, controlled trials on vitamin D supplementation during pregnancy in prevention of allergic diseases and wheezing have been conducted.[7-10] One study examined the effect of maternal vitamin D supplementation during lactation on infantile allergic disorders, but no large-scale postnatal randomized trials exist.[11]

The Vitamin D Intervention in Infants (VIDI) study was a randomized controlled 24-month trial of daily 10 μg or 30 μg vitamin D supplementation administered to healthy infants that evaluated the effect of vitamin D supplementation on bone health and infections.[12] The aim of the present study was, as a secondary analysis, to investigate the effect of the 2 different vitamin D supplemental doses on early allergic sensitization and allergy-related clinical outcomes, physician-diagnosed allergic diseases, allergy symptoms, and wheezing, during the first year of life.

Methods

A total of 987 healthy infants, born in Kätilöopisto Helsinki Maternity Hospital, Finland, were randomized to receive daily vitamin D_3 supplementation of 10 μg

25(OH)D	25-Hydroxyvitamin

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(400 IU) or 30 μg (1200 IU) from 2 weeks to 24 months of age.[12] Mothers were of northern European ethnicity without regular medication and with a singleton pregnancy. Infants included in the study were born at term ($37^{0/7}$ to $42^{0/7}$ weeks of gestation) with a birth weight appropriate for gestational age (birth weight SDS between −2.0 and +2.0). Those requiring intravenous glucose, antibiotics, nasal continuous positive airway pressure for >1 day, phototherapy for >3 days, or nasogastric tube feeding for >1 day, and with seizures were excluded. Study recruitment occurred between January 2013 and June 2014. We obtained written informed consent from the parents. The study was conducted in accordance with the Declaration of Helsinki, and the Research Ethics Committee of the Hospital District of Helsinki and Uusimaa provided ethical approval (107/13/03/03/2012). The project protocol is registered on ClinicalTrials.gov (NCT01723852) and has been reported previously.[12,13]

Randomization to the 2 vitamin D supplementation groups was performed in blocks of 50 by a pharmacist at Helsinki University Hospital Pharmacy. Study preparations, identical in appearance, contained vitamin D_3 dissolved in medium-chain triglyceride oil (Orion Pharmaceuticals, Espoo, Finland) and were administered orally with 5 drops for both groups. The use of other vitamin D supplements was not allowed during the study. The study was double blinded, with participants and investigators masked to group assignment. Compliance with the vitamin D supplementation was assessed from study diaries in which the parents prospectively recorded dosing of the supplement.

Data Collection

Family demographics were obtained from hospital records and structured questionnaires during follow-up. Pregnancy serum samples were collected at 11 weeks of gestation on average during routine follow-up visits at prenatal clinics and stored in the Finnish Maternity Cohort serum bank maintained by the National Institute for Health and Welfare. We measured the 25(OH)D concentration from pregnancy serum samples, cord blood, and at 12 months with a fully automated immunoassay (IDS-iSYS, Immunodiagnostic System Ltd., Bolton, UK).[12] At 12 months, we measured specific IgE antibodies toward food allergens (cow's milk, egg white, wheat, cod, peanut, soy) and toward aeroallergens (birch, mugwort, timothy, horse, cat, dog, *Dermatophagoides pteronyssinus*, and *Cladosporium herbarum*) with ImmunoCAP (Phadia, Uppsala, Sweden) at the Laboratory of Helsinki University Hospital. Allergic sensitization to food or aeroallergens was defined as a specific IgE concentration of ≥0.35 kU/L.

At 12 months, parents completed structured allergy questionnaires based on a modified International Study of Asthma and Allergies in Childhood questionnaire that included questions on occurrence of physician-diagnosed food allergy ever (cow's milk, wheat, or any food), atopic eczema, or asthma, and allergy symptoms in the child.[14] Allergy symptoms including wheezing or breathing difficulty, persistent cough, and itchy rash were queried. Wheezing or breathing difficulty was defined as a positive answer to the question, "Has your child ever had wheezing or difficulty in breathing in the preceding 12 months?" Persistent cough was defined as a positive answer to the question, "Has your child had persistent coughing for at least 6 weeks in the preceding 12 months?" Itchy rash was defined as a positive answer to the question, "Has your child had dry, red or itchy skin requiring regular care in the preceding 12 months?"

