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TITLE

Vitamin D supplementation in primary allergy prevention: systematic review of randomized and non-randomized studies

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SHORT TITLE

Vitamin D supplementation in primary allergy prevention

ABSTRACT

Background: To date, a systematic review of the evidence regarding the association between Vitamin D and allergic diseases development has not yet been undertaken. **Objective:** To review the efficacy and safety of Vitamin D supplementation when compared to no supplementation in pregnant women, breastfeeding women, infants and children for the prevention of allergies. **Methods:** Three databases were searched through 30 January 2016 including randomized (RCT) and non-randomized studies (NRS). Two reviewers independently extracted data and assessed the certainty in the body of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. **Results:** Among the 1932 articles identified, one RCT and four NRS were eligible. Very low certainty in the body of evidence across examined studies suggests that Vitamin D supplementation for pregnant women, breastfeeding women and infants may not decrease the risk of developing allergic diseases such as atopic dermatitis (in pregnant women), allergic rhinitis (in pregnant women, and infants), asthma and/or wheezing (in pregnant women, breastfeeding women, and infants), or food allergies (in pregnant women). We found no studies of primary prevention of allergic diseases in children. **Conclusion:** Limited information is available addressing primary prevention of allergic diseases after Vitamin D supplementation and its potential impact remains uncertain.

KEYWORDS

Allergy, GRADE, prevention, systematic review, Vitamin D

INTRODUCTION

Studies have established that the prevalence of asthma and allergic diseases in westernized countries has increased since the 1970s (1, 2). The hygiene hypothesis and the gut microbiome have gained prominence as explanatory factors for this increase. Other theories have associated Vitamin D with the development of asthma, wheezing, allergic rhinitis, food allergy and atopic dermatitis (3). The postulated mechanisms include decreased levels of Vitamin D at population level which increase susceptibility; genetic links between Vitamin D and the early development of lungs and asthma; and the function of immune cells and the gut

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microbiome related to Vitamin D (4). Support for these theories comes from a study suggesting that the active form of Vitamin D, calcitriol, modulates immune function in cell culture and animal models (5). Thus, primary prevention of asthma as well as reduction of asthma morbidity, and modulation of the severity of asthma attacks, could be influenced by Vitamin D immunomodulation on the innate and adaptive immune systems (6). Nevertheless, the understanding of the complex role of Vitamin D in immune function remains limited.

Although multiple studies have reported an association between low serum Vitamin D levels and the development of allergic diseases, this association may not be causal, and Vitamin D supplementation may have no role in the primary prevention of allergic diseases (7-10). Furthermore, two recent randomized trials reported that increased Vitamin D supplementation in pregnant women did not confer protection against allergic diseases in their children (11, 12).

This systematic review informed the recommendations of the World Allergy Organization-McMaster guidelines for the prevention of allergies or Guideline for Allergy Disease Prevention (GLAD-P) (13). We analyzed comparative studies that examined the effects of Vitamin D supplementation versus non Vitamin D supplementation on population and patient important outcomes in pregnant women, breastfeeding women, infants, and children.

METHODS

Inclusion and Exclusion Criteria

Types of studies

We included randomised control trials and non-randomized studies (NRS), specifically cohort and case-control studies.

Types of participants

Studies must have included one or more of the following groups of participants:

- Healthy pregnant women
- Healthy breastfeeding mothers

- Healthy infants
- Healthy children

We included studies that assessed the use and effects of Vitamin D in any age group, from newborn infants to pre-school, and school age children (up to 9 years of age).

Type of interventions

We included only studies that reported Vitamin D supplementation in isolation, irrespective of formulation (e.g. capsules, drops, suspension, etc.) or dose. We did not include studies that reported Vitamin D supplementation combined with other vitamins or nutrients, studies that compared different doses of Vitamin D supplementation and studies that reported Vitamin D intake using food-frequency questionnaires.

Type of outcomes

The outcomes were determined following a detailed guideline development process by the WAO guideline panel members (14). The following outcomes were deemed critical to the decision of whether or not to use Vitamin D for primary prevention of allergies:

- Asthma or wheezing
- Allergic rhinitis
- Eczema (including atopic dermatitis, atopic eczema, or any sort of eczema)
- Food allergy

Other outcomes were included for the panel, which were not related directly to prevention of allergies but could be critical for balancing the benefits against potential downsides vitamin D supplementation:

- Nutritional status (including weight at birth or weight gained during follow-up)
- Rickets
- Any adverse events
- Severe adverse events

Search methods

MEDLINE, EMBASE, and The Cochrane Central Register of Controlled Trials were searched from inception to January 30 2016. Restrictions on language of publication were not imposed. Search strategies for all databases are reported in the Table S1 at the Supporting Information. We checked reference lists of reviewed articles and contacted clinical experts in the speciality for additional references. We also searched The U.S. National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov) for ongoing studies.

Study Selection and Data Extraction

Six independent evaluators (JY, YZ, CC, GM, AA, SG) screened the titles and abstracts obtained through the electronic searches, to identify studies to include in the review. If a study was deemed potentially relevant we obtained the full-text and two authors (JY, CC) assessed it to make a final eligibility decision. In the case of any disagreement, it would have been discussed with a third reviewer (JLB). If additional information or clarification was needed about a study, we contacted the authors of the relevant article.

Two independent evaluators (JY, CC) read all reports of eligible studies in detail and summarised the pertinent details in a standard data extraction sheet (type of study; methodology; characteristics of participants, results and outcome measurements; as well as an evaluation of the risk of bias or study limitations). We discussed any disagreements, and aimed to reach agreement by consensus with a third reviewer if necessary (JLB).

