

ORIGINAL ARTICLE

Epidemiology and Genetics

Antenatal vitamin D exposure and childhood eczema, food allergy, asthma and allergic rhinitis at 2 and 5 years of age in the atopic disease-specific Cork BASELINE Birth Cohort Study

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Abstract

Background: Prospective studies of antenatal and infant vitamin D exposure and atopic disease from extensively characterised, disease-specific, maternal-infant cohorts with gold standard analysis of vitamin D status and clinically validated atopic outcomes are lacking. This study aimed to investigate associations between intrauterine vitamin D status and atopic outcomes in an extensively characterised, disease-specific, maternal-infant cohort.

Methods: Circulating 25-hydroxyvitamin D (25(OH)D) was measured in maternal sera at 15 weeks of gestation (n = 1537) and umbilical cord blood (n = 1050) using a CDC-accredited LC-MS/MS platform, and the association with clinically validated atopic disease outcomes (eczema, food allergy, asthma, allergic rhinitis) at 2 and 5 years was explored using multivariable logistic regression.

Results: Persistent eczema in the first 2 years of life was present in 5% of infants. Food allergy at 2 years was confirmed in 4%. The prevalence of aeroallergen sensitisation at 2 years was 8%. Asthma at 5 years was reported in 15% and allergic rhinitis in 5% of 5-year-olds. There were no significant differences in the distributions of maternal 25(OH)D at 15 weeks of gestation (mean [SD] 58.4 [26.2] and 58.5 [26.1] nmol/L) and cord 25(OH)D concentrations (mean [SD] 35.2 [17.8] and 35.4 [18.3] nmol/L) between children with and without atopic disease. Neither maternal (aOR [95% CI]: 1.02 [0.97, 1.08], *P* = 0.450) nor cord 25(OH)D (aOR [95% CI]: 1.00 [0.91, 1.09], *P* = 0.991) were significant predictors of atopic disease outcomes in fully adjusted models.

Conclusion: These data in a disease-specific cohort with prospectively collected, validated atopic outcomes do not support an association between antenatal exposure to vitamin D and atopic disease outcomes in childhood.

KEYWORDS

allergy, asthma, atopic disease, pregnancy, vitamin D

1 | INTRODUCTION

Vitamin D is a potent immunomodulator; local activation of 25-hydroxyvitamin D (25[OH]D) to 1,25-dihydroxyvitamin D (1,25[OH]₂D) in monocytes and macrophages increases the production of antimicrobial peptides, thus stimulating cellular immunity.^{1,2} Vitamin D inhibits the pro-inflammatory responses of the adaptive immune system and promotes proliferation of immunosuppressive regulatory T cells and their accumulation at sites of inflammation.¹ A protective effect of vitamin D supplementation in acute respiratory tract infections (RTIs),³ in a meta-analysis of individual participant data (IPD) from randomised controlled trials (RCTs), provides convincing evidence that prevention of vitamin D deficiency may be an important component in promoting resistance to infectious illness. The evidence for a protective effect of vitamin D on the incidence of asthma and wheeze is mixed. Two recent meta-analyses of maternal vitamin D status and childhood asthma and wheeze from prospective birth cohort studies^{4,5} show a trend towards a reduction in the risk of asthma and wheeze among children of mothers with the highest vitamin D status compared with the lowest. While a Cochrane review⁶ showed that vitamin D does not improve lung function or day-to-day asthma symptoms, a recently published IPD meta-analysis showed that in asthma sufferers, vitamin D reduced the rate of exacerbations requiring corticosteroids treatment.⁷

Two recently published RCTs of vitamin D supplementation during pregnancy to prevent childhood asthma and recurrent wheeze in the offspring at 3 years, the VDAART study⁸ and COPSAC₂₀₁₀,⁹ both reported >20% reduction in risk. While neither study was statistically significant, the IPD analysis of the two trials demonstrated a statistically significant and clinically meaningful 26% reduction in risk asthma/recurrent wheeze during the first 3 years of life.¹⁰ This effect was driven by a substantially reduced risk among women who entered the study with high vitamin D status (25[OH]D ≥ 75 nmol/L [30 ng/mL]) and was not observed in women with baseline 25(OH)D < 75 nmol/L.

