

Vitamin D intake during the first 4 years and onset of asthma by age 5: A nested case-control study

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Abstract

Background: Early-life vitamin D intake has been linked to asthma risk in childhood, but the role of longitudinal vitamin D exposure has not been previously evaluated. We investigated the association between vitamin D intake during the first 4 years of life and asthma risk by age 5.

Methods: Within a Finnish population-based birth cohort, 182 incident asthma cases were matched to 728 controls on sex, genetic risk for type 1 diabetes, delivery hospital, and time of birth. Vitamin D intake was assessed by age-specific 3 day food records. Parents completed a validated version of the International Study of Asthma and Allergies in Childhood questionnaire at 5 years.

Results: At 3 months, supplements were the main source of vitamin D intake; intake from foods increased from 3 months on, mainly from fortified milk products. Vitamin D intake at each specific age was associated with an increased risk of any asthma, atopic, and non-atopic asthma, but only intake at 1 and 2 years was statistically significantly associated with asthma. Longitudinal vitamin D intake was associated with an increased risk of asthma (OR 1.24; 95%CI 1.00-1.53).

Conclusions: Increased vitamin D intake in childhood, particularly intake at 1 and 2 years of age, may increase risk of childhood asthma. This might reflect a true effect or residual confounding by lifestyle or environmental factors. Repeated assessment of vitamin D intake allowed evaluation of the longitudinal and age-dependent impact of vitamin D on the risk of asthma. Further longitudinal studies are required to confirm or question these findings.

KEYWORDS

asthma, children, diet, longitudinal study, vitamin D

1 | INTRODUCTION

The immunoregulatory functions of vitamin D and its potential impact on asthma and allergy have stimulated several studies, particularly the role of prenatal and early-life vitamin D exposures in childhood asthma.¹⁻³ Vitamin D reduces inflammation by modulating cytokine production and by inhibiting Th2 cell responses; hence, insufficient vitamin D intake is perceived to elevate inflammatory responses and increase risk of asthma and allergy.¹⁻³

A systematic review of observational studies on maternal intake of dietary vitamin D during pregnancy showed that increased maternal intake may reduce the risk of asthma in the offspring.⁴ As a follow-up, two clinical trials reported 4%-6% non-significant lower absolute risk of asthma-like symptoms in offspring of mothers receiving additional vitamin D supplementation on top of usual care during pregnancy compared to those receiving placebo containing the recommended dose of vitamin D.⁵⁻⁷ On the other hand, two recent systematic reviews on the role of circulating vitamin D⁸ and supplemental intake⁹ during early life in the development of asthma in childhood indicated that existing studies are of poor quality, with mixed findings, although concluded that low serum vitamin D concentrations may increase asthma risk.⁸

The routes of dietary transfer during pregnancy (via the placenta) and early life (via the child's own intake) are different, and this may indicate differential immunological effects between prenatal and early-life dietary exposures. There may be a critical time window for the effect of diet on disease outcomes.^{10,11} Well-designed and longitudinal birth cohort studies will help to clarify the putative role of dietary vitamin D during early life in childhood asthma and allergy.^{10,11} Up to date, no study has evaluated the longitudinal intake of vitamin D during early life and childhood asthma. The aim of this study was therefore to investigate the longitudinal and age-dependent associations between dietary vitamin D intake during the first 4 years of life and asthma risk by the age of 5 years.

2 | METHODS

2.1 | Subjects and study design

The Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study started in 1994 and has been described in detail elsewhere.^{12,13} The

cohort comprised newborn infants from Turku, Tampere, and Oulu University hospitals, who were recruited on the basis of human leukocyte antigen (HLA)-conferred susceptibility to type 1 diabetes and followed at 3- to 12-month intervals for diabetes-associated antibodies, growth, viral infections, and environmental exposures. The local ethical committees approved the study, and written informed consent was obtained from the parents of the children.