Certainty in the body of evidence (confidence in the estimates of effects or quality of evidence)

Assessment of risk of bias in included studies

Two review authors (JY, CC) independently assessed risk of bias for each randomised control trial and non-randomized studies using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Intervention (15), and version 1.0 of the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI), now called ROBINS-I (16), respectively.

Data analysis

Measure of treatment effect

We calculated relative risk (RR) and 95% confidence intervals (95%CI) for dichotomous outcomes and mean difference with associated 95% CI for continuous outcomes. For NRS, we reported the measure of the relative effect reported by authors in their studies, odds ratio (OR) or relative risk (RR).

Dealing with missing data

We contacted authors where details about study design or descriptive statistics for outcomes were not presented in original papers. We did not impute data.

Assessment of statistical heterogeneity and inconsistency

We assessed inconsistency between studies by visual inspection of forest plots, confidence intervals (CI) and its minimal or no overlap, the Q statistic (with a P value ≤ 0.05 as a suggestion of important statistical heterogeneity), and the I^2 value. When inconsistency was found we planned to explain it by pre-specified differences in study populations, dosages, presentation, or type of Vitamin D used.

Assessment of reporting biases

We planned to create a funnel plot to assess publication bias by visual inspection if ten or more studies were available.

Data Synthesis

We assessed the treatment effect through mean difference for continuous outcomes, and RR for dichotomous outcomes for individual studies, and used a random-effects model to pool study data. We presented all measures with 95% CI. We carried out all statistical analyses using Review Manager 5.3 (17).

Subgroup analysis

We considered four main groups for subgroup analysis, one for each clinical question based on the population where the vitamin was administered: pregnant women, breastfeeding women, infants, and children.

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Sensitivity analysis

We planned analyses to determine the effect of including or excluding the studies with high risk of bias on treatment effect estimates. This analysis was planned *a priori*.

GRADE assessment of the overall certainty in the body of evidence by outcome

We then used the the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) methodology to rate the certainty in the body of evidence for each outcome as high, moderate, low, or very low (18). The assessment included judgments about risk of bias (19), imprecision (20), inconsistency (19), indirectness (20), and publication bias (21). We also rated the certainty in the body of evidence using a GRADE approach to observational studies (22). We created Evidence Profile and Summary of Findings Tables for each population using GRADE's electronic tool GRADEpro GDT (www.grade-pro.org). To assess the usefulness of including NRS, we applied the GRADE NRS framework for when to consider NRS (23). A senior methodologist checked all GRADE tables and ratings of the certainty in the body of evidence (HJS).

RESULTS

The search of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE yielded 1806 unique records after duplicates removed. Title and abstract screening by six review authors led to the exclusion of 1635 references. Figure 1 shows the PRISMA flow diagram (24). We reviewed the full text of 171 publications in detail. Overall, 25 RCTs reported in 26 publications, and four NRS reports (2 case-control studies and 2 cohort studies) met our inclusion criteria (25). One RCT reported information related to primary prevention of allergic diseases. The other 24 RCTs reported information related to other outcomes of interest such as nutritional status, development of rickets, and adverse events. The four NRS reported information about primary prevention of allergic diseases such as asthma/wheezing, allergic rhinitis, and food allergy. The numbers of studies according to the population exposed to Vitamin D are as follow: seven RCTs in pregnant women (reported in eight publications) (25-32), one RCT in breastfeeding women (33), five RCTs to infants (34-38), and twelve RCTs to children (39-50). For the four NRS, two studies reported information in two populations (pregnant women and infants' population) (51, 52), one in breastfeeding

women (53), and one in the infant population (54). All of the studies were included in the quantitative analysis. Two RCT published in 2016 (11, 12) did not meet the inclusion criteria defined for the systematic review since both studies compared high doses versus low doses of vitamin D supplementation in pregnant women. No additional information from the reports included was required; therefore, authors of the reports were not contacted.

Table S2 in the Supporting Information presents the characteristics of the 29 eligible studies according to the population of interest that received Vitamin D. The studies excluded, and the reasons for the exclusions, are reported in Table S3 in the Supporting Information.

Risk of bias in studies included

Overall risk of bias was deemed between moderate to very low either in RCT as NRS (see Fig S1 and Table S4 in the Supporting Information). For RCTs, the greatest concerns were related to allocation concealment and in the blinding of outcome assessment. In terms of the NRS, risk of bias was evaluated in five outcomes that were reported in four studies. All five outcomes presented moderate risk of bias. Only one study (53) presented a serious limitation due to selection bias of participants and departures from the intended intervention.

Effect of interventions

Table 1-4 describes the summary of findings for all four questions. The full evidence profiles with more detailed explanations are available in Table S5 in the Supporting Information. Forest plots of meta-analyses are depicted in Figure S2 in the Supporting Information

Vitamin D supplementation during pregnancy

Only one RCT (25) addressed the primary prevention of developing allergic diseases in children if Vitamin D supplementation was administered during pregnancy. No effect of Vitamin D was found for any allergy outcome: atopic dermatitis (RR, 0.96; 95% CI, 0.57 to 1.61), asthma and/or wheezing (RR, 1.12; 95% CI, 0.50 to 2.54), allergic rhinitis (RR, 0.76; 95% CI, 0.31 to 1.85), and food allergy (RR, 1.92; 95% CI, 0.57 to 6.50). We also found two NRSs, one cohort (52) and one case-control (51) reported development of asthma/wheezing and food allergy respectively. In the cohort study, Vitamin D was associated with low risk of

developing wheezing (OR, 0.65; 95% CI, 0.46 to 0.93). No benefit was observed in the case-control study that met the inclusion criteria in food allergy (OR, 1.50; 95% CI, 0.78 to 2.88). The overall certainty in the body of evidence was very low owing to the risk of bias and imprecision.