Given these promising trial data, the mixed results from observational studies of intrauterine vitamin D status and atopic diseases in children, including food allergy,^{11–15} eczema,^{4,13,15} asthma^{11,16–19} and allergic rhinitis,^{11,18–21} are puzzling. Liu et al²² proposed that vitamin D may interact with or modify inherited risk in children with a high-risk genotype, based on their report of a significant interaction between an IL-4 gene polymorphism and vitamin D deficiency, where increased risk of food sensitisation was observed among children with CC/CT genotypes (OR = 1.79, 95% CI: 1.15–2.77). To fully characterise relationships between intrauterine vitamin D exposure and allergic disease, analysis of well-constructed, large-scale prospective cohorts of maternal-infant dyads, which take due consideration of an individual's inherited risk, early-life exposures and environmental confounders, is still needed. This study aimed to evaluate the relationship between maternal and cord vitamin D status and atopic outcomes in an extensively characterised prospective birth cohort with clinically validated outcomes and long-term follow-up.

2 | MATERIALS AND METHODS

2.1 | Design, participants and procedures

The Cork BASELINE Birth Cohort Study (Babies after SCOPE: Evaluating the Longitudinal Impact on Neurological and Nutritional Endpoints),²³ a prospective birth cohort study of children in Cork, Ireland (51.9°N), was established as a paediatric follow-up to the SCOPE (Screening for Pregnancy Endpoints) pregnancy cohort study in Ireland.²⁴ Nulliparous women with a low-risk, singleton pregnancy (n = 1768) had their first SCOPE visit at 15 weeks of gestation (range, 14–16 weeks). Research midwives collected information on socio-economic status, educational attainment and a complete medical history. Data on nutritional supplement use, alcohol consumption, smoking history and recreational drugs were recorded for the period before conception, during the first trimester and at the time of the 15-week visit. Maternal anthropometric measurements were taken. Blood was processed within three hours to serum and stored at –80°C for future analysis.

Of the 1768 women enrolled in SCOPE, 1537 consented to participate in the Cork BASELINE Birth Cohort Study, which was formed with an *a priori* aim of investigating the incidence and determinants of food allergy and eczema in early childhood. Participants were not selected for any disease. Umbilical cord blood samples were processed within 3 hours of collection and bio-banked at –80°C using the SCOPE protocol.

2.2 | Clinical assessments

Interviewer-led questionnaires and clinical assessments were conducted at day 2 and at 2, 6, 12, 24 and 60 months. Questionnaires captured details on demography, parental self-reported atopy, maternal environment during pregnancy and baby's early-life home environment. Data on infant feeding, detailing breastfeeding, formula or combination feeding, frequency of feeds, name and brand of infant formula, complementary feeding, eating behaviour and supplementation were collected at each time point. Anthropometric measures of weight, length and abdominal circumference were measured using standard operating procedures. Body composition analysis was performed at day 2 and 2 months in a validated infant-sized air displacement plethysmography system, the PEA POD Infant Body Composition System (COSMED USA, Concord, Calif).

2.3 | Serum 25-hydroxyvitamin D (25[OH]D) analysis

Maternal and cord serum 25(OH)D concentrations were measured at the Cork Centre for Vitamin D and Nutrition Research laboratory using a LC-MS/MS method previously described^{25,26} that is assessed on an ongoing basis by participation in the Vitamin D External Quality Assessment Scheme (DEQAS) (Charing Cross Hospital, London, UK). We have been certified by the CDC Vitamin D Standardization

Certification programme, which reports accuracy and bias for total 25(OH)D, 25(OH)D₃, 3-epi-25(OH)D₃ and 25(OH)D₂,^{25,26} since 2013.

2.4 | Ethics

The SCOPE Ireland study and the Cork BASELINE Birth Cohort were approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (ECM5[10]05/02/08 and ECM5[9]01/07/2008, respectively) and are registered at the Australian New Zealand Clinical Trials Registry (ACTRN12607000551493) and the United States National Institutes of Health Clinical Trials Registry (NCT01498965), respectively. Both studies were conducted according to the guidelines laid down in the Declaration of Helsinki as revised in 2008. Written informed consent was obtained from mothers in SCOPE and on behalf of their infants in BASELINE.

2.5 | Outcome measures

2.5.1 | Eczema

Possible eczema was identified at each clinical assessment visit (at 6, 12 and 24 months) using serial allergy questionnaires from the EuroPrevall study²⁷ and formally diagnosed using the UK Working Party Diagnostic Criteria (UK WPDC).²⁸ In this study, we report persistent eczema that was present at each clinical assessment between 6 and 24 months.

2.5.2 | Food allergy

Longitudinal screening to assess suspected food allergy was performed at each clinical assessment visit using modified EuroPrevall criteria. Cross-sectional screening for food sensitisation was offered to all children at the 24-month clinical assessment visit using skin prick tests (SPT). The food allergen panel included cows' milk, egg, peanut, cod, soya and wheat. Other non-panel foods were tested if the child had suspected food-induced allergy symptoms on previous ingestion of the food. A positive SPT response for a food allergen (defined as a wheal diameter ≥ 3 mm) triggered a formal evaluation by a paediatric allergy specialist, where a non-blinded oral food challenge (OFC) was completed if the food had not been eaten previously or there was a history to suggest the risk of food allergy.