The number of hospitalizations owing to bronchiolitis or wheezing during the first 12 months was calculated from study diaries in which parents recorded all their child's infections including data on infection type, symptoms, medication, and possible hospitalization during the vitamin D intervention trial.[12]

At 12 months, the dietary intake of vitamin D was determined from a 3-day food record administered by the parents or daycare personnel. Nutrient intakes were processed with AivoDiet software (Aivo Oy Finland, Turku, Finland), which used Fineli, the National Food Composition Database maintained by the National Institute for Health and Welfare, Finland. The calculated total vitamin D intake did not include intake from breast milk.[12]

Statistical Analyses

Normality of the continuous variables was determined by visual inspection and with the Kolmogorov-Smirnov test of normality. For group comparisons, independent samples *t*-test or Mann-Whitney *U* test were used in case of continuous variables and the Pearson χ^2 or Fisher exact test in case of categorical variables. To evaluate the effect of vitamin D supplementation group on food or aeroallergen sensitization and clinical allergy outcomes, logistic regression was applied, with adjustment for potential confounders based on the associations observed in the present study. Similarly, logistic regression was used to evaluate the effect of pregnancy, cord blood, and the 25(OH)D concentration at 12 months on food allergen sensitization. All analyses were performed by intention-to-treat principle using SPSS software (IBM SPSS Statistics for Windows, version 22; IBM, Armonk, New York).

Results

Characteristics

A total of 975 infants fulfilled the trial inclusion criteria; 489 were randomized to 10 μg and 486 to 30 μg daily vitamin D supplementation. Study enrollment, allocation, and follow-up is presented (**Figure**; available at www.jpeds.com).

At 12 months, a total of 865 infants (91.5%) attended the follow-up visit. Parental history of allergic diseases or other baseline characteristics did not differ between intervention groups (**Table I**). Breastfeeding was continued for >6 months for 78.9% of the infants, with a mean duration of 10.7 months. Pregnancy or baseline cord blood 25(OH)D concentrations did not differ between the intervention groups (**Table I**). In pregnancy and at birth, 96.5% of the mothers and 95.7% of the infants, respectively, were

Table I. Characteristics of the study participants randomized to 10 or 30 μg vitamin D supplementation

Characteristics	Vitamin D 10 μg	Vitamin D 30 μg
Child	489/975 (50)	486/975 (50)
Girls	242/489 (50)	243/486 (50)
Boys	247/489 (50)	243/486 (50)
Birth weight, g*	3514 ± 379	3565 ± 410
Birth length, cm	50.3 ± 2	50.4 ± 2
Season of birth		
Winter	100/489 (20)	89/486 (18)
Spring	197/489 (40)	203/486 (42)
Summer	108/489 (22)	109/486 (22)
Autumn	84/489 (17)	85/486 (17)
Siblings	153/444 (34)	178/448 (40)
Breastfeeding >6 months	330/428 (77)	344/426 (81)
Daycare attendance at 12 months	15/435 (3)	23/431 (5)
Pets	131/380 (35)	129/377 (34)
Baseline 25(OH)D concentration, nmol/L†		
Pregnancy	82.0 ± 22.1	81.6 ± 18.0
Cord blood	81.7 (28)	81.3 (24)
Mother		
History of allergic disease		
Asthma	28/403 (7)	30/411 (7)
Allergic rhinitis	128/403 (32)	123/411 (30)
Atopic eczema	74/403 (18)	61/411 (15)
Food allergy	70/403 (17)	59/411 (14)
Smoking	17/427 (4)	15/442 (3)
Educational level‡		
Low	119/437 (27)	107/446 (24)
High	318/437 (73)	339/446 (76)
Use of vitamin D supplements in pregnancy	407/430 (95)	406/433 (94)
Father		
History of allergic disease		
Asthma	27/403 (7)	38/411 (9)
Allergic rhinitis	136/403 (34)	158/411 (39)
Atopic eczema	47/403 (12)	44/411 (11)
Food allergy	56/403 (14)	62/411 (15)
Smoking	60/419 (14)	64/425 (15)
Educational level‡		
Low	164/434 (38)	164/436 (38)
High	270/434 (62)	272/436 (62)