Two RCTs reported nutritional status at 1 year of age (29) and development of rickets (26). Vitamin D supplementation in pregnant women was not associated with a change in the weight in infants at 1 year old compared to no Vitamin D supplementation (mean difference, 100 g; 95% CI, -273.48 to 473.48). Development of rickets was not found in infants independently of whether their mothers were exposed to or not exposed to Vitamin D during the last trimester of pregnancy.

Adverse events were reported in seven reports corresponding to six RCTs (25-29, 31, 32). Vitamin D supplementation in pregnant women was not associated with a lower birth weight in infants compared to no vitamin D (mean difference, 52.78 g; 95% CI, -64.34.80 to 169.90). The certainty in the body of evidence of the risk of adverse events in pregnant mothers ranged between low to very low due to the development of few events in both arms. Other adverse effects as measured by infants being born small for gestational age, gestational age, symptomatic hypocalcaemia, as well as severe adverse effects in a newborn and in the mother were very infrequent and any estimates are very imprecise. There was no difference between the groups (see forest plots in Figure S2).

Vitamin D supplementation by mother during breastfeeding

No RCT addressed the primary prevention of developing allergic diseases in children if the supplementation was administered in breastfeeding mothers. One case-control study (53) addressed this question and reported the risk of developing asthma in children. Vitamin D supplementation in breastfeeding mothers did not

appear to influence the development of asthma and/or wheezing in children: (OR, 1.09; 95% CI, 0.84 to 1.40).

In one RCT (33), 60 children of breastfeeding mothers that used or did not use vitamin D supplements did not develop rickets after 6 weeks of treatment. The time of follow-up was 6 weeks and the outcome was evaluated as biochemical evidence of developing rickets.

No information about adverse events was reported by the studies that we retrieved from our search strategy in the breastfeeding population that was exposed to vitamin D. The overall certainty in the body of evidence was very low (see forest plot in Figure S2).

Vitamin D supplementation in infants

No RCT addressed any allergy outcome for the primary prevention of allergic diseases with vitamin D supplementation in infants. Three NRSs reported information for the allergy outcomes: allergic rhinitis (54), asthma/wheezing (52, 54), and food allergy (51).

A cohort study (54) reported the association of vitamin D supplementation with allergic rhinitis and asthma. Regular vitamin D supplementation during the first year of life may have increased the risk of developing allergic rhinitis but the confidence interval was extremely wide (RR, 1.95; 95% CI, 0.69 to 5.54). Authors of this study also combined a group that did not receive vitamin D with a group that used it irregularly. If those using vitamin D regularly were compared with those who either did not use it, or used it irregularly the RR between the groups is 1.31 (95% CI, 1.15 to 1.49); therefore, regular use increased the risk of allergic rhinitis. In the same study, the point estimate suggested that regular vitamin D supplementation during the first year of life increased the risk of developing asthma/wheezing but the extremely wide confidence interval showed the data was essentially uninformative (RR, 2.93; 95% CI, 0.19 to 45.35). In a comparison of those using vitamin D regularly with those who either did not use it or used it irregularly, the RR would be 1.33 (95% CI, 1.00 to 1.79). The certainty in the body of evidence for these two outcomes was very low. The other cohort study (52) suggested no impact of Vitamin D supplementation in childhood on asthma/wheezing (OR, 1.00; 95% CI, 0.81 to 1.23).

In the case-control study (51), supplementation of vitamin D in infants reduced the risk of developing food allergy during the 1st year of life (RR, 0.49; 95% CI, 0.27 to 0.88). However, the confidence in this estimate is also very low owing to indirectness of the evidence and risk of bias.

Other outcomes such as development of rickets, nutritional status and adverse events were reported in 5 RCTs (34-38). Estimates of nutrition status and the risk of rickets or adverse effects were imprecise owing to small numbers of events and participants in the studies; they did not differ between the groups receiving or not receiving vitamin D supplements.

Adverse events were infrequent, and the estimates imprecise (RR, 0.85; 95% CI, 0.23 to 3.14). Only one study (37) reported one serious adverse event (RR, 0.17; 95% CI, 0.01 to 3.70), sudden infant death syndrome, in the group of infants that was not receiving vitamin D supplementation. According to the author, this event was not related to the study. The certainty in the body of evidence was very low due to serious risk of bias and imprecision (see forest plot in Figure S2).

Vitamin D supplementation in children

No RCT or NRS addressed the efficacy or association of primary prevention of allergic diseases in children after vitamin D supplementation.

Three RCTs (40, 45, 49) evaluated the efficacy of vitamin D supplementation on nutritional status finding that this supplementation did not benefit nutritional status, measured as weight, on children who received this supplementation (mean difference, 0.87 kg; 95% CI, 0.1 to 1.64). The certainty in the body of evidence was low because of the risk of bias and imprecision.

Few adverse events were reported in eight RCTs (RR, 0.78; 95% CI, 0.26 to 2.32). One study (41) reported two serious adverse events (cyanosis owing to croup, Rota-positive gastroenteritis), one in the vitamin D supplementation group and the other one in the non-supplementation group (RR, 0.74; 95% CI, 0.05 to 11.40). None of these serious adverse events were related to the study. The confidence in the estimates was moderate to low owing risk of bias and imprecision (see forest plot in Figure S2).

Sensitivity analysis

Since the number of studies was small in each particular population for any individual outcome, a sensitivity analysis that considered only low risk of bias studies was not carried out.