2.5.3 | Aeroallergen sensitisation

In addition to the food allergen panel at 24 months, cross-sectional screening for sensitisation (defined as a wheal diameter ≥ 3 mm) to pollen, dust mite, cat, dog, bee and wasp was performed using SPT.

2.5.4 | Asthma

Two of the following three criteria were used to identify children with asthma at the 5-year clinical assessment: (a) parental report of

physician diagnosis of asthma, (b) use of asthma medications at 5 years and (c) wheeze at 5 years.

2.5.5 | Allergic rhinitis

Our cohort adopted standardised allergy questionnaires from the EuroPrevall Study²⁷ and the ISAAC project.²⁹ We evaluated allergic rhinitis outcome measures in a number of ways, including (a) parental report of problems with sneezing or runny/blocked nose, in the absence of a cold; (b) parental report of problems with sneezing or runny/blocked nose, in the absence of a cold, accompanied by itchy watery eyes; and (c) physician diagnosis of allergic rhinitis.

2.6 | Statistical analysis

Maternal and infant characteristics and serum 25(OH)D concentrations were compared in children with and without each of the atopic outcomes using a Student's T test or Mann-Whitney U test for continuous variables and Pearson's chi-squared or Fisher exact tests for categorical variables. Univariate and multivariable logistic regression models were used to examine associations between antenatal and cord vitamin D status (per 10 nmol/L increment in 25[OH]D) with atopic outcomes in early childhood. Models were adjusted for potential confounders of the association between vitamin D status and atopy identified individually within univariable models: maternal age, maternal body mass index at 15 weeks' gestation, smoking during pregnancy, parental history of atopic disease, infant and complementary feeding practices, weight and fat mass at birth. We also ran the multivariable models adjusting for a limited number of confounders with strong support in the literature: parental allergy status, sex of infant, mode of delivery and age of introduction to complementary foods. Interactions between the significant risk factors were explored. Serum 25(OH)D was also examined as a deseasonalised continuous variable and a categorical variable (maternal 25[OH]D ≥ 75 nmol/L and cord 25[OH]D ≥ 50 nmol/L as the reference categories) within multivariable models. Additionally, we examined the prevalence of atopic outcomes across categories of combined low/high maternal and cord serum 25(OH)D concentrations. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) software.

As the vast majority of women in the SCOPE study were white-Caucasian and given the ethnic disparities in vitamin D status and efficacy of cutaneous synthesis,³⁰ the analysis in this study is limited to children born to white-Caucasian women with a maternal and/or a cord serum sample.

3 | RESULTS

3.1 | Study population

Of the 1537 infants recruited to the BASELINE Birth Cohort Study from the SCOPE pregnancy study, 1412 white-Caucasian mothers

were included in the analysis of antenatal 25(OH)D status and atopic disease. Of these 1412 mothers, cord 25(OH)D data were available for 1035 infants (Figure 1).

Mothers tended to be older (74% aged 25-34 years and 17% aged ≥ 35 years), were highly educated (87% attended university) and 8% smoked during pregnancy (Table 1). Almost half (49%) of mothers and 37% of fathers reported previous history of allergy, while allergy was reported by both parents in 19% of participants.

The mean (SD) birthweight was 3458 (537) g. While 73% of infants had been breastfed by the time they were discharged from the hospital, this had decreased to 45% by 2 months of age (of which 17% were receiving both breastmilk and formula). The mean (SD) duration of breastfeeding was 11.9 (16.3) weeks. Complementary foods were introduced between 17 and 26 weeks in 82% of children and 14% received solids between 15 and 17 weeks of age.

Infants included in this analysis did not differ significantly from those excluded in terms of eczema, allergy or asthma prevalence and were representative of the entire cohort in most respects, with two exceptions. Mothers in this analysis were slightly younger at delivery (mean [SD]: 30.7 [4.4] years) than the overall cohort (mean [SD]: 32.2 [4.7] years) and had a lower birthweight (mean [SD]: 3458 [537] g) than the cohort average (mean [SD]: 3576 [466] g).

3.2 | Maternal and cord serum 25(OH)D concentrations

The mean (SD) maternal serum 25(OH)D concentration was 58.6 (25.8) nmol/L. Maternal 25(OH)D concentrations were <30 nmol/L in

15%, between 30 and 49.9 and 50 and 74.9 in 26 and 31% and ≥ 75 nmol/L in 28% of women. The mean (SD) cord 25(OH)D concentration was 35.5 (18.2) nmol/L. Cord 25(OH)D concentrations were <30 nmol/L in 44% of infants, between 30 and 49.9 and 50 and 74.9 in 35 and 18% and ≥ 75 nmol/L in 3% of infants.