In 1996 in Oulu and 1997 in Tampere, a nutritional component (DIPP Nutrition Study) was initiated within the DIPP study evaluating the role of fetal and early-life diet in the development of type 1 diabetes, asthma, allergies, overweight, and obesity. Altogether, 7782 children were invited to take part in the study and 6081 participated. At the age of 5 years, 4075 children who were still participating in the dietary follow-up were invited to take part in the allergy study by completing a modified version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire on the child's history of allergic symptoms and to provide a blood sample for the measurement of IgE antibodies for common food and inhalant allergens; 3781 (93%) participated in the study.^{14,15}

The current study is a case-control analysis nested within the DIPP Nutrition cohort and comprising all incident asthma cases ($n = 182$) and four randomly selected matched controls ($n = 728$). The controls were matched to the cases on sex, genetic risk for type 1 diabetes (high/moderate risk), delivery hospital (Oulu or Tampere), and time of birth (range ± 3 months). The control must have been observed for asthma until the age of 5 years and must not come from the same family as the case. The controls were selected independently, and thus, one control child can be a control for more than one case and can become a case at a later time point. All subjects must have completed the ISAAC questionnaire and have at least one 3 day food record available for analysis.

2.2 | Dietary assessment

Child's diet was measured by means of age-specific 3 day food records at the ages of 3, 6, and 12 months, and annually from the age of 1 to 6 years. Parents completed the food records at home and at daycare by the daycare personnel.¹⁶ Families and daycare personnel recorded every food, drink, supplements, etc., that the child had consumed during the recording days. The time and place of eating, type and amounts of foods, drinks and supplements, food preparation

methods, brand names, and recipes were inquired. Identification of foods and dietary supplements was undertaken by continuously updated food-product brochures. Trained nutrition researchers entered the food record data. Food and nutrient intakes were calculated using Finnish national food database Fineli and an in-house software developed at the National Institute for Health and Welfare, Finland.¹⁶

2.3 | Assessment of asthma and analysis of allergen-specific IgEs

At age 5 years, families completed the modified ISAAC questionnaire on the child's and parental history of allergic symptoms and asthma as well as, for example, pets at home during the first year of life. The asthma component of the questionnaire has been validated, resulting in excellent validity estimates.¹⁷ Asthma was defined as doctor-diagnosed asthma plus either any wheezing symptom or use of asthma medication during the past 12 months preceding the completion of the questionnaire. Age of the child at the diagnosis of asthma was determined by the question "At what age was asthma diagnosed?" A blood sample was also obtained at the age of 5 years for the analysis of serum IgE levels, testing for egg, cow's milk, fish, wheat, house dust mite, cat, timothy grass, and birch allergens. A value of ≥ 0.35 kU/L was taken as cutoff for IgE positivity. We defined atopic asthma as IgE-positive asthma and non-atopic asthma as IgE-negative asthma.

2.4 | Socio-demographic and perinatal characteristics

Parents completed a structured questionnaire after delivery, collecting information on the child's sex, maternal age, maternal education, and number of siblings. Mode of delivery, birthweight, maternal smoking status, gestational age, and number of previous deliveries were obtained from the medical birth registries of Oulu and Tampere University hospitals.

2.5 | Statistical analysis

We used conditional logistic regression to examine the relation of background characteristics to asthma risk. We estimated the mean intake of vitamin D at the different ages from foods and supplements and both combined. Similarly, we calculated the mean vitamin D intake from different food sources and estimated the proportional contribution of each food source to total vitamin D intake.

The association between vitamin D intake and the risk of asthma at 5 years was estimated both for each age of vitamin D assessment (3 months to 4 years) and longitudinally. The age-specific associations were estimated using conditional logistic regression. For the longitudinal association, we used generalized estimating equations (GEE)¹⁸ Vitamin D was treated as a continuous variable in the analysis but was $\log(x + 1)$ transformed before analyses.

In both age-specific and longitudinal models, the following confounding variables were used in the adjusted models: gestational age, maternal age, maternal smoking during pregnancy, number of previous deliveries, maternal asthma or allergic rhinitis, paternal asthma or allergic rhinitis, birthweight, mode of delivery, maternal vocational education, pets at home during first year of life, maternal vitamin D intake during pregnancy, and duration of total breastfeeding.

Given missing values in the intake of vitamin D and across the potential confounding variables, we performed multiple imputations following the algorithm proposed by Nevalainen et al for use with longitudinal data.¹⁸ We then repeated these analyses using the imputed data. We took multiplicity issues into account by cautious interpretation of the results. Statistical significance was taken as two-sided P -value $< .05$. SAS version 9.2 (SAS Institute, Cary, NC, USA) was used for the analyses.