Values are n/N (%) or mean ± SD.
*Statistically significant difference between groups ($P = .042$).
†n = 809 for pregnancy 25(OH)D; n = 955 for cord blood 25(OH)D.
‡Low is defined as less than a bachelor's degree and high as at least a bachelor's degree.

vitamin D sufficient, defined as 25(OH)D ≥50 nmol/L. At 12 months, the mean 25(OH)D concentration was significantly higher in the 30 μg vitamin D group compared with the 10 μg group (115.0 nmol/L vs 82.7 nmol/L; $P < .001$). At 12 months, the mean daily vitamin D intake from food was 6.2 (SD, 3.7) μg with no differences between the groups ($P = .322$).

Effect of Vitamin D Supplementation on IgE Sensitization

At 12 months of age, we obtained serum samples for measurement of specific IgE antibodies from 723 of the 975 children (74.2%; ie, from 83.6% of those attending the 12-month follow-up visit). IgE sensitization to food allergens was observed in 114 of 723 children (15.8%) and to aeroallergens in 25 of 719 children (3.5%). Food IgE sensitization was most common to egg white (10.4%) and cow's milk (5.8%; Table II) and occurred more often in children born to parents with a history of allergic disease (OR, 1.16; 95% CI, 1.02-1.33) and in those attending daycare at 12 months (OR, 2.45; 95% CI, 1.13-5.29). Season of birth, duration of breastfeeding, existence of older siblings, or parental smoking did not affect the risk of allergic sensitization at 12 months. We found no difference in specific IgE sensitization between the intervention groups (Table II). The results did not change after adjustment for potential confounding factors (ie, parental history of allergy or daycare attendance). We also repeated the analyses using a higher cut-off for food IgE sensitization (ie, food IgE of >0.5 and 5.0 kU/L), but the findings remained unaltered showing no differences in IgE sensitization between the groups. The distribution of cow's milk IgE did not differ between groups: the mean cow's milk IgE was 0.94 (SD 2.3) kU/L in the 10 μg vitamin D group and 1.35 (SD 4.2) kU/L in the 30 μg group ($P = .866$). No statistically significant differences were seen in cow's milk IgE sensitization stratified by birth season ($P = .872$).

Effect of Vitamin D Supplementation on Allergic Diseases and Allergy Symptoms

Data on physician-diagnosed allergic diseases and allergy symptoms reported by parents were obtained from 770 of 975 children (79%) at 12 months. We found no difference between the intervention groups in physician-diagnosed wheat allergy, any food allergy, atopic eczema, or asthma (Table III). Physician-diagnosed cow's milk allergy was reported more often in the group receiving 30 μg vitamin D supplementation compared with the 10 μg vitamin D group (20/387 [5.2%] vs 9/377 [2.4%]; $P = .044$; Table III). The findings were unaltered after adjustment for potential confounding factors, that is, a parental history of allergic disease and the duration of breastfeeding. Of infants with reported cow's milk allergy (n = 29), IgE sensitization to cow's milk was observed in only 4 of 25 children (16%; 4 missing blood samples).

Wheezing or breathing difficulty during the first year of life was reported in 76 of 763 of the cohort (10.1%) with no difference between the intervention groups (Table III). Likewise, the number of children hospitalized for bronchiolitis or wheezing was similar in both groups (Table III). At 12 months, physician-diagnosed asthma was rare, with only 1 child reported to have an asthma diagnosis.