3.3 | Association between intrauterine and neonatal vitamin D exposure with atopic outcomes

Persistent eczema in the first 2 years of life was seen in 5% of infants. Physician-validated food allergy at 2 years was confirmed in 4% of infants. The prevalence of aeroallergen sensitisation at 2 years was 8%, and of those with a positive SPT, 7% of children had a positive response to house dust mite, 1% were positive to grass/pollen, 2% had a positive response to cat and $<1\%$ to bee or wasp. Asthma at 5 years was reported in 15% of children, and physician-diagnosed allergic rhinitis was reported in 5% of 5-year-olds.

In our analysis of infants with maternal antenatal 25(OH)D data ($n = 1412$), there was no association with any childhood atopic outcome at 2 or 5 years (Table 2). In the subsample of infants with cord 25(OH)D data ($n = 1035$), our analysis did not show any association between cord serum 25(OH)D concentrations and childhood atopic outcomes (Table 2). These findings remained consistent irrespective of whether models were adjusted for a wide range of univariate analysis-defined confounders (Table 2) or a limited range of literature-identified confounders (data not shown). Stratification of maternal 25(OH)D concentrations by 75 nmol/L and cord 25(OH)D by 50 nmol/L did not reveal any differences in the prevalence of atopic outcomes between the groups (Table 3). We also stratified maternal

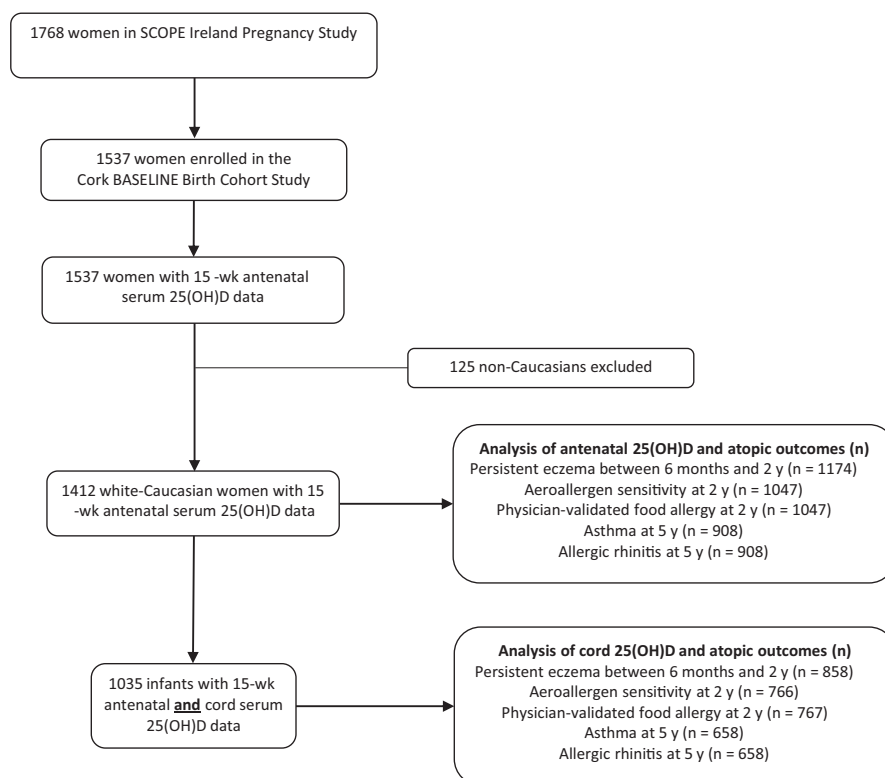


FIGURE 1 Flow diagram of study participants and allergic disease outcomes

TABLE 1 Characteristics of participants of the SCOPE-BASELINE maternal-infant dyad cohort included in analysis of maternal and infant vitamin D status and atopic disease outcomes at 2 and 5 years ($n = 1315$) and stratified by the presence of atopic outcome in first 5 years of life