3 | RESULTS

3.1 | Characteristics of the study population

The analysis included 182 and 623 unique cases and controls (Table 1). Control children had longer duration of gestation, longer duration of breastfeeding, and were less likely to have allergic parents (Table 1).

3.2 | Intake of vitamin D from 3 months to 4 years and sources of intake

At 3 months of age, most vitamin D intake of both cases and controls came from supplements (Table 2). Vitamin D intake from foods increased from 3 months to 6 months and then decreased afterward. On the other hand, intake from supplements continuously decreased from 3 months on (Table 2). Overall, mean total vitamin D intake continuously decreased by age after the first 2 years as a result of decreasing supplemental vitamin D intake during this period (Table 2).

During the first year, most intake of vitamin D from foods came from fortified milk and milk products (accounting for 80% to 100% of the total vitamin D intake) (Table 3). As the proportional contribution of milk and milk products to total vitamin D intake decreased over time, the contribution of other foods (fortified dietary fats; fish products; and other foods) increased, each food group contributing comparable amount of intake in cases and controls (Table 3).

3.3 | Association between vitamin D intake and asthma by age of vitamin D assessment

In the complete case analyses, the strongest evidence of an association was seen for vitamin D intake at 1 and 2 years of age (Table 4). These results were similar to the multiple imputation results, in which vitamin D intake at 1 and 2 years was significantly associated with

TABLE 1 Distributions of background characteristics and their associations with asthma (odds ratio [OR], 95% confidence interval [95% CI])

Characteristic	All ^a N = 805	Cases N = 182	Controls N = 623	OR (95% CI)	P-value
Maternal age (y), n(%)					.464
<25	136 (17)	34 (19)	102 (16)	1	
25–29	282 (35)	64 (35)	218 (35)	0.87 (0.54–1.42)	
30–34	248 (31)	59 (32)	189 (30)	0.92 (0.56–1.52)	
≥35	139 (17)	25 (14)	114 (18)	0.63 (0.34–1.15)	
Maternal vitamin D intake during pregnancy, median micrograms (IQR)					
Intake from food	4.9 (3.4–7.0)	4.5 (3.2–6.7)	5.0 (3.5–7.1)	0.96 (0.90–1.03)	.262
Intake from supplement	0.0 (0.0–2.2)	0 (0–1.9)	0.0 (0.0–2.4)	0.96 (0.90–1.04)	.359
Total intake	6.0 (3.9–9.3)	5.5 (3.5–9.4)	6.1 (4.1–9.3)	0.96 (0.92–1.01)	.170
Gestational age (wk), in quarters, n(%)					.015
<38.9	181 (22)	49 (27)	132 (21)	1	
38.9–39.9	207 (26)	57 (31)	150 (24)	1.02 (0.64–1.60)	
40.0–40.7	214 (27)	36 (20)	178 (29)	0.54 (0.32–0.88)	
>40.7	198 (24)	39 (21)	159 (26)	0.62 (0.38–1.02)	
Missing information	5 (1)	1 (1)	4 (1)		
Mode of delivery, n(%)					.794
Vaginal	690 (86)	155 (85)	535 (86)	1	
Cesarean section	110 (13)	26 (14)	84 (13)	1.06 (0.67–1.70)	
Missing information	5 (1)	1 (1)	4 (1)		
Duration of total breastfeeding, median months (IQR)	7.0 (3.9–10.5)	6.0 (3.0–9.0)	7.0 (4.0–11.0)	0.96 (0.93–1.00)	.039
Number of previous deliveries, n(%)					.119
0	374 (47)	80 (44)	294 (47)	1	
1	253 (31)	66 (36)	187 (30)	1.24 (0.84–1.82)	
2	108 (13)	26 (14)	82 (13)	1.18 (0.70–1.98)	
≥3	63 (8)	7 (4)	56 (9)	0.46 (0.20–1.06)	
Missing information	7 (1)	3 (2)	4 (1)		
Maternal smoking during pregnancy, n(%)					.598
No	710 (88)	163 (90)	547 (88)	1	
Yes	69 (9)	14 (8)	55 (9)	0.84 (0.45–1.60)	
Missing information	26 (3)	5 (2)	21 (3)		
Maternal asthma or allergic rhinitis, n(%)					<.0001
No	373 (46)	57 (31)	316 (51)	1	
Yes	405 (50)	120 (66)	285 (46)	2.27 (1.60–3.26)	
Missing information	27 (3)	5 (3)	22 (3)		
Paternal asthma or allergic rhinitis, n(%)					.001
No	445 (55)	84 (46)	361 (58)	1	
Yes	316 (39)	89 (49)	227 (36)	1.80 (1.27–2.60)	
Missing information	44 (5)	9 (5)	35 (6)		
Maternal vocational education, n(%)					.719
None	42 (5)	8 (5)	34 (5)	1	
Vocational school or course	216 (27)	48 (26)	168 (27)	1.32 (0.56–3.12)	
Secondary vocational education	365 (45)	86 (47)	279 (45)	1.42 (0.62–3.23)	
University studies or degree	171 (21)	33 (18)	138 (22)	1.15 (0.48–2.76)	
Missing information	11 (1)	7 (4)	4 (1)		

