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Title: Is antenatal or early-life vitamin D associated with eczema or food allergy in childhood? A systematic review

Short title: Systematic review of vitamin D and eczema/food allergy

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Abstract

Objective: To summarise the associations between antenatal or early-life blood vitamin D and the development of eczema/ food allergy in childhood.
Design: A systematic review and meta-analyses were conducted to synthesize the published literature. Two reviewers independently performed the study selection and data extraction on Covidence. We assessed the risk of bias for observational studies by using the Newcastle-Ottawa Scale and the Cochrane Risk of Bias tool for clinical trials. The certainty of the evidence was assessed using Grading of Recommendations, Assessment, Development and Evaluations (GRADE).
Data sources: We systematically searched PubMed and Embase from inception and April 2022.
Eligibility criteria: Human studies that investigated prospective associations between antenatal or early-life blood vitamin D levels, dietary intake or supplementation, and childhood eczema/ food allergy.
Results: Forty-three articles including six randomised controlled trials (RCTs) were included. Four RCTs of vitamin D supplementation during pregnancy showed no evidence of an effect on the incidence of eczema (pooled odds ratio [OR] = 0.85; 0.67-1.08, I^2=6.7%, n=2074). Three RCTs reported null associations between supplementation in pregnancy/infancy and food allergy. From six cohort studies, increasing cord blood vitamin D levels were associated with reduced prevalence of eczema at/close to age one (OR per 10 nmol/L increase= 0.89; 0.84-0.94, I^2=0%, 2025 participants). We found no evidence of an association between maternal antenatal or infant vitamin D level or dietary intake and the development of food allergy or eczema in offspring.
Conclusions: We found an association between higher vitamin D levels in cord blood and reduced risk of eczema in cohort studies. Further trials with maternal and infant supplementation are needed to confirm if vitamin D supplementation can effectively prevent eczema or food allergy in childhood.
Systematic review registration: PROSPERO, No. CRD42013005559

Keywords: Cord blood, Eczema, Food allergy, Systematic review, Vitamin D

Key messages

- Higher vitamin D status at birth may protect against the development of eczema in childhood.
- No strong evidence of the association between vitamin D supplementation during pregnancy and offspring's eczema.

- More trials are needed to confirm vitamin D's effectiveness in preventing eczema and food allergy.

Background

Allergic diseases, including asthma, allergic rhinitis, eczema (atopic dermatitis), and food allergy, are major public health issues.(1, 2) Globally, about 200 to 250 million people have food allergies (3) and around 5% to 10% of adults have eczema.(4) These chronic allergic conditions not only impact the quality of life of children and their families but also are a substantial burden on healthcare systems(5-7).

Low levels of vitamin D have been suggested to be a cause of eczema and food allergy.(8, 9) Identification of the role of vitamin D in early life and its biological pathway for eczema and food allergy, may lead to preventive strategies as vitamin D levels are modifiable by sun exposure and supplementation.(10) There are two main forms of vitamin D: D2 (ergocalciferol, from radiated mushrooms), and D3 (cholecalciferol, from 7-dehydrocholesterol in the skin from sun exposure).(11) As eczema and food allergy are generally present in the first year of life and are the earliest manifestations of allergic diseases(12), adequate exposure to vitamin D during pregnancy and very early life may be critical. The complex of vitamin D receptor (VDR) and vitamin D has been found to decrease sensitization and downregulate inflammation.(13, 14) A previous study found that vitamin D supplementation during pregnancy may increase the mRNA levels of immunoglobulin-like transcripts (ILT)3 and ILT4 in cord blood, so maternal vitamin D intake may induce a tolerogenic immune response and ultimately impact the Th1/Th2 balance and eczema/food allergy(15), and previous studies have implicated low levels of maternal vitamin D deficiency in the development of eczema in offspring(16, 17).

Given the increasing literature on this topic, evidence needs to be systematically synthesised. To date, five systematic reviews(18-22) have previously explored the association between vitamin D and eczema, and some(18, 19) of these reviews included cross-sectional observational studies, which may be impacted by reverse causation. Associations between vitamin D and food allergy have not been previously synthesised. To address these knowledge gaps, we conducted a systematic review to synthesize the evidence on early life vitamin D levels and intake/supplementation and the risk of developing eczema and food allergy in prospective observational studies and clinical trials.

Methods

We have undertaken this systematic review and meta-analyses, applying the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement(23) and Meta-analysis of Observational Studies in Epidemiology (MOOSE)(24) (See PRISMA and MOOSE checklist in Document S1). The protocol for this systematic review was prospectively registered with the Internal Prospective Register of Systematic Review (PROSPERO, CRD42013005559) which included a broader range of allergic diseases. As we have published a systematic review exploring the association between vitamin D and asthma/wheeze(25), here we focus only on eczema and food allergy.

Data sources and search strategies

We searched for original journal articles on PubMed and Ovid Embase (last search performed on 27 April 2022) that reported on antenatal and early-life vitamin D serum levels, intake and supplementation and the development of eczema/food allergy in offspring up to 18 years old (Document S2). We also searched for eligible studies from the references of the included papers and previous systematic reviews.