	Total sample ($n = 1315$)	No atopic outcome ($n = 839$)	≥ 1 atopic outcome ($n = 476$)	P
Maternal characteristics				
Age (y) at delivery, mean (SD)	30.9 (4.2)	30.7 (4.3)	31.2 (4.1)	0.042
≥ 35	17.1	16.7	17.9	0.642
Education, any 3rd level (%)	86.5	85.6	88.2	0.215
Marital status, married/living with partner (%)	94.4	94.9	93.5	0.355
Maternal BMI at 15 wks' gestation (kg/m^2), mean (SD)	24.8 (4.0)	24.9 (4.0)	24.8 (3.9)	0.861
Maternal BMI $\geq 30 \text{ kg/m}^2$ (%)	11.8	11.8	11.8	1.000
Smoked during pregnancy (%)	8.1	8.7	7.1	0.374
Delivery, vaginal (%)	71.7	72.1	70.9	0.711
Self-reported atopy (%)				
Maternal	48.7	44.2	56.7	<0.001
Paternal	37.4	31.3	48.1	<0.001
Both parents	19.2	15.3	26.1	<0.001
Maternal 25(OH)D, nmol/L				
Mean (SD)	58.6 (25.8)	58.7 (26.0)	58.5 (25.4)	0.887
<30 nmol/L (%)	15.4	16.1	14.1	0.371
30-49.9 nmol/L (%)	25.7	24.4	27.9	0.183
50-74.9 nmol/L (%)	31.2	31.1	31.3	0.991
≥ 75 nmol/L (%)	27.8	28.4	26.7	0.554
Deseasonalised 25(OH)D, nmol/L				
Mean (SD)	58.4 (24.1)	58.4 (24.8)	58.3 (23.0)	0.925
Infant characteristics				
Persistent eczema between 6 and 24 mo (%)	5.3			
Physician-validated food allergy at 24 mo (%)	4.0			
Aeroallergen sensitivity at 24 mo (%)	8.2			
Allergic rhinitis at 5 y (%)	5.4			
Asthma at 5 y (%)	15.4			
Gender, male (%)	51.3	50.4	52.9	0.411
Birthweight, g	3458 (537)	3437 (530)	3496 (548)	0.055
Fat mass at birth, g	378 (171)	371 (170)	388 (174)	0.154
Fat-free mass at birth, g	2950 (351)	2928 (351)	2977 (361)	0.015
Age last breastfed, weeks (mean, SD)	12.5 (16.6)	12.1 (16.3)	13.2 (17.1)	0.259
Received formula at 2 mo (%)	72.3	72.4	72.2	1.000
Received formula at 6 mo (%)	87.9	88.5	86.9	0.442
Cord 25(OH)D, nmol/L				
Mean (SD)	35.5 (18.2)	35.7 (18.5)	35.2 (17.7)	0.685
<30 nmol/L (%)	44.4	44.0	45.0	0.833
30-49.9 nmol/L (%)	35.0	34.8	35.2	0.965
50-74.9 nmol/L (%)	18.0	18.2	17.5	0.835
≥ 75 nmol/L (%)	2.7	2.9	2.4	0.779
Deseasonalised cord 25(OH)D, nmol/L (mean, SD)	35.3 (16.4)	35.6 (16.6)	34.8 (15.8)	0.505

25(OH)D by 30 and 50 nmol/L and cords by 30 nmol/L but did not see any differences in the prevalence rates across the distribution of maternal or cord 25(OH)D (data not shown). Table 4 shows the

sample stratified by combined measures of high/low or low/high maternal/cord vitamin D status, on the basis of maternal and cord 25 (OH)D stratified by 75 and 50 nmol/L in combination, with no

TABLE 2 Summary of associations between maternal and umbilical cord serum 25-hydroxyvitamin D [25(OH)D] and atopic outcomes in children in the Cork BASELINE Birth Cohort Study

Atopic outcome		n	Mean (SD) 25(OH)D	OR (95% CI)	aOR (95% CI) ^a	P
Maternal 25(OH)D analysis (per 10 nmol/L)						
Eczema status between 6 and 24 mo ^a	Never	803	58.6 (25.8)	Reference	Reference	0.995
	Persistent	68	57.9 (22.3)	0.99 (0.90, 1.09)	1.00 (0.90, 1.11)	
Food allergy at 2 y ^c	No	704	58.2 (25.9)	Reference	Reference	0.805
	Yes	30	61.5 (25.3)	1.05 (0.93, 1.18)	1.02 (0.89, 1.16)	
Positive aeroallergen SPT at 2 y ^e	No	697	58.4 (26.2)	Reference	Reference	0.853
	Yes	70	58.3 (23.3)	1.00 (0.92, 1.09)	1.00 (0.91, 1.08)	
Asthma at 5 y ^g	No	723	58.4 (26.3)	Reference	Reference	0.640
	Yes	133	57.4 (25.6)	0.99 (0.92, 1.06)	1.02 (0.95, 1.10)	
Allergic rhinitis at 5 y ⁱ	No	811	58.4 (26.3)	Reference	Reference	0.238
	Yes	47	55.1 (24.3)	0.95 (0.85, 1.07)	0.93 (0.83, 1.05)	
Cord 25(OH)D analysis (per 10 nmol/L)						
Eczema status between 6 and 24 mo ^b	Never	586	35.7 (18.3)	Reference	Reference	0.565
	Persistent	46	34.7 (16.2)	0.97 (0.82, 1.15)	0.95 (0.79, 1.14)	
Food allergy at 2 y ^d	No	565	35.0 (18.0)	Reference	Reference	0.257
	Yes	23	35.9 (18.0)	1.14 (0.94, 1.38)	1.12 (0.82, 1.37)	
Positive aeroallergen SPT at 2 y ^f	No	491	35.4 (18.3)	Reference	Reference	0.971
	Yes	50	34.7 (16.2)	1.03 (0.90, 1.18)	1.00 (0.85, 1.19)	
Asthma at 5 y ^h	No	434	28.7 (15.1)	Reference	Reference	0.634
	Yes	76	28.6 (15.0)	1.00 (0.89, 1.13)	1.04 (0.90, 1.19)	
Allergic rhinitis at 5 y ⁱ	No	586	28.2 (14.7)	Reference	Reference	0.679
	Yes	38	32.6 (15.6)	0.97 (0.81, 1.17)	0.96 (0.79, 1.16)	