(Continues)

TABLE 1 (Continued)

Characteristic	All ^a N = 805	Cases N = 182	Controls N = 623	OR (95% CI)	P-value
Birthweight (grams), in quarters, n(%)					.163
<3238	200 (25)	56 (31)	144 (23)	1	
3238–3589	196 (24)	42 (23)	154 (25)	0.72 (0.45–1.16)	
3590–3900	208 (26)	46 (25)	162 (26)	0.73 (0.46–1.14)	
>3900	196 (24)	37 (20)	159 (25)	0.60 (0.36–0.94)	
Missing information	5 (1)	1 (1)	4 (1)		
Pets at home during first year of life, n(%)					.941
No	546 (68)	123 (67)	423 (68)	1	
Yes	221 (27)	52 (29)	169 (27)	1.01 (0.70–1.50)	
Missing information	38 (5)	7 (4)	31 (5)		

^aOf the 182 cases and 728 matched controls included in this study, 76 children served as control for more than one case but were included only once in the total number of controls in the analysis; 15 controls became cases at later date and were counted only as cases.

IQR, interquartile range.

TABLE 2 Intake of vitamin D between 3 mo and 4 y in asthma cases and controls

Age at vitamin D measurement	Frequency		Vitamin D intake from foods Mean µg (SD)		Vitamin D intake from supplements Mean µg (SD)		Total vitamin D intake Mean µg (SD)	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
3 mo	172	608	4.06 (5.52)	3.56 (5.23)	6.78 (3.54)	7.30 (3.19)	10.84 (4.64)	10.86 (4.71)
6 mo	165	594	6.10 (5.15)	5.32 (4.85)	6.65 (3.22)	6.78 (3.54)	12.75 (4.38)	12.10 (4.15)
1 y	157	541	5.84 (4.01)	4.96 (3.83)	6.27 (3.36)	6.07 (3.54)	12.11 (4.73)	11.03 (4.70)
2 y	108	395	3.68 (2.78)	3.05 (2.53)	5.20 (4.18)	4.25 (3.95)	8.88 (4.68)	7.30 (4.90)
3 y	69	259	2.96 (2.06)	3.26 (2.05)	3.57 (5.03)	2.23 (3.44)	6.53 (5.93)	5.49 (4.42)
4 y	35	132	3.76 (2.34)	3.53 (2.04)	2.76 (4.21)	1.59 (2.89)	6.51 (5.18)	5.12 (3.65)

increased risk of any asthma and non-atopic asthma, also after adjustment for possible confounders (Table 5).

3.4 | Association between longitudinal vitamin D intake and asthma

Taking into account vitamin D intake from 3 months to 4 years in a longitudinal analysis, increasing intake of vitamin D was associated with an increased risk of asthma and its atopic and non-atopic asthma phenotypes in both the complete case (Table 4) and multiple imputation (Table 5) analyses.

4 | DISCUSSION

Examining age-specific and longitudinal associations between vitamin D intake during early childhood and asthma onset by 5 years, we observed that, whereas increasing vitamin D intake at each specific age after 3 months and longitudinally appeared to increase the risk of asthma, only intake at the ages of 1 and 2 years significantly increased the risk of asthma. These associations were similar when we examined any asthma and by atopic phenotypes.