Allergic Sensitization according to Vitamin D Status

We observed no correlation between pregnancy or cord blood 25(OH)D and specific food or aeroallergens IgE concentrations at 12 months ($P > .1$ for all). However, when dividing cord blood 25(OH)D concentration in subgroups <75 nmol/L (n = 295), 75.0-99.9 nmol/L (n = 286), and ≥100 nmol/L (n = 126), the risk for IgE sensitization to food allergens was higher in infants with cord blood 25(OH)D concentration was >100 nmol/L compared with

Table II. Allergic sensitization to food or aeroallergens at 12 months in infants randomized to 10 μg or 30 μg vitamin D supplementation

Allergic sensitizations at 12 months	All	Vitamin D 10 μg	Vitamin D 30 μg	*P* value*	OR (95% CI)†
Food IgE sensitization	**114/723 (15.8)**	**57/358 (15.9)**	**57/365 (15.6)**	**.910**	**0.98 (0.66-1.46)**
Cow's milk	42/720 (5.8)	21/358 (5.9)	21/362 (5.8)	.974	
Wheat	17/720 (2.4)	10/358 (2.8)	7/362 (1.9)	.448	
Egg white	75/720 (10.4)	40/358 (11.2)	35/362 (9.7)	.509	
Cod	3/720 (0.4)	2/358 (0.6)	1/362 (0.3)	.622	
Soybean	8/720 (1.1)	6/358 (1.7)	2/362 (0.6)	.175	
Peanut	23/720 (3.2)	16/358 (4.5)	7/362 (1.5)	.053	
Aeroallergen IgE sensitization	**25/719 (3.5)**	**14/356 (3.9)**	**11/363 (3.0)**	**.509**	**0.76 (0.34-1.71)**
Birch	10/718 (1.4)	6/356 (1.7)	4/362 (1.1)	.543	
Mugwort	0/718	0	0	‡	
Timothy	3/718 (0.4)	3/356 (0.8)	0/362 (0)	.121	
Dog	13/718 (1.8)	7/356 (2.0)	6/362 (1.7)	.765	
Cat	10/718 (1.4)	5/356 (1.4)	**5/362 (1.4)**	**0.979**	
Horse	2/716 (0.3)	2/355 (0.6)	0/361 (0)	.245	
Dermatophagoides pteronyssinus	1/718 (0.1)	1/356 (0.3)	0/362 (0)	.496	
Cladosporium herbarum	1/718 (0.1)	1/356 (0.3)	0/362 (0)	.496	

Allergic sensitization defined as serum food or aeroallergen IgE of ≥0.35 kU/L.Total food and aeroallergen IgE sensitization is presented in bold.
Values are n/N (%).
*P values are from a Pearson χ^2 or Fisher exact test when the cell count is ≤5.
†OR from logistic regression with 95% CI.
‡Not applicable owing to the small number of subjects.

those with a concentration between 75.0 and 99.9 nmol/L (OR, 2.00; 95% CI, 1.19-3.39; Table IV). The finding persisted after adjustment for potential confounding factors, including adjustment for the intervention group (Table IV). No similar effect was seen when analyzed by pregnancy 25(OH)D concentration (Table IV). When analyzed according to 25(OH)D concentration measured at 12 months divided in the same subgroups (<75.0, 75.0-99.9, ≥100 nmol/L), we found no difference in allergic sensitization to food allergens in the unadjusted model (Table IV). However, in the adjusted analysis, the risk for food IgE sensitization was higher in infants with a 25(OH)D concentration at 12 month of >100 nmol/L compared with those with a concentration between 75.0 and 99.9 nmol/L. Proportions of aeroallergen-positive infants did not differ according to maternal, cord blood, or 25(OH)D concentration at 12 months (data not shown).