Study eligibility criteria

We included cohort studies and case-cohort studies that measured the maternal antenatal, cord blood, or infant 25(OH)D levels and/or maternal or infant dietary intake prior to the assessment of eczema/food allergy. Randomised controlled trials (RCTs) that investigated the effect of vitamin D supplementation during pregnancy or infancy on the risk of eczema and food allergy in childhood were also included. Eczema was defined as (i) (parental report of) physician-diagnosed eczema, (ii) parental reports of using eczema medication, (iii) assessed by the International Study of Asthma and Allergies in Children (ISAAC)(26), (iv) Hanifin & Rajka criteria(27), and (v) the UK Working Party's diagnostic criteria(28). The presence of food allergy was defined as (i) positive oral food challenge, and/or (ii) (parental report of) physician-diagnosed food allergy using history and skin prick testing (SPT), and/or (iii) parental reports of food allergy including medication or history, and/or (iv) assessed by modified EuroPrevall criteria(29). Non-English and non-human studies were excluded. Papers that studied the cross-sectional associations between early-life vitamin D levels and outcomes were excluded.

Two reviewers (RZ & YL) independently performed title and abstract screening and full-text review, according to inclusion and exclusion criteria in Covidence (Document S3). All discrepancies of selection were resolved through consensus with the involvement of a third reviewer (AJL).

Data extraction and risk of bias assessment

Two independent reviewers (RZ & YL) extracted the basic study characteristics and outcomes information, including author, country, year of publication, number of participants included in the analysis, study design, method of measurement and categorization of vitamin D level exposure, vitamin D dietary intake assessment method and category, experimental/exposed and control/unexposed group, vitamin D dose and duration, and adjusted confounders. The reported measure of association (i.e., the crude or adjusted odds ratios [ORs] and 95% confidence intervals [CIs]) were also extracted.

Two independent reviewers (RZ & CC) assessed the risk of bias by using the Newcastle-Ottawa Scale(30) (Table S1) for observational studies and the Cochrane Risk of Bias tool (RoB 2.0)(31) for RCTs. Key potential confounders included family atopy history, maternal age, prenatal maternal smoking, the number of children, the presence of older siblings, pets and the season of blood drawn/the season of birth. Any disagreement was resolved by consulting a third reviewer (AJL).

Data synthesis and statistical analysis

We performed meta-analyses when there were two or more studies with similar study designs and reported associations with comparable exposures and outcomes. We pooled the estimates of the prevalent (symptoms within the past12 months) eczema/food allergy as well as ever eczema/food allergy (which indicates the cumulative incidence of outcomes). For eczema prevalence assessed at multiple timepoints within studies, we chose the effect estimates (i) at or close to 1-year old and (ii) at the longest follow-up time point.

We pooled association estimates by different vitamin D exposure categories: (i) for every 10 nmol/L increase of blood vitamin D level and (ii) sufficiency vs. deficiency group (using the cut-off value defined by each study) ; (iii) higher group vs. lower group, where the lower group was the reference group. Risk ratio (RR) estimates and their corresponding 95% CI, were converted to odds ratios (OR) using the following formula: $OR=[(1-P_0) *RR/(1-RR*P_0)]$, where P_0 is the prevalence of eczema or food allergy in the non-exposed group. (32)

Where RCTs reported associations at multiple ages, we only included the results which were assessed at (or as close as reported to) 1 year of age, to minimize potential bias due to loss to follow-up and as eczema and food allergy are commonly expressed at this age. We contacted three authors of studies that used mean difference to recalculate the risk estimates in ORs.(33-35) We also contacted eight authors for additional data(36-43), while three authors were contacted for the details to assist with the quality assessment(17, 36, 44). In total, seven authors responded and provided additional data.(17, 33, 36, 37, 41-43)

We used both fixed and random effect models for meta-analysis. Heterogeneity was assessed by using the I^2 statistics (I^2> 30%, moderate heterogeneity; I^2>75%, considerable heterogeneity). If I^2 was higher than 75%, results were not pooled. Results were reported separately for the type of vitamin D exposure (measured vitamin D level, dietary intake, or supplementation) and the time of vitamin D exposure (during pregnancy, at birth or infancy). Restricted analyses, using only studies with low risk of bias or studies with the outcomes at age one, were conducted. Forest plots were used to present the pooled estimates. We used the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) methodology to rate the certainty in the body of evidence in our key findings.(45-49) All analyses were performed by Stata 16 (StataCorp).

Results

Search results

We identified 2137 records with 1389 from Embase and 748 from PubMed. Searching bibliographies from other review articles yielded no additional references. 43 manuscripts were included in this study (Fig. S1 & Table S2 for exclusion reasons).

Study characteristics

The included papers were based on 33 separate study populations, including six RCTs (eight papers (33, 50-56)), 25 longitudinal cohorts (33 papers(17, 34-37, 40-42, 44, 57-80)) and two case-cohort studies(81, 82). Two RCTs (Project VDAART(53, 54) and Rueter et al.'s studies(50, 51)) and seven prospective studies generated multiple publications. These studies came from 16

countries/regions, with latitudes ranging from 38°S(82) to 65°N(62). The number of participants varied between 116 and 806 for the RCTs, while the number varied from 92 to 4921 for observational studies (Table 1 and Table S3).

RCTs

Study design, settings and period: The six clinical trials were all parallel-group RCTs that were heterogeneous regarding the intervention dose, starting age, duration of vitamin D supplementation and definition of eczema or food allergy (Table 1). Among the six trials, four trials were conducted in Europe(33, 52, 55, 56), one in Australia(50), and one in America(54). Two trials(50, 54) recruited newborn infants with a family history of allergic diseases while four trials(33, 52, 55, 56) comprised participants from the general population. Four clinical trials were only in pregnancy(33, 52, 53, 56) while one commenced in infancy(51) and one began in pregnancy and continued into infancy (55).