OR, odds ratio; aOR, adjusted odds ratio; 95% CI, 95% confidence intervals.

^aModel adjusted for maternal age, maternal atopy status and paternal atopy status.

^bAdjusted for maternal age, maternal allergy, paternal allergy, smoking during pregnancy and infant birthweight.

^cAdjusted for maternal BMI at 15 weeks of gestation, maternal allergy, paternal allergy, smoking during pregnancy, infant birthweight and duration of breastfeeding.

^dAdjusted for maternal allergy, paternal allergy and duration of breastfeeding.

^eAdjusted for maternal age, maternal allergy, paternal allergy, infant birthweight and infant sex.

^fAdjusted for maternal allergy, paternal allergy, fat mass at birth, duration of breastfeeding, mother's exposure to pets during pregnancy and transepidermal water loss (TEWL).

^gAdjusted for maternal education level, marital status, maternal allergy, paternal allergy, infant birthweight, infant sex and duration of breastfeeding.

^hModel for maternal allergy, paternal allergy, fat mass at birth, duration of breastfeeding, infant sex and age of introduction to solid foods.

ⁱAdjusted for maternal allergy, paternal allergy, infant birthweight, infant sex and duration of breastfeeding.

significant effects on atopic outcomes (Table 4). These classifications were also explored using 30 and 50 nmol/L thresholds, with no effect (data not shown). Deseasonalised maternal and cord 25(OH)D concentrations were not associated with any atopic disease outcome (data not shown). No interaction effects were observed between 25 (OH)D and childhood atopy risk in children born to parents with or without atopy.

4 | DISCUSSION

Our analysis of this extensively phenotyped, disease-specific, prospective cohort of maternal-infant dyads showed no significant association between antenatal or neonatal 25(OH)D concentrations

and eczema, food allergy, aeroallergen sensitisation, allergic rhinitis or asthma when adjusted for a range of potential confounding factors.

4.1 | Eczema

Our findings of no effect modification of intrauterine vitamin D exposure on persistent eczema in the first 24 months builds upon our comprehensive evaluation of persistent, transient and late-onset eczema in the first year of life, in which we identified inherited risk and neonatal adiposity as risk factors for persistent eczema.³¹ Our study is one of very few to evaluate the relationship of in utero 25 (OH)D with the persistent eczema phenotype. This is important given high prevalence of transient rashes during infancy and early

TABLE 3 Prevalence of atopic disease outcome (%), stratified by (a) maternal 25(OH)D status <75 nmol/L and ≥75 nmol/L, (b) cord 25(OH)D <50 nmol/L and ≥50 nmol/L

Maternal 25(OH)D at 15 wks' gestation	<75 nmol/L n = 950	≥75 nmol/L n = 365	P
Persistent eczema (6-24 mo)	5.3	5.0	0.942
Aeroallergen sensitivity	8.4	7.8	0.862
Food sensitivity	6.3	6.4	0.957
Food allergy	3.9	4.3	0.947
Asthma	16.5	12.3	0.148
Allergic rhinitis	5.7	4.5	0.592
Cord 25(OH)D	<50 nmol/L n = 829	≥50 nmol/L n = 206	P
Persistent eczema (6-24 mo)	5.1	4.1	0.697
Aeroallergen sensitivity	9.0	9.7	0.921
Food sensitivity	6.1	5.8	0.900
Food allergy	3.6	5.1	0.518
Asthma	14.0	16.2	0.630
Allergic rhinitis	6.4	4.6	0.565

childhood, and the differing distribution of subsequent atopic conditions across eczema phenotypes.³²

Recently published data from two large-scale, unselected prospective birth cohort studies in New Zealand¹⁶ and the UK¹⁷ also showed no association between vitamin D status in early pregnancy and parental report of eczema at school age. However, Wegienka and colleagues¹³ have shown that maternal 25(OH)D, but not cord 25(OH)D, was inversely associated with eczema in a sample of 707 children in the United States. The strength of this association weakened when the cohort was split by race. Smaller unselected^{14,18,21} and at-risk cohort studies^{11,12,15} have presented conflicting findings.