DISCUSSION

Our findings, from RCT and NRS, show very low certainty in the body of evidence for the primary prevention of allergic diseases when vitamin D supplementation was administered in four different populations: pregnant women, breastfeeding women, infants, and children. In pregnant woman, we found only one RCT that met our inclusion criteria. In this study, vitamin D did not provide benefit in primary prevention of allergic diseases, independently of whether vitamin D was administered daily [atopic dermatitis (RR, 0.91; 95% CI, 0.50 to 1.66), asthma and/or wheezing (RR, 0.70; 95% CI, 0.35 to 1.40), allergic rhinitis (RR, 0.89; 95% CI, 0.34 to 2.36), and food allergy (RR, 2.38; 95% CI, 0.67 to 8.46)] or in single dose [atopic dermatitis (RR, 1.02; 95% CI, 0.56 to 1.85), asthma and/or wheezing (RR, 1.03; 95% CI, 0.56 to 1.91), allergic rhinitis (RR, 0.61; 95% CI, 0.19 to 1.94), and food allergy (RR, 1.36; 95% CI, 0.32 to 5.78)].

We did not observe benefit of vitamin D supplementation for primary prevention of allergic diseases in other subgroups of the population such as breastfeeding women, infants, and children. Indeed, supplementation of vitamin D was associated with an increase of risk of developing allergic rhinitis in infant populations, although as in all other evidence this was of very low quality.

We also found no effect of vitamin D supplementation on other outcomes, including adverse events. In particular, our review found very few adverse events in all four populations. For most of these other outcomes, the certainty in the body of evidence was between low and very low.

Our systematic review has several strengths. We established a comprehensive and explicit eligibility criteria, conducted a comprehensive search, assessed eligibility and risk of bias, extracted data in duplicate, and applied the GRADE criteria to determine the certainty in the body of evidence. Moreover, we included both RCTs and NRSs to broaden the results and applicability our findings

Limitations of our systematic review are inherent to the evidence retrieved from our search. Only one RCT, and four NRSs, addressed information related to primary prevention of allergic diseases after exposition to vitamin D in four different populations. There are two reasons that explain these findings. First, we had interest only in the primary prevention of allergic diseases. Second, our interest was focused on the primary prevention of allergic diseases when vitamin D was supplemented, not if serum levels of vitamin D were measured. Thus, we excluded a number of studies that addressed the effect of vitamin D in secondary prevention of allergic diseases, and also, studies that reported the efficacy of vitamin D on primary prevention of allergic diseases that were based only on serum levels of this vitamin D. There is also a limitation in the certainty in the body of evidence of the studies available on this topic, resulting in very low to moderate confidence in estimates for our outcomes. Serious considerations about the susceptibility of bias and imprecisions of the pool estimates (Table 1-4) were noted in most of studies. Thus, these studies are unable to adequately address whether vitamin D supplementation on specific population could be beneficial in primary prevention of allergic diseases.

Other systematic reviews have explored the association between vitamin D intake and primary prevention of allergic diseases. In 2012, a systematic review (2) identified seven observational studies (54-60) which determined a reduction in the risk of wheezing in early childhood (OR, 0.56; 95% CI, 0.42 to 0.73) when vitamin D was taken during pregnancy. These studies used food frequency questionnaires or diet history questionnaires to measure exposure to vitamin D. Another study (61) described the association between maternal 25(OH)-vitamin D concentrations, and atopic eczema and asthma at age 9 months and at age 9 years. Non-statistically significant associations were found between a high concentration of maternal 25(OH)-vitamin D and atopic eczema in their children at 9 months (OR, 1.62; 95%

CI, 0.67 to 3.89) and at 9 years old (OR, 1.89; 95% CI, 0.51 to 6.99). Also, a high concentration of maternal 25(OH)-vitamin D was associated with an increase in the risk of developing asthma in children at 9 years old compared with those who were exposed to low concentrations of maternal 25(OH)-vitamin D (OR, 5.40; 95% CI, 1.09 to 26.65). The authors did not report information about vitamin D supplementation and its association with atopic eczema or asthma.

Two other RCTs, published in 2016 (11, 12), explored the effect of prenatal high doses versus low doses of vitamin D supplementation in pregnant women for primary prevention of persistent wheezing or asthma in children. In a RCT conducted by Chawes et al (11), healthy pregnant women who were receiving the usual dosage of vitamin D3 as part of usual pregnancy care (400 IU/day) received Vitamin D3 (2400 IU/day; n = 315) or placebo tablets (n = 308) between pregnancy week 24 and week 1 postpartum. Persistent wheeze and eczema were evaluated through age 3, and asthma was diagnosed at age 3. Vitamin D3 did not show an effect on reducing the risk of persistent wheeze (HR, 0.76; 95% CI, 0.52 to 1.12), asthma (OR, 0.82; 95% CI, 0.50 to 1.36), or eczema (HR, 0.90; 95% CI, 0.65 to 1.26). Litonjua et al (12) compared higher doses of vitamin D3 supplementation (4400 IU/day; n= 440) versus placebo plus usual dose vitamin D3 supplementation (400 IU/day; n= 436). The participants were pregnant women with history of asthma, eczema, or allergic rhinitis, or pregnant women where the biological father of the child had a history of asthma, eczema, or allergic rhinitis. The pregnant women were randomized at gestational stages between 10 to 18 weeks. The outcomes evaluated in this RCT were asthma/recurrent wheeze, and eczema with rash in typical distribution developed during the first three years of age. Vitamin D did not show an effect on reducing the risk of asthma/recurrent wheezing (HR, 0.8; 95% CI, 0.6 to 1.0) or eczema (HR, 0.9; 95% CI, 0.7 to 1.2) in children by 3 years of age. Thus, in these two RCTs, high doses of vitamin D offered to healthy pregnant women or those with history of asthma, eczema, or allergic rhinitis (including pregnant women where the biological father of the child had a history of asthma, eczema, or allergic rhinitis) did not reduce the risk of asthma, recurrent wheezing, or eczema in their children through age 3.