Study intervention and control condition: Five trials(51, 52, 54-56) gave daily vitamin D supplements, ranging from 400 IU(50, 51) to 4400 IU(54). One study(33) gave a one-time bolus of 200,000 IU or 800 IU daily in the intervention groups. One RCT had two different vitamin D interventions (isolated vitamin D supplementation vs. vitamin D from multivitamins).(54) For the control groups, three trials used placebos(33, 51, 56), while the rest three trials gave 400 IU of daily vitamin D to participants(52, 54, 55). The trials' supplementation durations ranged from eight weeks(54) to 24 months(55). The lag period between vitamin D supplementation and outcome assessment differed from one year(55) to six years(54).

Study outcomes: All RCTs reported eczema outcomes, while only three trials reported food allergy outcomes.(33, 51, 55) These studies applied different eczema assessment methods, with the use of the ISAAC questionnaire(33, 55), the parental report of doctor-diagnosed eczema(54), the Hanifin & Rajka criteria(50, 52) and the UK Working Party's diagnostic criteria(56). Similarly, different food allergy definitions were used, including parental reports of doctor-diagnosed food allergy(33, 50, 55) and the primary health care records(33) (Table 1).

Study quality: For eczema outcomes, one clinical trial was classified as high risk of bias, four with some concerns of risk of bias and one with low risk of bias (Fig. 1 & Fig.S2). For food allergy outcome quality assessment, one trial was assessed as high risk of bias and two trials were classified with some concerns of risk of bias (Fig.1 & Fig.S3). The main reasons for potential bias in both eczema and food allergy trials were related to missing outcome data and outcome measurement (Fig. S2 & Fig.S3). The RCTs results were rated from very low to high by GRADE (Table 2).

Synthesis of study findings

Three studies(51, 55, 56) measured the prevalence of eczema/food allergy at one year of age, while three studies(33, 52, 54) reported the cumulative incidence of eczema/food allergy between three and six years of age. Where a longer period was not available, we treated the prevalence at age one as a cumulative incidence to estimate the pooled association.

Eczema: Pooled results from the maternal supplementation during pregnancy did not show strong evidence of an effect on cumulative incidence or prevalence of eczema, but estimates showed a trend of reduced risk (cumulative incidence of eczema from four studies(33, 52, 54, 56), OR= 0.85, 95% CI=0.67-1.08, I^2=6.7%, 2074 participants, Table 2, Fig. 1; the prevalence of eczema from two studies(33, 56) OR=0.80, 95% CI=0.5-1.81, I^2=57.4%, 787 participants, Table 2, Fig. S4). While the other three studies on pregnant women gave vitamin D doses from 800 IU to 1200 IU daily, the VDAART study (Litonjua et al) gave an extremely high dose of vitamin D (4000 IU/day) to the intervention group, and 400IU/day to the control group, which may mask any protective effects (Table 2, Fig. 1). One trial assessed with some concerns showed a protective effect of vitamin D supplementation during pregnancy (OR=0.57, 95%CI=0.33-0.98, 635 participants)(56), while the study with low risk of bias(52) did not show strong evidence.

The two studies(51, 55) that examined infancy supplementation showed highly heterogeneous findings for eczema outcomes (Fig. 1, I^2=76.8%), so we did not pool these results. The possible reason for the high heterogeneity may be the variations in intervention dose vs control dose (1200 IU vs. 400 IU in Rosendahl et al.'s study, compared with 400 IU vs. 0 IU in Rueter et al.'s study), the study population (general population in Rosendahl et al.'s study vs. infants with a family history of atopy in Rueter et al.'s study), and that the locations with different levels of sunlight (Rosendahl's study 60.1°N vs. Rueter et al.'s study 31.9°S).

Food allergy: The effect of maternal vitamin D supplementation on food allergy outcome was only reported in one RCT(33) (OR=1.81, 95% CI 0.48-6.85, 151 participants). The results for the cumulative incidence of food allergy outcomes had limited power (pooled OR=1.35, 95% CI 0.78-2.34, I^2=0.0%, two studies, 945 participants, Table 2, Fig. 1).

Observational studies

Of the 35 observational study articles, 29 explored the associations between vitamin D blood levels and eczema/food allergy, while six studies only reported vitamin D dietary intake(40, 58, 66, 67, 72, 80) (Table S3). Two papers measured both vitamin D levels and dietary intake.(36, 76) As the cutoff values for vitamin D sufficiency varied between studies (50 nmol/L was applied the most(34, 37, 42, 59-61, 63, 65, 77, 78, 82), while other studies used 27.5 nmol/L(70), 25 nmol/L(36), 75 nmol/L(41)), we pooled sufficiency vs. deficiency group studies with the higher vs. lower group studies by combing them into a new category of vitamin D measurement ((More (sufficiency/higher group) or Less (deficiency or lower group)).

Study quality: The included studies were of mixed quality (e.g., eight poor quality studies vs. six good quality studies regarding the association between maternal vitamin D level and eczema outcome) (Table S4 & S5). The adjustment of confounders, outcome assessment methods, and follow-up adequacy were the main domains for concerns for the quality of the studies. The certainty in the body of evidence was rated from very low to low (Table 3 and Table 4).

Outcome assessment

Eczema: Although some studies used the term "atopic dermatitis", they did not divide eczema into atopic versus non-atopic subtypes. Therefore, we have elected to use the term "eczema" no

matter what term was used in the original studies. 31 studies assessed eczema outcomes, by using the ISAAC questionnaire(35, 44, 62, 63, 66-68, 72), the Hanifin & Rajka criteria(17, 37, 57, 59-61, 73), the UK Working Party Criteria(41, 64, 71, 74, 82), clinician skin examination(37, 59-61, 74) and parental report of doctor-diagnosis(34, 36, 42, 58, 65, 69, 70, 73-77, 80)(Table S3). The outcome assessment age ranged from one to seven years of age.