The DIPP Nutrition Study is a well-defined population-based prospective birth cohort with careful and repeated assessments of diet

from pregnancy up to early childhood. This provided a unique setting to examine longitudinal and age-dependent associations between vitamin D and childhood asthma. The collection of dietary data prior to asthma and participants unselected by the history of allergy helped minimize differential reporting of dietary intake. The assessment of dietary intake may, however, not exclude some errors associated with food records. We minimized these by carefully instructing families and daycare personnel on how to complete the food records, emphasizing reporting food products with their brand names to accurately trace information on their nutritional content. Regularly trained research staff checked the completed food records, and we ensured a continuous update of all training materials.¹⁶ It may be asked, whether a 3-day food record covers a time-period long enough to accurately measure vitamin D intake from diet. In our data, the main sources of vitamin D up to 2 years of age were vitamin D supplements and fortified milk products, which are, according to our observations, used on a daily basis at this age. For the 3- and 4-year-old children, the situation changed so that the contribution of vitamin D supplements to the intake of vitamin D decreased. Accordingly, we are confident that using a 3-day food record to measure vitamin D intake may not greatly affect this particular population of children between the ages of 3 months and 4 years.

We measured asthma using a modified version of the ISAAC questionnaire, which provided excellent validity estimates to identify clinically diagnosed asthma.¹⁷ Children in this study carried HLA genotypes

TABLE 3 Mean intake of vitamin D by food source (and proportional contribution of each food source to overall vitamin D intake) between 3 mo and 4 y in asthma cases and controls

Age at vitamin D measurement	Frequency		Mean vitamin D intake from milk and milk products, µg (% of total vitamin D intake) ^a		Mean vitamin D intake from margarines, butter, oils, and fats, µg (% of total vitamin D intake)		Mean vitamin D intake from fish products, µg (% of total vitamin D intake)		Mean vitamin D intake from other foods, µg (% of total vitamin D intake)	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
3 mo	172	608	4.0 (100.0)	3.4 (99.9)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.1)
6 mo	165	594	4.5 (98.2)	3.7 (97.4)	0.0 (0.1)	0.0 (0.1)	0.0 (0.6)	0.0 (1.1)	0.1 (1.1)	0.1 (1.4)
1 y	157	541	3.6 (86.8)	3.0 (81.7)	0.1 (3.2)	0.2 (4.5)	0.2 (5.3)	0.3 (8.3)	0.2 (4.6)	0.2 (5.5)
2 y	108	395	1.6 (55.8)	1.3 (50.9)	0.5 (17.1)	0.5 (18.8)	0.4 (14.9)	0.4 (16.4)	0.3 (12.2)	0.4 (13.9)
3 y	69	259	1.3 (46.5)	1.5 (48.6)	0.8 (29.0)	0.7 (23.1)	0.3 (10.5)	0.4 (14.2)	0.4 (14.0)	0.4 (14.1)
4 y	35	132	1.6 (45.5)	1.6 (45.9)	0.9 (26.5)	0.8 (23.7)	0.5 (13.9)	0.6 (17.3)	0.5 (14.1)	0.5 (13.1)

^aAlso include infant formulas.**TABLE 4** Age-specific and longitudinal associations between total vitamin D intake (from foods and supplements combined) up to age 4 y and risk of asthma by the age of 5 y: odds ratio (OR); 95% confidence interval (95% CI): complete case analysis