In terms of practice implications, the data in this review together with the two recent RCTs comparing high with low doses of vitamin D supplementation should not make patients, doctors, and public health authorities confident that vitamin D can primarily prevent allergic diseases.

Suggestions for future research

Further research must be done in order to increase the certainty in the body of evidence, including the precision and directness of the findings. Additional RCTs may help evaluating the effects of using vitamin D supplementation in breastfeeding mothers and during pregnancy, as well as in infants who did not receive vitamin D prenatally and/or during breastfeeding. Different ways of administration and additional doses of vitamin D could be tested and analyzed in these studies. Finally, new RCTs may address if pregnant women, breastfeeding mothers, or infants would benefit from vitamin D supplementation for the primary prevention of allergic diseases.

CONCLUSION

Although different mechanisms have been proposed for how vitamin D can modulate certain immune functions, limited information is available addressing primary prevention of allergic diseases. Our data suggests that supplementation of vitamin D in different populations does not have an effect in primary prevention of allergic diseases. Future trial studies may be carried out to evaluate the impact of vitamin D in primary prevention of allergic diseases in order to address the remaining uncertainty.

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World Allergy Organization

AUTHORS' CONTRIBUTIONS

JJYN was involved in the methodological design of the systematic review, conducted the acquisition of data, analyses, and interpretation; contributed in drafting the article.

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JLB directed and organized the systematic review and the methodologist team; was involved in the initial concept and methodological design of the systematic review, conducted data acquisition and interpretation, and helped writing the final manuscript.

AF was involved in the initial concept and methodological design of the systematic review, conducted data interpretation, and provided substantial feedback on the drafted manuscript.

RP was involved in the initial concept and methodological design of the systematic review, conducted data interpretation, and provided substantial feedback on the drafted manuscript.

CACG was involved in the initial concept and methodological design of the systematic review. Conducted the acquisition of data, analyses, and interpretation; drafted the article and modified according to substantial feedback on the drafted manuscript.

YZ conducted data acquisition, analyses, and interpretation; provided significant feedback for the draft of the manuscript.

GPM conducted data acquisition, analyses, and interpretation; provided significant feedback for the draft of the manuscript.

AA conducted data acquisition, analyses, and interpretation; provided significant feedback for the draft of the manuscript..

SG conducted data acquisition, analyses, and interpretation; provided significant feedback for the draft of the manuscript..

LR was involved in the analysis and interpretation of the evidence, and provided significant feedback for the final manuscript.

HJS was involved in the initial concept and methodological design of the manuscript, conducted data interpretation, and provided substantial feedback on the drafted manuscript.

CONFLICT OF INTERESTS

The following are potential conflicts of interest (within last 4 years) for authors of this work.

Juan José Yepes-Nuñez; declares no competing interest related to this systematic review. Part of scholarship paid by WAO funding received by HJS and JLB for developing the GLAD-P guidelines.

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Yuan Zhang; declares no competing interest.