Food allergy: Associations between vitamin D levels and food allergy outcomes were reported in 12 observational studies.(17, 35, 42, 64, 68, 71, 76-79, 81, 82) The association between vitamin D dietary intake and food allergy were reported only in three studies.(40, 76, 80) Studies used several food allergy assessment methods, including SPT and oral food challenge up to two years old (64, 78, 79, 82), SPT and food allergy history report at one year(76) and three years old(17) and nine years old(35), SPT and peanut allergy under six years old(81), the physician diagnosed cow milk allergy up to three years old(40), parental report of food allergy symptoms and IgE level testing at one year old(71), and parental report of doctor diagnosis from one to nine year-old(42, 77, 80) (Table S3).

Vitamin D level and eczema

Most studies reported a median/mean vitamin D level of higher than 50 nmol/L in maternal blood during pregnancy, while the cord blood vitamin D levels were much lower, with the lowest mean vitamin D level being only 15.6 (SD 1.4) nmol/L.(35) Included studies applied different vitamin D measurement methods, with liquid chromatography-tandem mass spectrometry (LC-MS/MS)(17, 34, 59, 63-65, 73, 75, 76, 78, 79, 82) being the most common method, compared with chemiluminescent immunoassays(36, 37, 41, 44, 60, 61, 71), high-performance liquid chromatography (HPLC)(35, 42, 68-70, 77) and radioimmunoassay(74) (Table S3).

Cord blood vitamin D level and eczema

Associations with umbilical cord blood sample (UCB) vitamin D levels were reported in 18 studies. Among these studies, eight studies controlled for the season during analysis.(36, 42, 44, 57, 59, 63, 75, 76) There was consistent evidence that increasing levels of vitamin D in cord blood were associated with reduced prevalence of eczema at or close to one year of age (pooled OR per 10 nmol/L increase = 0.89, 95% CI=0.84-0.94, I^2=0%, six studies, n=2025, Table 3 & Fig. 2). There was no evidence of an association between More vs. Less vitamin D in cord blood and eczema outcomes (Table 3). We did not include two studies in the meta-analyses because they used per quartile as the unit of vitamin D exposure(42, 77) which was cohort specific. The inclusion of the two estimates (OR (95%CI) =1.17 (0.76-1.81), n=272, and 1.34 (1.00-1.80), n=305, respectively) may attenuate the association between cord blood vitamin D and eczema (Table 3). Similar associations were observed between cord blood vitamin D and the prevalence of eczema at the longest follow-up time point (Fig. S5). We did not find any evidence of an association between cord blood vitamin D levels and the cumulative incidence of eczema (Fig. S6). The sensitivity analysis which only included the studies that measured eczema at one year of age or studies with low risk of bias did not substantively change the finding (Fig. S7).

Maternal vitamin D level and eczema

Maternal blood was obtained in 13 studies, with four studies assessing vitamin D levels in mid-pregnancy (2nd trimester(34, 36, 63, 64)) and seven studies measuring late pregnancy (3rd trimester(42, 65, 70, 71, 74, 76, 82)). Two studies measured vitamin D levels in both trimesters. (41, 69) Five studies controlled for season.(36, 41, 42, 60, 63, 74) Analysis by vitamin D category, regardless of the prevalence or cumulative incidence of eczema, we found no evidence of an association between maternal blood vitamin D level and the risk of eczema (Table 3 & Fig. S8).

Infant vitamin D level and eczema

The association between infant blood vitamin D levels and eczema was investigated by five studies(57, 73, 75, 77, 82), among which only two studies controlled for season(57, 75). We did not find any evidence for an association between vitamin D in infant blood and the prevalence of eczema (pooled OR for more vs less =0.82, 95% CI 0.51-1.32, I^2=0.0%, three studies(57, 73, 82), Fig. S9; per 10 nmol/L increase of vitamin D, OR=1.03, 95% CI 0.89-1.20, one study(75)).

Vitamin D dietary intake and eczema

Vitamin D dietary intake during pregnancy or infancy with offspring's risk of eczema from age one to nine years were investigated in eight studies(36, 40, 58, 66, 67, 72, 76, 83), among which two studies reported the results from the same cohort(36, 58)(Table S3). Data on vitamin D intake were collected by diet history questionnaire (DHQ) or food frequency questionnaire (FFQ).

A variety of vitamin D intake units were used and the cutoff values for the higher/lower vitamin D intake were substantially heterogeneous among studies, so we could not pool the estimates from all the studies (Table S3). There was no evidence of an association between maternal vitamin D dietary intake and the cumulative incidence of eczema (Fig. S10). The association between infant vitamin D dietary intake and cumulative incidence of eczema was examined in one study, which showed higher intake was associated with an increased risk.(72) For every 1 ug/kg body weight of vitamin D intake increase, the adjusted OR was 3.63 (95%CI 1.49-8.87).