4.2 | Food allergy

The hypothesis for a role of vitamin D in food allergy stems from the relationship between season of birth and infantile food allergy in both Northern³³ and Southern hemispheres.³⁴ Allen and colleagues have shown a cross-sectional association between vitamin D status at 12 months and contemporaneous challenge-proven food allergy.³⁵ However, the evidence for a relationship between antenatal 25(OH)D and food allergy is mixed and inconsistent. Our study, the first to our knowledge to report on maternal and cord 25(OH)D and physician-validated food allergy, found no association between antenatal vitamin D status and clinically confirmed food allergy or food sensitisation. Other large-scale, unselected birth cohort studies have not demonstrated an association between maternal or cord 25(OH)D status and IgE-mediated sensitivity to food allergens.^{13,20} However, smaller scale unselected cohorts have shown both positive¹⁴ and inverse²¹ associations with food sensitivity. Studies of at-risk groups have not shown any significant associations of vitamin D with food allergy or food sensitivity.^{11,12,15}

TABLE 4 Prevalence of atopic disease outcome (%), stratified by combined maternal and neonatal vitamin D status

Prevalence (%)	Combined maternal and cord 25(OH)D status				P
	HH n = 94	HL n = 171	LL n = 589	LH n = 104	
Persistent eczema (6-24 mo)	3.2	6.1	4.8	4.9	0.791
Aeroallergen sensitivity	8.0	9.8	8.8	11.3	0.874
Food sensitivity	5.3	6.1	6.1	6.3	0.995
Food allergy	3.9	3.8	3.5	6.3	0.720
Asthma	14.8	9.7	15.2	17.4	0.440
Allergic rhinitis	4.9	5.3	6.7	4.3	0.814

HH = mother ≥75 nmol/L and cord ≥50 nmol/L.

HL = mother ≥75 nmol/L and cord <50 nmol/L.

LL = mother <75 nmol/L and cord <50 nmol/L.

LH = mother <75 nmol/L and cord ≥50 nmol/L.

The potential for vitamin D to interact with or modify inherited risk is worth considering. While Liu and colleagues²² did not show a significant association between vitamin D status at birth and risk of food sensitisation in an unselected US cohort, a significant inverse association in a subgroup of children with high-risk genotypes was observed. Our analyses did not show any modification effect of vitamin D status on the risk of any childhood allergy outcome when stratified by parental atopy.

4.3 | Asthma

A recent IPD analysis of two maternal vitamin D supplementation RCTs^{8,9} (n = 1387) has demonstrated a statistically significant and clinically meaningful 26% reduction in risk of asthma/recurrent wheeze during the first 3 years of life.¹⁰ No other atopic outcomes were modified by the interventions. The effect on wheeze/asthma was driven by a substantially reduced risk among women who entered the study with 25(OH)D ≥75 nmol/L (30 ng/mL) and were randomised to the treatment arm and was not observed in women with 25(OH)D <75 nmol/L at enrolment.¹⁰ This significant effect of maternal vitamin D status at trial entry on risk lends support to the idea that a crucial window of opportunity exists in early pregnancy for vitamin D to impact upon lung maturation^{10,36-38} which may be as early as the start of the second trimester.³⁹ Our study, which evaluated maternal vitamin D status at 15 weeks of gestation, showed no association between vitamin D exposure and the incidence of asthma. Neither maternal 25(OH)D at 15 weeks' gestation ≥75 nmol/L (28% of mothers) nor cord 25(OH)D ≥50 nmol/L (20% of newborns) modified asthma risk at 5 years in our study, echoed by numerous other large-scale unselected birth cohorts.^{13,16,17,20,40-43} Further, our analysis of maternal and cord status stratified by 25(OH)D concentrations of 75 and 50 nmol/L, respectively, did not show any association with asthma risk or any other atopic outcome. While it is possible that the distribution of antenatal and

cord 25(OH)D in our cohort is too low to achieve sufficient power at the upper end of the distribution to detect a signal, it is also worth noting that VDAART and COPSAC₂₀₁₀ had a higher prevalence of wheeze/asthma, at 29% and 18%, respectively, than the 15% prevalence in our analysis.