Discussion

In this randomized, controlled trial comparing daily vitamin D supplementation of 10 μg and 30 μg in infancy, we observed no differences in allergic sensitization between the groups at 12 months of age. Physician-diagnosed allergic diseases and occurrence of wheezing were similar in both intervention groups. Exception was for cow's milk allergy, which was reported more often in infants administered 30 μg vitamin D daily compared with the 10 μg dose. In addition, we observed that infants with high cord blood 25(OH)D levels before the intervention had an increased risk for allergic sensitization compared with those with a lower vitamin D status. The main observation of our study is that increasing vitamin D status by higher vitamin D supplementation in infancy does not protect from allergic sensitization, allergic diseases, or wheezing during the first year of life.

Table III. Parental report of physician-diagnosed allergic disease and allergy symptoms at 12 months in infants randomized to 10 or 30 μg vitamin D supplementation

Allergic disease or symptoms	All	Vitamin D 10 μg	Vitamin D 30 μg	*P* value*	OR (95% CI)†
Physician-diagnosed allergic disease					
Cow's milk allergy	29/764 (3.8)	9/377 (2.4)	20/387 (5.2)	.044	2.23 (1.00-4.96)
Wheat allergy	11/762 (1.4)	5/377 (1.3)	6/385 (1.6)	.788	1.18 (0.36-3.89)
Any food allergy	47/770 (6.1)	20/382 (5.2)	27/388 (7.0)	.318	1.35 (0.75-2.46)
Atopic eczema	128/769 (16.6)	72/381 (18.9)	56/388 (14.4)	.097	0.72 (0.49-1.01)
Asthma	1/765 (0.1)	1/378 (0.3)	0/387 (0)	.494	‡
Allergy symptoms					
Wheezing or breathing difficulty	76/763 (10.0)	39/380 (10.3)	37/383 (9.7)	.781	0.94 (0.58-1.50)
Hospitalization owing to bronchiolitis or wheezing	25/901 (2.8)	14/451 (3.1)	11/450 (2.4)	.547	0.78 (0.35-1.74)
Persistent cough	46/756 (6.1)	20/377 (5.3)	26/379 (6.9)	.371	1.32 (0.72-2.40)
Itchy rash	126/765 (16.5)	72/380 (18.9)	54/385 (16.5)	.067	0.70 (0.48-1.03)

Values are n/N (%) unless otherwise indicated.
*P values from Pearson χ^2 or Fisher exact test when the cell count is ≤5.
†OR from logistic regression with 95% CI.
‡Not applicable owing to small the number of subjects.

Table IV. Allergic sensitization to food allergens at 12 months by 25(OH)D concentration in pregnancy, cord blood and at 12 months

	Food IgE sensitization (≥0.35 kU/L)				
25(OH)Ds (nmol/L)	n/N (%)	Unadjusted OR (95% CI)*	*P* value	Adjusted OR (95% CI)†	*P* value
Pregnancy					
<75.0	38/224 (17.9)	1.28 (0.79-2.08)	.313	1.40 (0.83-2.35)	.202
75.0-99.9	40/291 (13.7)	Reference		Reference	
≥100	20/99 (20.2)	1.59 (0.88-2.88)	.126	1.47 (0.76-2.89)	.244
Cord blood					
<75.0	43/295 (14.6)	1.05 (0.66-1.67)	.839	1.11 (0.67-1.85)	.689
75.0-99.9	40/286 (14.0)	Reference		Reference	
≥100	31/126 (24.6)	2.00 (1.19-3.39)	.009	2.18 (1.25-3.80)	.006
12 months					
<75.0	26/149 (17.4)	1.32 (0.76-2.30)	.331	1.82 (0.96-3.47)	.069
75.0-99.9	34/246 (13.8)	Reference		Reference	
≥100	54/325 (16.6)	1.24 (0.78-1.98)	.360	2.10 (1.18-3.71)	.011

*OR from logistic regression with 95% CI.
†Adjusted for vitamin D supplementation group, sex, parental allergy history, and attendance in daycare at 12 months of age.