Vitamin D level and food allergy

We did not find any evidence of an association between maternal vitamin D levels and the prevalence of food allergy (For More vs. Less category, pooled OR=1.62, 95% CI 0.74-3.51, I^2=0.0%, two studies(71, 82); For per 10 nmol/L increase of vitamin D level, OR=1.02, 95% CI 0.89-1.16, one study(64), Table 4). There was no overall evidence of an association between cord blood vitamin D level and the prevalence of food allergy (per 10 nmol/L increase of vitamin D level, pooled OR=0.93, 95% CI 0.73-1.19, I^2=72.6%, three studies(17, 64, 76), Fig. 3), neither for the cumulative incidence of food allergy (Fig. S11). We found no evidence of an association between vitamin D levels during infancy and the cumulative incidence of food allergy (OR=1.28, 95% CI 0.75-2.17, I^2=0.0%, two studies).(81, 82)

Vitamin D dietary intake and food allergy

No association between maternal vitamin D intake during pregnancy and the cumulative incidence of food allergy were found, although the results were highly heterogeneous (I^2=73.9%, two studies).(40, 80) One study reported the association between maternal vitamin D dietary intake and the prevalence of food allergy, reporting no evidence of an association (OR=1.08 (0.97-1.19)).(76) One study also investigated the association between maternal vitamin D intake during lactation and cow's milk allergy by 3 years of age (OR=0.92, 95% CI 0.75-1.13). (40)

Discussion

In this systematic review, we found evidence from observational studies that higher 25(OH)D levels in cord blood were associated with a reduced prevalence of eczema in childhood, but not with the risk of food allergy. While there was no strong evidence of an effect of maternal vitamin D supplementation on eczema outcomes from existing RCTs, the findings were relatively consistent with the findings in observational studies. No associations were observed between maternal or infant vitamin D levels/dietary intake/supplements and risk of eczema and food allergy. Previous systematic reviews(20, 21) have included vitamin D dietary intake or supplementation and eczema studies, but they did not synthesize the evidence due to huge heterogeneity among studies. Our systematic review addressed this issue by synthesizing the estimates for different categories of vitamin D and eczema.

Strengths and limitations

Our systematic review has several strengths. We only included RCTs and prospective observational studies that ensured the temporal order of vitamin D exposure prior to the development of eczema/food allergy. Moreover, we searched for a wide range of vitamin D exposures at multiple times, which provides a comprehensive assessment of the literature on these associations.

However, some of the evidence of pooled RCTs and observational studies, including the vitamin D supplementation during pregnancy and eczema development in offspring and cord blood vitamin D level and cumulative incidence of eczema, have been downgraded due to serious heterogeneity, serious imprecision and risk of bias.

Comparison with previous studies

Our finding for increased cord blood vitamin D levels and reduced eczema risk is consistent with a previous meta-analysis(84) that pooled estimates from six studies. A key strength of our study is that we harmonized the measurement of association between cord vitamin D and change of eczema risk as the association per 10 nmol/L increase in vitamin D level, allowing us to directly compare results between the studies.

Our review did not find any association between maternal vitamin D level and eczema in childhood, while a previous systematic review based on three studies found that higher maternal vitamin D status during pregnancy was associated with a decreased eczema in childhood.(85) The limitation of the previous meta-analysis(85) is that it pooled estimates from different exposures, including maternal/cord serum vitamin D, and vitamin D dietary intake and

supplements and the discrepancy of exposure measurements may attenuate the estimate of association.

The discrepancy of results from RCTs and observational studies

While there is an association between cord blood vitamin D level and eczema outcome, we did not see strong evidence of protective effect of vitamin D supplementation in RCTs. The discrepancy in results between RCTs and observational studies may derive from several reasons. First, there is serious imprecision due to wide 95%CI in the pooled estimates of RCTs, which made the results hard to draw a conclusion. However, it is also possible that the observational studies may be biased by residual confounding related to race and ethnicity, and factors impacting sun exposure. This is particularly an issue when we consider that the GRADE assessment levels are higher in the pooled estimates in the included RCTs than observational studies. Moreover, it remains possible that maternal inflammation due to active allergic disease may both suppress the level of cord vitamin D (which is an acute phase reactant(86)), and also predispose to or predict eczema in the child. As vitamin D supplementation is a relatively cheap and safe intervention, and the existing evidence remains compatible with a potentially important protective effect, further trials are required.

Possible implications

Our meta-analysis found that for every 10 nmol/L increase of vitamin D level in cord blood, there was an 11% reduction in eczema risk. If it is considered that at least a 30% risk reduction in the prevalence of eczema is required to warrant this form of intervention, then an increase of 30 nmol/L for vitamin D levels in cord blood would be required. There is no clear formula for the association between the dose of vitamin D supplementation and the increased level of vitamin D in cord blood. However, a dose of 25 ug of vitamin D3 (1000 IU), has been found to raise 25(OH)D serum level by 15-25 nmol/L on average(87, 88), so it is possible a 2000 IU/day or more supplementation may increase more than 30 nmol/L vitamin D serum level in maternal or cord blood. In our systematic review, we did not see strong evidence of a protective effect of maternal supplementation/intake during pregnancy. However, the real effect may be masked as some trials(52, 54) gave 400 IU vitamin D to control groups. Therefore, we need more clinical trial to confirm this hypothesis.

Interestingly, the results of the associations between cord blood vitamin D and eczema outcomes are inconsistent with the results seen in maternal vitamin D levels during pregnancy. While maternal 25(OH)D concentrations being strongly associated with cord blood vitamin D levels(89, 90), cord blood vitamin D levels are much lower than maternal blood levels(91). It should be noted that the strength of the association between maternal and cord blood vitamin D levels is attenuated when maternal vitamin D levels are low (<37.5 nmol/L) and this association is stronger in White compared with Black children.(92). As only two studies(64, 82) reported the associations for both maternal and cord blood vitamin D, it is challenging to directly compare between these findings.