Although the combined IPD analysis of the two RCTs^{8,9} achieved statistical significance, there are some important methodological differences between the studies. Both the timing and dose of the interventions were substantially different: VDAART enrolled at 10-18 weeks of gestation and women received 110 µg/d; COPSAC₂₀₁₀ enrolled at 24 weeks, with a dose of 70 µg/d. Neither study included infant supplementation. We must therefore consider whether earlier initiation and maintenance of the interventions would have increased the impact of vitamin D exposures on lung maturation and subsequent risk of wheeze/asthma. Lastly, the analytical methods for 25(OH)D were different which may have affected the representation of participant vitamin D status at trial entry.^{44,45}

4.4 | Allergic rhinitis and aeroallergen sensitivity

Allergic rhinitis and aeroallergen sensitisation are often considered alongside asthma as part of the same airway disease based on their shared physiological response. Consistent with other large-scale cohort studies on intrauterine vitamin D exposures and allergic rhinitis²⁰ or hay fever¹⁷ and aeroallergen sensitisation,^{17,20,40} in addition to a recent meta-analysis,⁴⁶ we found no significant association between maternal or cord 25(OH)D status and allergic rhinitis or aeroallergen sensitivity. However, smaller scale studies have presented inverse^{13,21} or U-shaped¹⁹ associations between vitamin D and IgE-mediated sensitivity to aeroallergens.

4.5 | Strengths and limitations

Interpretation of the literature on vitamin D status and atopy is hampered by considerable heterogeneity in the types of studies conducted, study populations (unselected vs high risk), study location and latitude, sample sizes and duration of follow-up. Of particular concern is the variation in defining outcomes for atopic disease. Physician diagnosis and in-clinic assessment to define atopic outcomes using clinically validated criteria are preferable to parental identification as misclassification of symptoms and health outcomes cannot be ruled out. Our cohort includes detailed characterisation of participants, with data on all currently considered environmental modifiers of atopic disease.⁴⁷ A key strength is the use of prospectively collected, clinically validated atopic disease outcomes at multiple time points throughout the early childhood.^{27,28,47}

Attrition is a major methodological concern in all longitudinal studies, as it can affect generalisability of the study findings. In the current study, 86% of women from the SCOPE Ireland Pregnancy Study enrolled in the Cork BASELINE Birth Cohort Study. These women were more likely to be Caucasian and have a university

education and nonsmokers compared with nonresponders.²³ Throughout BASELINE, attrition rates were very low, with 78% of children returning for the 2-year assessment and 61% attending follow-up at 5 years. No significant differences were observed in maternal ethnicity, maternal education level or alcohol use during pregnancy in participants retained and those lost to follow-up; however, mothers with children still enrolled at 2 and 5 years tended to be older, married or in a relationship and were less likely to have smoked during their pregnancy.

While some studies have published relationships between maternal vitamin D intake and infant atopic outcomes,^{48,49} evaluation of the biomarker of exposure, 25(OH)D, is preferable to an estimate of dietary intake. A further consideration is the considerable variability between different analytical methods used to quantify serum 25(OH)D concentrations.^{50,51} It has been suggested that commercial assays produce more unreliable estimates at the higher and lower ends of the distribution of 25(OH)D concentrations, due to higher limits of detection and cross-reactivity with downstream metabolites.⁵¹ Particular attention should be given to chromatographically resolving minor circulating vitamin D metabolites known to interfere with 25(OH)D assays, especially in paediatric populations.⁵² This study reports 25(OH)D quantified at our CDC-accredited and DEQAS-certified laboratory.

Our study has limitations worth considering. We used self-reported data for parental atopy status, which are subjective. We did not explore genetic variants associated with IgE synthesis or vitamin D receptor polymorphisms. Despite the sample size, atopy prevalence was relatively low in this unselected cohort, which may reduce the power of this study to identify clinically relevant associations.

5 | CONCLUSIONS

In this unselected, white-skinned, prospectively and extensively characterised, clinically supervised, disease-specific cohort with gold standard analysis of 25(OH)D, we did not observe any association between vitamin D status during pregnancy or at birth with allergic disease outcomes at 2 and 5 years. Clearly, further studies are required to understand the importance of vitamin D in allergic disorders, either solely or in combination with other environmental and genetic factors.

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CONFLICT OF INTEREST

All authors declare that they have no relevant conflict of interests to disclose.

AUTHOR CONTRIBUTIONS

ÁH and MEK designed the research and wrote the manuscript. ÁH extracted the data, and ÁH and LM performed the statistical analysis. DMM is the BASELINE Study Principal Investigator, and JO'BH, LCK, ADI and MEK are co-PIs leading the research in BASELINE in their specialist fields. All authors reviewed and approved the final submission.

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