This study examined the effects of postnatal vitamin D supplementation on allergic diseases in a randomized, controlled setting. Prenatal vitamin D supplementation studies show mixed results. Vitamin D supplementation, administered daily or in a single dose during the third trimester of pregnancy, did not decrease the risk of allergic diseases in the first 3 years of life.[7] Two randomized trials examined high-dose (70 μg/d and 110 μg/d) vitamin D supplementation regimens compared with a standard dose (10 μg/d) during pregnancy on the risk of recurrent wheezing, asthma, or eczema in the offspring at 3 years of age.[8,9] Both studies failed to report a statistically significant decrease in the risk of asthma/wheeze with higher prenatal vitamin D supplementation compared with the standard dose. Subsequently, the 2 research groups performed a combined analysis of these trials, which showed that risk of asthma/recurrent wheeze was in fact decreased by 26% in the offspring.[15]

We found no effect of postnatal vitamin D supplementation on the risk of wheezing at 12 months. It has been suggested that vitamin D has a role in fetal lung development, and vitamin D deficiency alters normal lung function and structure.[16,17] Our mothers and infants were, however, mostly vitamin D sufficient during pregnancy and at birth, and during the intervention the 25(OH)D concentration increased to relatively high levels in the 30 μg vitamin D group. Our results indicate that, in already vitamin D-sufficient infants, there is no advantage of higher vitamin D supplementation against wheezing in the early postnatal period. This finding is supported by our initial finding of vitamin D supplementation not decreasing the incidence of infections during the first 2 years of life, because early childhood wheezing is often related to respiratory infections.[12]

Unexpectedly, the occurrence of cow's milk allergy was more frequent in infants supplemented with 30 μg of vitamin D compared with the 10 μg dose. The association of vitamin D supplementation in infancy and an increased risk of allergic conditions have also been reported by others. In a Finnish population-based study, high-dose vitamin D supplementation in infancy was associated with an increased risk of atopy, allergic rhinitis, and asthma in adulthood.[18] Similarly, in a Japanese study, short-term vitamin D supplementation of lactating mothers of breast-fed infants with facial eczema did not decrease the severity of infantile eczema, but instead increased the risk of later food allergy.[11] Furthermore, Weisse et al reported that maternal and cord blood 25(OH)D levels were positively associated with children's risk for food allergy and food allergen sensitization during the first 2 years of life.[2]

The risk of IgE sensitization to food allergens at 12 months of age differed according to cord blood vitamin D status. We observed that infants with cord blood 25(OH)D concentrations in the highest range (>100 nmol/L) had increased the odds of food IgE sensitization at 12 months. Previously, conflicting results have been reported. Both low, and, similar to our study, high cord blood 25(OH)D concentrations have been associated with IgE sensitization, suggesting more a U-shaped or nonlinear association.[19-21] Because vitamin D deficiency (<50 nmol/L) was rare in our cohort, we could not confirm the U-shaped association.

The molecular mechanisms of the immunomodulatory effects of vitamin D are not fully understood. Vitamin D has effects on the innate and adaptive immune response, and for example induces antimicrobial peptide production, and modulates T-cell, dendritic cell, and B-cell functions.[22] In relation to allergy, vitamin D may be important in the maintenance of type 1 T helper cell–type 2 T helper cell balance, and by modulating regulatory T cells, which are essential in development of immune tolerance.[23] Interestingly, 2 studies reported a correlation between high cord blood 25(OH)D levels and low numbers of cord blood regulatory T cells, providing a biological explanation for how high 25(OH)D levels could increase the risk for allergic sensitization.[2,24] Furthermore, the response to vitamin D supplementation may differ between individuals owing to genetic and epigenetic factors.[25]