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FIGURES AND TABLES

Figure 1. PRISMA flow chart of study selection

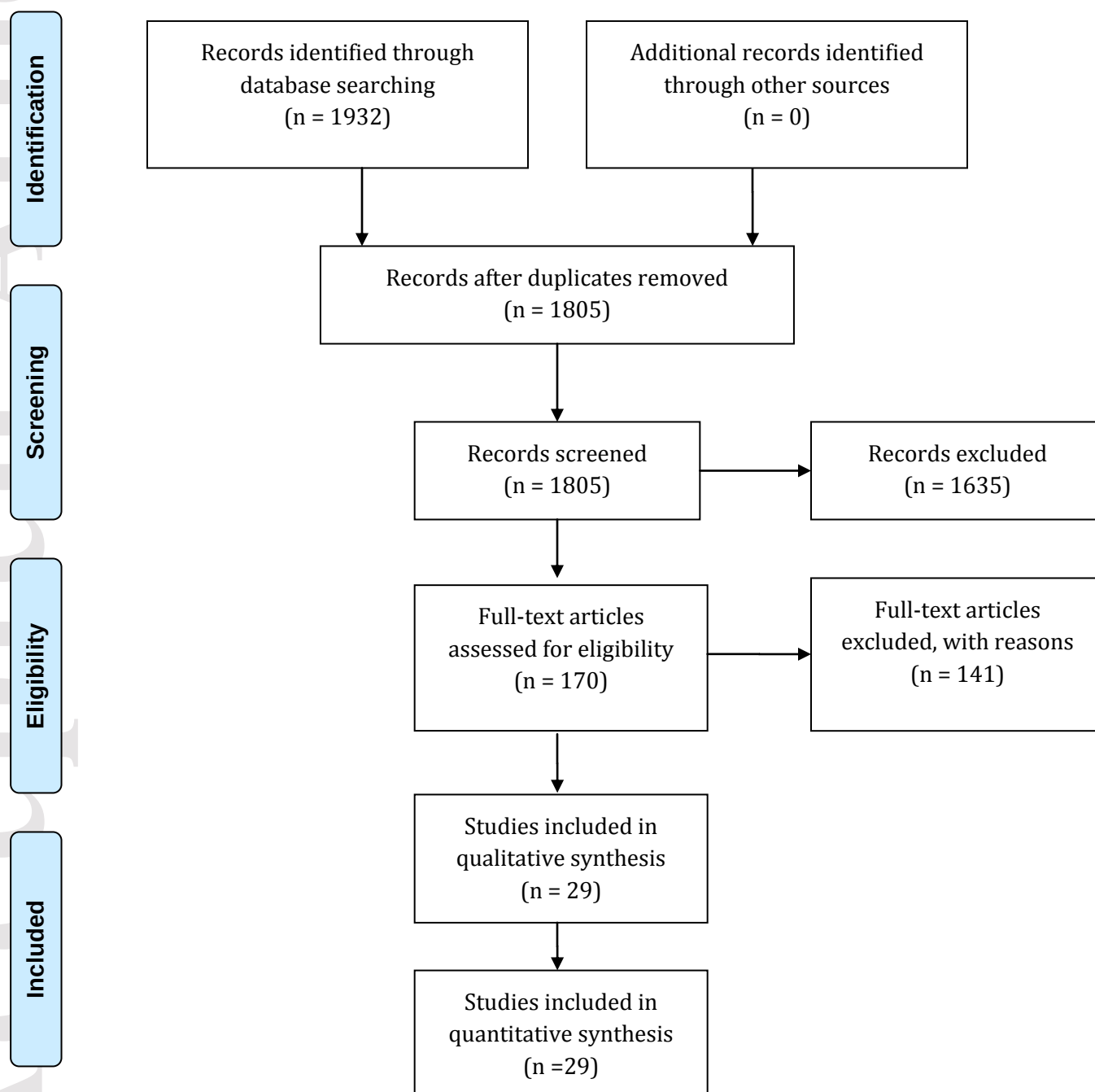


Table 1. Summary of Findings table for Vitamin D versus no vitamin D supplementation in PREGNANT women for the primary prevention of allergy in their children and other important outcomes

Outcomes	№ of participants (studies)	Certainty in the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no Vitamin D	Risk difference with Vitamin D
Eczema follow up: 3 years	151 (1 RCT)	 VERY LOW ^{1,2,3}	RR 0.96 (0.57 to 1.61)	Study population	
				306 per 1000	12 fewer per 1000 (132 fewer to 187 more)
				Moderate	
				10 per 1000	0 fewer per 1000 ⁵ (4 fewer to 6 more)
Allergic rhinitis follow up: 3 years	150 (1 RCT)	 VERY LOW ^{1,2,3}	RR 0.76 (0.31 to 1.85)	Study population	
				143 per 1000	34 fewer per 1000 (99 fewer to 121 more)
				Moderate	
				146 per 1000	35 fewer per 1000 ⁶ (101 fewer to 124 more)

Asthma/wheezing follow up: 3 years	158 (1 RCT)	 VERY LOW ^{1,2,3}	RR 1.12 (0.50 to 2.54)	Study population	
				140 per 1000	17 more per 1000 (70 fewer to 216 more)
				Moderate	
				94 per 1000	11 more per 1000 ⁷ (47 fewer to 145 more)
				Moderate	
Asthma/wheezing ⁸	2478 (1 observational study)	 VERY LOW ³	OR 0.65 ⁹ (0.46 to 0.92)	Moderate	
				94 per 1000	31 fewer per 1000 ⁷ (48 fewer to 7 fewer)
Food allergy follow up: 3 years	151 (1 RCT)	 VERY LOW ^{1,2,3}	RR 1.92 (0.57 to 6.50)	Study population	
				61 per 1000	56 more per 1000 (26 fewer to 337 more)
				Moderate	
				33 per 1000	30 more per 1000 ¹⁰ (14 fewer to 182 more)
				Low	
Food allergy	27 cases 213		OR 1.50 ⁹		

	controls (1 observational study)	VERY LOW ³	(0.78 to 2.88)	33 per 1000	16 more per 1000 ¹⁰ (7 fewer to 56 more)
Rickets	126 (1 RCT)	 LOW ³	Not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Nutritional status: birth weight (gr)	821 (6 RCTs)	 MODERATE ⁴	-	The mean nutritional status birth weight was 0	MD 52.78 more (64.34 fewer to 169.9 more)
Any adverse events (children)	234 (2 RCTs)	 LOW ³	Not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Any adverse events (62) assessed with: Preeclampsia	520 (3 RCTs)	 VERY LOW ^{3,11}	RR 1.46 (0.31 to 6.78)	Study population	
				117 per 1000	54 more per 1000 (80 fewer to 674 more)
Serious adverse events	426		RR 0.79	Study population	

(children)	(3 RCTs)	LOW ³	(0.33 to 1.90)	47 per 1000	10 fewer per 1000 (31 fewer to 42 more)
Serious adverse events (62)	321 (2 RCTs)	 LOW ³	RR 1.55 (0.65 to 3.69)	Study population	
				49 per 1000	27 more per 1000 (17 fewer to 132 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **OR:** Odds ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- Serious risk of bias. One study was rated as high risk of bias due to lack of concealment of allocation, and lack of blinding of participants and caregivers
- Indirectness. One study assessed the impact of the intervention in 3-year-old children. However, the estimate of the treatment effect could be different in other populations
- Very serious imprecision. Wide confidence interval due to a small number of events
- Very serious imprecision. Wide confidence interval crosses 0
- Difference in anticipated absolute effect was calculated based on the range of prevalence of eczema in International Study for Asthma and Allergy in Childhood (ISAAC) Phase Three (1%)
- Difference in anticipated absolute effect was calculated based on the total global prevalence of rhinoconjunctivitis symptoms for the 13- to 14-year old children according with Phase Three ISAAC (14.6%)
- Difference in anticipated absolute effect was calculated based on the total global prevalence of asthma symptoms in the 6-7 year old children according with Phase Three ISAAC in 9.4%
- Wheezing was measured using the ISAAC questionnaire
- Odds ratio adjusted by sociodemographic and environmental factors, health history, and individual activities