Conclusion

We found an association between higher vitamin D levels in cord blood and reduced risk of eczema in infants in cohort studies, but we did not see strong evidence of protective effects in studies focusing on maternal vitamin D intake/supplementation or maternal blood vitamin D levels. Further trials with maternal and infant supplementation are needed to confirm if vitamin D supplementation can effectively prevent eczema or food allergy in childhood.

(Word count: 4482)

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Conflict of Interest

AJL, CJL, and SCD have received an investigator-initiated grant from GlaxoSmithKline for unrelated research, and SCD holds a similar grant from AstraZeneca. AJL has received investigational product (EpiCeram TM) free of charge from Primus Pharmaceuticals for use in unrelated research. KPP's institution has received research grants from DBV Technologies, Novartis and Siolta Therapeutics and consultant fees from Aravax outside the submitted work. Other authors have nothing to disclose.

Table 1 Characteristics of the randomised controlled trials

Reference	Trial Design Name	City/ Country (latitude)	Participants characteristics	Intervention (Number of participants)	Comparator (Number of participants)	Outcome assessment method/age
Goldring 2013(33)	Single-center, Non-blinded	London, UK (51.5°N)	Healthy women ≤ 27 weeks gestation	1) 800 IU ergocalciferol daily from 27 weeks gestation until delivery (n=60). 2) single oral bolus of 200,000 IU cholecalciferol at 27 weeks gestation (n=60)	Standard care (n=60)	1. Ever eczema (ISAAC, at age 3). 1b. Eczema period prevalence (in the year prior to age 3) 1c. Ever eczema (Primary health care records, at age 3) 2a. Ever food allergy (parental report of doctor-diagnosed food allergy, at age 3). 2b. Ever food allergy (Primary health care records, at age 3)
Rueter 2019(50) Rueter 2020(51)	Single-center, Double-blinded	Perth, Australia (31.9°S)	Healthy term singleton newborns infants with a family history of allergic diseases. Excluding infants whose mothers a) smoked during pregnancy, b) had immunodeficiency/ autoimmune disease or c) had <50 nmol/L or >100 nmol/L 25[OH]D in late pregnancy.	400 IU of vitamin D3 per day orally from newborn to 6 months of age (n=97)	Coconut and palm kernel oil from newborn to 6 months of age (n=98)	1. Ever Eczema (Hanifin criteria & steroids treatment records, at age 1 and 2.5) †, ŧ 2. Ever IgE-mediated Food allergy (parental report of doctor-diagnosed food allergy history, at age 1 and 2.5) ‡

Chawes 2016(52)	Single-center Double-blinded COPSAC2010	Copenhagen, Demark (55.6°N)	Pregnant women with the exclusion of gestational age above week 26, any endocrine, cardiovascular, or nephrological disorders; or vitamin D3intake more than 600 IU/d	2400 IU of vitamin D3 plus 400 IU of vitamin D3 daily from 24 gestational weeks to 1 week postpartum (n=315)	Matching placebo tablets (Camette A/S) plus 400 IU of vitamin D3 daily from 24 gestational weeks to 1 week postpartum (n=308)	Ever eczema (Hanifin & Rajka criteria at age 3) §
Litonjua 2016(53) Litonjua 2020(54)	Multicenter Double-blinded VDAART	Boston, St. Louis, San Diego, the USA (42.3°N, 38.6°N, and 32.7°N)	English or Spanish speaking pregnant women aged 18 to 39 years, gestational ages of 10 and 18 weeks, who or whose partner had a history of allergic diseases,	Daily 4000 IU of vitamin D plus a multivitamin with 400 IU of vitamin D from about 22 to 30 weeks of gestation (n=440)	Daily placebo pill plus a multivitamin with 400 IU of vitamin D from about 22 to 30 weeks of gestation (n=436)	Ever eczema (parental report of doctor's diagnosis of eczema with rash, at 3 years (53) and 6 years of age(54))
Rosendahl 2019(55)	Single-center Double-blinded	Helsinki, Finland (60.1°N)	a) Health pregnant women of northern European ethnicity with a singleton pregnancy. b) Healthy infants born at 37 to 42 weeks of gestation with an appropriate birth weight)	1200 IU of vitamin D3 (30 ug) daily from the age of 2 weeks to 24 months of age (n=486)	400 IU (10 ug) of vitamin D3 daily from the age of 2 weeks to 24 months of age (n=489)	1. Eczema period prevalence (ISAAC, at age 12 months) ¶. 2. Ever food allergy (Parental report of a history of doctor's diagnosis, at age 12 months) ʒ
El-Heis 2022(56)	Multicenter Double-blinded MAVIDOS	Southampton United Kingdom	Women aged over 18 years, having a singleton pregnancy with a gestational age <17 weeks, and serum 25(OH)D between 25 and 100nmol/l and calcium <2.75mmol/l	Cholecalciferol 1000 IU daily from 14 weeks' gestation until delivery (n=352)	Daily placebo from 14 weeks' gestation until delivery (n=351)	Atopic eczema (the UK Working Party diagnostic criteria at 12, 24 and 48 months) ŧ

Abbreviations: ISAAC, the International Study of Asthma and Allergies in Children; COPSAC2010, the Copenhagen Prospective Studies on Asthma in Childhood 2000; VDAART, the Vitamin D Antenatal Asthma Reduction Trial; MAVIDOS, the Maternal Vitamin D Osteoporosis.

† Eczema was defined according to the criteria of Hanifin et al. on medical review or when a typical history was taken of an itchy rash distributed to the facial, extensor or flexural surface of the skin following a chronic or fluctuating course.