Vitamin D intake	Any asthma OR (95% CI)		Atopic asthma ^a OR (95% CI)		Non-atopic asthma ^a OR (95% CI)	
	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
3 mo	n = 882	n = 676	n = 479	~ ^c	n = 364	~ ^c
P-value	0.98 (0.75-1.29)	0.89 (0.61-1.31)	0.89 (0.61-1.30)		1.22 (0.78-1.91)	
	0.909	0.561	0.560		0.393	
6 mo	n = 860	n = 653	n = 476	~ ^c	n = 351	~ ^c
P-value	1.28 (0.84-1.93)	1.15 (0.65-2.01)	1.14 (0.69-1.89)		1.31 (0.62-2.74)	
	0.250	0.635	0.614		0.480	
1 y	n = 789	n = 599	n = 448	~ ^c	n = 314	~ ^c
P-value	1.53 (1.04-2.24)	1.46 (0.87-2.46)	1.11 (0.70-1.76)		2.54 (1.24-5.19)	
	0.031	0.156	0.656		0.011	
2 y	n = 541	n = 417	n = 340	~ ^c	n = 186	~ ^c
P-value	1.78 (1.25-2.54)	1.76 (1.04-2.97)	1.65 (1.09-2.51)		2.00 (1.02-3.92)	
	0.002	0.034	0.019		0.045	
3 y	n = 345	n = 272	n = 231	~ ^c	n = 110	~ ^c
P-value	1.33 (0.84-2.12)	1.43 (0.70-2.92)	1.16 (0.66-2.05)		1.70 (0.73-3.94)	
	0.226	0.328	0.600		0.212	
4 y	n = 169	n = 137	n = 104	~ ^c	n = 61	~ ^c
P-value	1.49 (0.74-3.02)	2.11 (0.57-7.87)	1.65 (0.68-4.01)		1.30 (0.37-4.60)	
	0.266	0.266	0.273		0.682	
Longitudinal (3 mo to 4 y)	n = 910	n = 688	n = 495	n = 364	n = 375	n = 291
P-value	1.33 (1.06-1.65)	1.22 (0.94-1.58)	1.19 (0.90-1.58)	1.14 (0.83-1.56)	1.60 (1.09-2.34)	1.16 (0.72-1.86)
	0.012	0.133	0.216	0.414	0.017	0.544

^aAtopic asthma was defined as IgE-positive asthma and non-atopic asthma as IgE-negative asthma.^bAdjusted for gestational age, maternal age, maternal smoking during pregnancy, number of previous deliveries, maternal asthma or allergic rhinitis, paternal asthma or allergic rhinitis, birthweight in grams, mode of delivery, maternal vocational education, pets at home during first year of life, duration of total breastfeeding, and maternal vitamin D intake from foods and supplements during pregnancy.^cDue to small numbers, we were unable to undertake adjusted analyses for atopic and non-atopic asthma.

conferring susceptibility to type 1 diabetes, which may limit the application of the current findings to the general population. The impact of HLA genes on asthma has, however, been mixed as both increased and decreased risk have been reported.¹⁹⁻²³ While the prevalence of type 1 diabetes in the DIPP cohort ranges between 3% and 4% during childhood, it stands close to 1% in the Finnish population.¹³

As far as we are aware, this is the first study to examine the age-specific and longitudinal associations between vitamin D intake and childhood asthma. Whereas prospective studies investigating the association between dietary vitamin D intake during early life and childhood asthma risk are sparse, the majority of the studies have examined the role of serum 25-hydroxy vitamin

TABLE 5 Age-specific and longitudinal associations between vitamin D intake (from foods and supplements combined) up to age 4 y and risk of asthma by the age of 5 y: odds ratio (OR); 95% confidence interval (95% CI): multiple imputation analysis

Vitamin D intake	Any asthma OR (95% CI)		Atopic asthma ^a OR (95% CI)		Non-atopic asthma ^a OR (95% CI)	
	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b	Unadjusted	Adjusted ^b
3 mo	0.95 (0.73-1.25)	0.84 (0.62-1.14)	0.81 (0.56-1.17)	0.80 (0.51-1.23)	1.20 (0.76-1.88)	0.97 (0.59-1.60)
6 mo	1.31 (0.88-1.95)	1.19 (0.76-1.86)	1.22 (0.75-2.00)	1.34 (0.75-2.39)	1.46 (0.73-2.95)	0.91 (0.40-2.09)
1 y	1.52 (1.03-2.24)	1.55 (1.01-2.36)	1.19 (0.74-1.91)	1.16 (0.67-1.99)	2.26 (1.15-4.45)	2.88 (1.29-6.42)
2 y	1.67 (1.19-2.36)	1.58 (1.08-2.33)	1.47 (0.97-2.21)	1.41 (0.87-2.30)	2.29 (1.19-4.42)	2.45 (1.10-5.45)
3 y	1.25 (0.81-1.94)	1.40 (0.84-2.35)	1.17 (0.69-1.99)	1.34 (0.72-2.51)	1.42 (0.67-3.01)	3.35 (0.62-18.06)
4 y	1.46 (0.75-2.84)	1.95 (0.80-4.81)	1.51 (0.67-3.42)	^{-c}	1.44 (0.47-4.42)	^{-c}
Longitudinal (3 mo to 4 y)	1.30 (1.05-1.62)	1.24 (1.00-1.53)	1.17 (0.89-1.54)	1.16 (0.88-1.54)	1.59 (1.09-2.32)	1.42 (0.98-2.04)

^aAtopic asthma was defined as IgE-positive asthma and non-atopic asthma as IgE-negative asthma.