10. Difference in anticipated absolute effect was calculated based on the prevalence of food allergy in the population as a result of food challenge tests to any food according with metanalysis of Rona et al. 2007
11. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to selective outcome reporting

Table 2. Summary of Findings table for Vitamin D versus no vitamin D supplementation in BREASTFEEDING women for the primary prevention of allergy in their children and other important outcomes

Outcomes	Nº of participants (studies)	Certainty in the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no Vitamin D	Risk difference with Vitamin D
Eczema	(0 studies)	-	Not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Allergic rhinitis	(0 studies)	-	Not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Asthma/wheezing	483 cases 483 controls	⊕○○○	OR 1.09	Moderate	

Table 2. Summary of Findings table for Vitamin D versus no vitamin D supplementation in BREASTFEEDING women for the primary prevention of allergy in their children and other important outcomes

Outcomes	№ of participants (studies)	Certainty in the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no Vitamin D	Risk difference with Vitamin D
(follow-up: up to 16 years)	(1 observational study)	VERY LOW ^{1,2,3}	(0.84 to 1.40)	94 per 1000	8 more per 1000 ⁴ (14 fewer to 33 more)
Food allergy	(0 studies)	-	Not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Rickets follow up: 6 weeks	28 (1 RCT)	 VERY LOW ^{5,6}	Not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Nutritional status	(0 studies)	-	Not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)

Table 2. Summary of Findings table for Vitamin D versus no vitamin D supplementation in BREASTFEEDING women for the primary prevention of allergy in their children and other important outcomes

Outcomes	No of participants (studies)	Certainty in the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no Vitamin D	Risk difference with Vitamin D
Any adverse events	(0 studies)	-	Not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Severe adverse events	(0 studies)	-	Not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

Table 2. Summary of Findings table for Vitamin D versus no vitamin D supplementation in BREASTFEEDING women for the primary prevention of allergy in their children and other important outcomes

Outcomes	№ of participants (studies)	Certainty in the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no Vitamin D	Risk difference with Vitamin D

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Serious risk of bias. Controls were sampled from a population that is unlikely to be representative of the population from which cases were selected, and analysis was not adjusted for confounding factors
2. Indirectness. Over 80% of the children in the study had mild to severe vitamin D deficiency
3. Serious imprecision. Wide confidence interval
4. Difference in anticipated absolute effect was calculated based on the total global prevalence of asthma symptoms in the 6-7 year old children according with Phase Three ISAAC in 9.4%
5. Serious risk of bias. One study was rated as unclear risk of bias due to insufficient information about random sequence generation, allocation concealment, and incomplete outcome data
6. Very serious imprecision with no events in a small study

Table 3. Summary of Findings table for Vitamin D versus no vitamin D supplementation in INFANTS for the primary prevention of allergy and other important outcomes

Outcomes	№ of participants (studies)	Certainty in the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no vitamin D	Risk difference with Vitamin D
Eczema	(0 studies)	-	not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Allergic rhinitis ¹ follow up: 31 years	6768 (1 observational study)	⊕○○○ VERY LOW ^{2,3}	RR 1.95 (0.69 to 5.54)	Study population	
				150 per 1000	143 more per 1000 (47 fewer to 681 more)
				Moderate	
				146 per 1000	139 more per 1000 ⁴ (45 fewer to 663 more)
Asthma/wheezing ¹	6768	⊕○○○	RR 3.07	Study population	

follow up: 31 years	(1 observational study)	VERY LOW ^{2,3}	(0.19 to 50.88)	0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
				Moderate	
				94 per 1000	195 more per 1000 ⁵ (76 fewer to 4689 more)
Asthma/wheezing ⁶ follow up: 72 months	2478 (1 observational study)	 VERY LOW ³	OR 1.00 (0.81 to 1.23)	Moderate	
				94 per 1000	0 fewer per 1000 ⁵ (16 fewer to 19 more)
Food allergy follow up: 1 years	481 (1 observational study)	 VERY LOW ^{7,8,9}	OR 0.49 (0.27 to 0.88)	Study population	
				145 per 1000	68 fewer per 1000 (101 fewer to 15 fewer)
				Moderate	
				33 per 1000	17 fewer per 1000 ¹⁰ (24 fewer to 4 fewer)
Rickets	177		Not estimable	Study population	