‡ IgE-mediated food allergy was defined by a history of an immediate (within 90 min) skin rash (urticaria, erythema), angioedema, gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) and/or irritability associated with or without cardiovascular symptoms (collapse) and/or respiratory symptoms (wheeze, stridor, persistent cough, hoarse voice) following the ingestion of a specific food trigger combined with a matching food allergen sensitization.

§ Eczema at age 0 through 3 years was diagnosed according to the criteria of Hanifin and Rajka including typical morphology and localization of skin lesions.

¶ The cut off value for vitamin D deficiency is 50 nmol/L.

ʒ Food allergy ever to cow's milk, wheat, or any food.

ŧ Atopic eczema definition was based on the UK Working Party diagnostic criteria, assessed by trained research nurses who undertook a standardized questionnaire an examination. Itchy skin condition in the past 12 months was a mandatory criterion in addition to three of: onset age <2 years, history of eczema (flexural or of cheeks and extensors in under 18 months), history of dry skin the last year, and visible flexural eczema (or visible eczema of the cheeks and extensors if under 18 months).

Table 2 Meta-analysis of randomised controlled trials for vitamin D supplementation and eczema or food allergy

Supplementation Timepoint	Outcome	Outcome category	Number of RCTs	Number of participants	Pooled Odds ratio (95%CI) P-value for the pooling, I^2(%)	GRADE
During pregnancy	Eczema	Prevalence	2 (24, 33)	787	0.80 (0.35-1.81) P= 0.587, I^2=57.4%	⊕◯◯◯ Very Low [a, b, c]
		Cumulative incidence	4 (33, 37, 52, 54)	2074	0.85 (0.67-1.08) P= 0.189, I^2=6.7%	⊕⊕⊕◯ Moderate [c]
	Food allergy	Cumulative incidence	1 (33)	151	1.81 (0.48-6.84)	⊕⊕◯◯ Low [a, d]
During infancy	Eczema	Prevalence	2 (51, 55)	944	No pooled estimate due to serious heterogeneity, I^2=76.8%[‡]	⊕⊕⊕◯ Moderate [b]
	Food allergy	Cumulative incidence	2 ((51, 55)	945	1.35 (0.78-2.34) P= 0.279, I^2=0.0%	⊕⊕⊕◯ Moderate [d]

[‡] Random effect model used. CI: confidence interval.

[a] GRADE score downgraded for risk of bias or limitations; [b] GRADE score downgraded for serious heterogeneity or inconsistency; [c] GRADE score downgraded for serious imprecision, 95%CI includes important benefit and potential harm; [d] GRADE score downgraded for imprecision, small sample size.

Table 3. The summary of pooled estimates by vitamin D level timepoint and eczema category

Vitamin D timepoint	Eczema Category	Category of vitamin D assessment	Included studies	Number of studies (Study reference)	Pooled Odds ratio (95%CI) P-value for the pooling, I^2(%)	GRADE
Birth[§,ℑ] (Cord blood)	Prevalence	Per 10 nmol/L increase	Studies with eczema at/close to 1-year old	n=6 (17, 44, 59, 64, 75, 76)	**0.89 (0.84-0.94)** [*] **P<0.001**, I^2=0.0	⊕⊕◯◯ Low
			Studies with the longest follow-up (1- to 7-year-old)	n=6 (17, 44, 59, 64, 75, 76)	**0.88 (0.83-0.93)** [*] **P<0.001**, I^2=0.0	⊕⊕◯◯ Low
			Studies measuring eczema at 1-year old	n=4 (17, 44, 75, 76)	**0.87 (0.82-0.92)** [*] **P<0.001**, I^2=0.0	⊕⊕◯◯ Low
			Studies with good quality	n=4 (17, 44, 64, 76)	**0.88 (0.83-0.94)** [*] **P<0.001**, I^2=0.0	⊕⊕◯◯ Low
		More vs. Less [†]	Studies with eczema at/close to 1-year old	n=4 (57, 59, 61, 63)	0.89 (0.65-1.22) P=0.462, I^2=0.0	⊕◯◯◯ Very Low [c]
			Studies with the longest follow-up	n=4 (57, 59, 61, 63)	0.78 (0.53-1.14) P=0.197, I^2=3.4	⊕◯◯◯ Very Low [c]
			studies measuring eczema at 1-year old	n=3 (57, 61, 63)	0.93 (0.67-1.28) P=0.646, I^2=0.0	⊕◯◯◯ Very Low [c]
	Cumulative incidence	Per 10 nmol/L increase	all eligible studies	n=3[€](17) (36, 69)	0.96 (0.87-1.04) [‡] P=0.311, I^2=56.1	⊕◯◯◯ Very Low [b]
		More vs. Less	all eligible studies	n=5 (36, 63, 68, 75, 82)	1.15 (0.69-1.91) [‡] P=0.584, I^2=70.8	⊕◯◯◯ Very Low [b]
Pregnancy[¶,ℑ]	Prevalence	Per 10 nmol/L increase	all eligible studies	n=2[ℑ] (41, 64)	1.02 (0.94-1.11) P=0.629, I^2=0.0	⊕⊕◯◯ Low
		More vs. Less	all eligible studies	n=6 (41, 60, 63, 70, 71, 74)	1.04 (0.88-1.22) P=0.648, I^2=0.0	⊕◯◯◯ Very Low [a]