^bAdjusted for gestational age, maternal age, maternal smoking during pregnancy, number of previous deliveries, maternal asthma or allergic rhinitis, paternal asthma or allergic rhinitis, birthweight in grams, mode of delivery, maternal vocational education, pets at home during first year of life, duration of total breastfeeding, and maternal vitamin D intake from foods and supplements during pregnancy.

^cDue to small numbers, we were unable to undertake adjusted analyses for vitamin D at the age of 4 y and atopic and non-atopic asthma.

D levels. Yet, as reported by a recent synthesis of these studies,⁸ conflicting findings and methodological limitations impede on the robustness of the overall evidence.⁸ Similarly, a recent systematic review on the role of vitamin D supplementation during early childhood concluded that existing primary studies are of low quality.⁹

All existing studies have measured serum vitamin D concentrations and the intake of vitamin D supplements at only one single time point, which fails to reflect long-term vitamin D levels or supplemental intake.^{3,8,9} The evidence base will be advanced by undertaking repeated measurements of vitamin D over time, allowing assessment of the impact of longer-term exposure, seasonal and age-dependent variations on asthma risk.^{3,8,9} There is also need to control for known potential confounding lifestyle and environmental factors, including social strata, ultraviolet exposures, and maternal vitamin D intake during pregnancy.^{8,9}

The presence of vitamin D receptors in the immune system and the expression of specific immune signals for the synthesis of active calcitriol suggest a paracrine immune-modulatory role for calcitriol.²⁴⁻²⁶ Fetal vitamin D exposures may act as an immunoregulatory hormone on the maturation of the immune system by interfering with cytokine production or monocytes and lymphocytes.²⁴⁻²⁶ Vitamin D selectively suppresses Th1 cell activity but not that of Th2 or CD8 + cell.²⁴⁻²⁶ In cord blood T cells, calcitriol seems to inhibit Th1 and Th2 differentiation.^{3,24-26} Despite these beneficial effects, which are hypothesized to decrease the risk of asthma, our findings suggest in contrast an increased risk of asthma with increasing vitamin D intake during the first 4 years of life.

Previous evidence linking early-life vitamin D to the development of asthma in childhood has been conflicting.³ Clear evidence so far supporting a beneficial role has come from a few observational cohort studies on maternal vitamin D intake during pregnancy.^{3,4} Nevertheless, results from two recent clinical trials comparing high

dose to the recommended levels showed a non-significant lower risk.^{5,6} We may speculate that the beneficial role of vitamin D in the development of childhood asthma may occur with prenatal exposure rather than exposure during early childhood, which highlights possible fetal programming in this context. On the other hand, rather than a direct effect of early-life vitamin D exposures, our findings may reflect residual confounding by other lifestyle factors, for example, social gradients, or environmental factors, for example, levels of ultraviolet exposures, which have not been taken into account in our study. Furthermore, given the increased number of statistical tests performed, the type 1 error rate might not be at the 0.05 level; therefore, we emphasize cautious interpretation of our findings. We can also not rule out the possibility that our results could be explained by reverse causality, but we lacked the statistical power to explore this further by excluding children with allergy symptoms early in life. Additional well-designed longitudinal studies with repeated assessment of vitamin D during early childhood, with consideration of these perspectives, are required to confirm the findings from the current study, which will help to provide a clearer picture of the putative role of vitamin D in the subsequent development of asthma in children.

5 | CONCLUSIONS

Dietary intake of vitamin D during early childhood, particularly at ages 1 and 2 years, appeared to increase the risk of asthma in children. It is unclear whether this reflects a true effect or residual confounding by lifestyle or environmental factors. The repeated assessment of vitamin D intake provided us with the opportunity to evaluate the role of age-dependent and longitudinal intake of vitamin D in asthma in childhood. Similarly designed studies are required to confirm or call these findings to question.

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