The main strength of our study is the setting: a large, randomized, controlled trial with good adherence to the study protocol.[12] We measured 25(OH)D concentrations repeatedly, and allergy outcomes included both clinical and laboratory data. As a limitation, we acknowledge the study to be a secondary analysis of a randomized trial with the sample size not computed for the allergy outcomes. Some of the observed findings could have arisen by chance owing to the multiple comparisons performed. The initial trial length was for 24 months, but unfortunately we were able to measure IgE levels only at the 12 months of follow-up. However, food sensitization prevalence is highest at 12 months of age and may identify children at risk for subsequent allergic disease. In addition, bronchiolitis and wheezing in infancy may serve as early predictors of asthma justifying the selected time-point for outcome evaluation.[26,27] Our data on clinical allergic diseases were based on parental report, which may have led to bias. At 12 months, the prevalence of food allergies in our study was similar to that of the general population, whereas, for example, wheezing was most likely underreported by parents.[28,29] However, by measurement of specific IgE levels from a large sample of healthy infants, we were able to obtain unbiased data on allergic sensitization. Furthermore, it is likely that the reporting error would be similar in both intervention groups. Our study lacked vitamin D-deficient infants, which is most likely the result of current health policies in Finland, that is, the recommendation of daily 10 μg vitamin D supplementation to all pregnant women and fortification of food products with vitamin D.[30] Still, the improved vitamin D status at birth enabled us to detect the positive association of high cord blood 25(OH)D concentration with allergic sensitization, which emphasizes the need for further studies concerning possible adverse health effects of high 25(OH)D levels and the optimal vitamin D dosage.[31]

Conclusions

We observed that, in vitamin D-sufficient infants, higher vitamin D supplementation did not decrease allergic sensitization, allergic diseases, or wheezing during the first year of life. However, the risk for allergic sensitization was higher in infants with high cord blood 25(OH)D concentration, suggesting that high vitamin D levels at birth may modify the immune response related to allergy development. However, the connection of vitamin D and allergy is complex and requires further studies. Because allergic diseases manifest more clearly in later childhood, long-term follow-up of the study cohort is essential. ■

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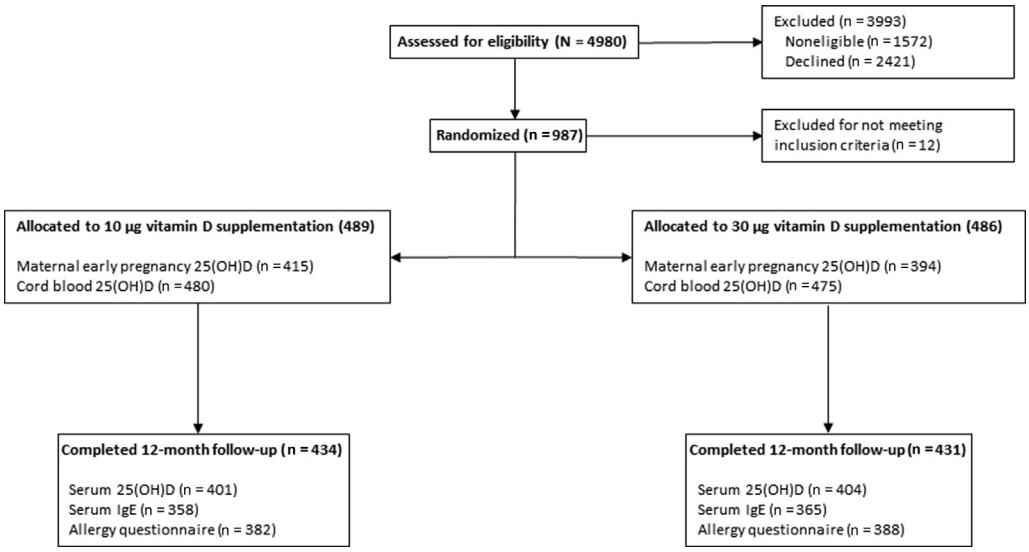

Figure. Flow chart of the study enrollment, allocation, and follow-up.