(Maternal blood)	Cumulative incidence	Per 10 nmol/L increase	all eligible studies	n=2 (36, 69)	I^2=82.1[ŧ]	-
		More vs. Less	all eligible studies	n=4 (36, 63, 65, 82)	0.75 (0.45-1.26)[‡] P=0.281, I^2=57.8	⊕◯◯◯ Very Low [b, c]
Infancy (Infant blood)	Prevalence	Per 10 nmol/L increase	all eligible studies	n=1 (75)	1.03 (0.89-1.20)	⊕◯◯◯ Very Low [d]
		More vs. Less	all eligible studies	n=3 (57, 73, 82)	0.82 (0.51-1.32) P=0.412, I^2=0.0	⊕◯◯◯ Very Low [c]

* $p<0.005$

† More vs. Less: Due to the limited number of studies which used the sufficiency vs. deficiency vitamin D groups as the measurements, we combined this type of studies with the higher v. lower vitamin D level groups. Here "More" means sufficient or higher vitamin D levels groups, while "Less" means deficient or lower vitamin D groups.

‡ Random effect model used.

§ Three studies (33-35) using mean difference as the measure were contacted for more data and only one study(33) provided extra data for the analysis and the estimate from the raw data was included in the cord blood vitamin D and eczema meta-analysis. In the other two studies, (34, 35) were not included in the analysis due to lack of response. One study(35) was not included in the cord blood vitamin D and eczema meta-analysis due to the lack of OR data, so the pooled estimate could be impacted. One study(37) measuring the cord blood vitamin D level and eczema was not included in the meta-analysis due to insufficient data.

¶ One study(34) was not included in the maternal blood vitamin D and eczema meta-analysis due to the lack of OR data, so the pooled estimate could be impacted.

ʒ Two studies(42, 77) were not included in the meta-analysis of maternal and cord blood vitamin D and eczema because of the heterogenous unit of vitamin D level, we could also not pool these two studies as the vitamin D levels for per quartile are different between these two studies. The OR (95%CI) for per quartile increase of vitamin D in maternal blood during pregnancy and offspring's eczema at age one) is 1.16 (0.79-1.71) and OR (95%CI) for per quartile increase of vitamin D in cord blood and offspring's eczema at age one is 1.17 (0.76-1.81))in study(42). The OR (95% CI) for per quartile increase of vitamin D in cord blood and eczema at age three is 1.34 (1.00-1.80) in study(77). Our pooled estimate of the association between cord blood vitamin D (per 10 nmol/L) and eczema was OR =0.89 (95%CI=0.84-0.94). As both studies reporting results per quartile increase had an OR greater than 1, inclusion of these studies may have somewhat attenuated the pooled estimate.ŧ Results not pooled due to substantial heterogeneity of findings between the two included studies.

[a] GRADE score downgraded for risk of bias or limitations; [b] GRADE score downgraded for serious heterogeneity or inconsistency; [c] GRADE score downgraded for serious imprecision, 95%CI includes important benefit and potential harm; [d] GRADE score downgraded for imprecision, small sample size.

Table 4 Summary of pooled estimates by vitamin D level and food allergy category

Vitamin D timepoint	Food allergy Category	Category of vitamin D level	Number of studies (Study reference)	Pooled Odds ratio (95%CI) P-value for the pooling, I^2 (%)	GRADE
During pregnancy	Prevalence	Per 10 nmol/L increase	n=1 (64)	1.02 (0.89-1.16)	⊕⊕◯◯ Low
		More vs. Less	n=2 (71, 82)	1.62 (0.74-3.51) P=0.225, I^2=0.0	⊕◯◯◯ Very Low [c]
At birth	Prevalence	Per 10 nmol/L increase	n=3 (17, 64, 76)	0.93 (0.73-1.19) ‡ P=0.568, I^2=72.6	⊕◯◯◯ Very Low [b, c]
	Cumulative incidence	More vs. Less	n=3 (68, 78, 82)†	I^2=80.0§	⊕◯◯◯ Very Low [b]
		Per 10 nmol/L increase	n=1 (17)	0.78 (0.55-1.11)	⊕◯◯◯ Very Low [c]
During infancy	Cumulative incidence	More vs. Less	n=2 (81, 82)	1.28 (0.75-2.17) P=0.363, I^2=0.0	⊕◯◯◯ Very Low [c]

† One study used dried spotted sample which was taken at the first 48-72 hours after birth.(82) Two studies(78, 79) are from the same cohort and reported association using different vitamin D sufficiency threshold. We chose the one(28) used 20 ng/ml as the threshold to pool the estimate.

‡ Random effect applied.

§ Results not pooled due to substantial heterogeneity of findings among the three included studies.

‡ Random effect model used. CI: confidence interval.

[a] GRADE score downgraded for risk of bias or limitations; [b] GRADE score downgraded for serious heterogeneity or inconsistency; [c] GRADE score downgraded for serious imprecision, 95%CI includes important benefit and potential harm; [d] GRADE score downgraded for imprecision, small sample size.

Figure legends

Fig. 1 Associations between vitamin D supplementation and the cumulative incidence of eczema/food allergy in RCTs. All reference groups were the control groups in the trials. Random-effect models were used. Horizontal lines represent 95%CI. Estimates of vitamin D supplementation during infancy and eczema were not pooled as the I^2 is higher than 75%.

Fig. 2 Cord blood vitamin D level and the prevalence of eczema at or close to one-year old. More vs. Less: More represents the higher vitamin D level or vitamin D sufficient group, while less represents the lower vitamin D level or vitamin D deficient group. Horizontal lines represent 95%CI. Fixed-effect models were used.

Fig. 3 Cord blood vitamin D level and the prevalence of food allergy. Random-effect model was used. Horizontal lines represent 95%CI.

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