follow up: range 2 months to 12 months	(4 RCTs)	VERY LOW ^{11,12,3}		0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Nutritional status (body weight in grams) follow up: range 6 months to 12 months	80 (1 RCT)	 LOW ^{13,14}	-	The mean nutritional status (body weight in grams) was 0	0 (0 to 0)
Any adverse events	109 (2 RCTs)	 LOW ^{15,3}	RR 0.85 (0.23 to 3.14)	Study population	
				78 per 1000	12 fewer per 1000 (60 fewer to 168 more)
Serious adverse events	25 (1 RCT)	 LOW ^{15,3}	RR 0.17 (0.01 to 3.70)	Study population	
				125 per 1000	104 fewer per 1000 (124 fewer to 338 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Information corresponds to case control study, Hypponen 2004
2. Serious risk of bias. Criteria for diagnosis of asthma and allergic rhinitis were not provided, and results were not adjusted for confounding factors
3. Serious imprecision. Wide confidence interval
4. Difference in anticipated absolute effect was calculated based on the total global prevalence of rhinoconjunctivitis symptoms for the 13- to 14-year old children according with Phase Three ISAAC (14.6%)
5. Difference in anticipated absolute effect was calculated based on the total global prevalence of asthma symptoms in the 6-7 year old children according with Phase Three ISAAC (9.4%)
6. Information corresponds to cohort study, Anderson 2015
7. Serious risk of bias. Results were not adjusted for confounding factors
8. Serious indirectness. The outcome was measured after 1 year of life, which is likely a short frame time to reliably measure development of food allergy
9. Serious imprecision with only 51 events in total
10. Difference in anticipated absolute effect was calculated based on the prevalence of food allergy in the population as a result of food challenge tests to any food according with meta-analysis of Rona et al. 2007 (3.3%)
11. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of blinding and incomplete outcome data
12. Serious indirectness. Patients included in the study were follow-up for a short time to assess the outcome
13. Serious risk of bias. One study was rated as high risk of bias due to lack of random sequence generation
14. Serious imprecision. Mean weights were not significant different between patients who received vitamin D supplementation versus no vitamin D supplementation
15. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to incomplete outcome data

Table 4. Summary of Findings table for Vitamin D versus no vitamin D supplementation in CHILDREN for the primary prevention of allergy and other important outcomes

Outcomes	No of participants (studies)	Certainty in the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no Vitamin D	Risk difference with Vitamin D
Eczema	(0 studies)	-	Not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Allergic rhinitis	(0 studies)	-	Not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Asthma/wheezing	(0 studies)	-	Not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Food allergy	(0 studies)	-	Not estimable	Study population	

Table 4. Summary of Findings table for Vitamin D versus no vitamin D supplementation in CHILDREN for the primary prevention of allergy and other important outcomes

Outcomes	No of participants (studies)	Certainty in the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no Vitamin D	Risk difference with Vitamin D
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Rickets	(0 studies)	-	Not estimable	Study population	
				0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Nutritional status	495 (3 RCTs)	⊕⊕○○ LOW ^{1,2}	-	The mean nutritional status was 0 kg	MD 0.87 more (0.1 more to 1.64 more)
Any adverse events	1895 (8 RCTs)	⊕⊕⊕○ MODERATE ²	RR 0.78 (0.26 to 2.32)	Study population	
				8 per 1000	2 fewer per 1000 (6 fewer to 11 fewer)
Serious adverse events	80	⊕⊕○○	RR 0.74	Study population	

Table 4. Summary of Findings table for Vitamin D versus no vitamin D supplementation in CHILDREN for the primary prevention of allergy and other important outcomes

Outcomes	No of participants (studies)	Certainty in the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no Vitamin D	Risk difference with Vitamin D
	(1 RCTs)	LOW ²	(0.05 to 11.40)	29 per 1000	8 fewer per 1000 (28 fewer to 306 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **SMD:** Standardised mean difference; **OR:** Odds ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as unclear risk of bias due to insufficient information about random sequence generation, allocation concealment, blinding of outcome assessment, and incomplete outcome data.
2. Serious imprecision. Wide confidence interval
3. Serious risk of bias. One studies that carried large weight for the overall effect estimate rated as unclear risk of bias due to insufficient information about allocation concealment, an blinding of outcome assessment

REFERENCES

1. Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. *Clinical and experimental immunology*. 2010;160(1):1-9.
2. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. *The Journal of allergy and clinical immunology*. 2011;127(3):724-33 e1-30.
3. Bacharier LB. Vitamin D status at birth: an important and potentially modifiable determinant of atopic disease in childhood? *The Journal of allergy and clinical immunology*. 2014;133(1):154-5.
4. Weiss ST, Litonjua AA. Vitamin D, the gut microbiome, and the hygiene hypothesis. How does asthma begin? *American journal of respiratory and critical care medicine*. 2015;191(5):492-3.
5. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *Bmj*. 2014;348:g2035.
6. Arikoglu T, Kuyucu S, Karaismailoglu E, Batmaz SB, Balci S. The association of vitamin D, cathelicidin, and vitamin D binding protein with acute asthma attacks in children. *Allergy and asthma proceedings : the official journal of regional and state allergy societies*. 2015;36(4):51-8.
7. Rudders SA, Camargo CA, Jr. Sunlight, vitamin D and food allergy. *Current opinion in allergy and clinical immunology*. 2015;15(4):350-7.
8. Chiu CY, Huang SY, Peng YC, Tsai MH, Hua MC, Yao TC, et al. Maternal vitamin D levels are inversely related to allergic sensitization and atopic diseases in early childhood. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2015;26(4):337-43.
9. Maalmi H, Berraies A, Tangour E, Ammar J, Abid H, Hamzaoui K, et al. The impact of vitamin D deficiency on immune T cells in asthmatic children: a case-control study. *Journal of asthma and allergy*. 2012;5:11-9.

- Accepted Article
10. Hollams EM, Hart PH, Holt BJ, Serralha M, Parsons F, de Klerk NH, et al. Vitamin D and atopy and asthma phenotypes in children: a longitudinal cohort study. *Eur Respir J*. 2011;38(6):1320-7.
 11. Chawes BL, Bonnelykke K, Stokholm J, Vissing NH, Bjarnadottir E, Schoos A-MM, et al. Effect of Vitamin D3 Supplementation During Pregnancy on Risk of Persistent Wheeze in the Offspring: A Randomized Clinical Trial. *Jama*. 2016;315(4):353-61.
 12. Litonjua AA, Carey VJ, Laranjo N, Harshfield BJ, McElrath TF, O'Connor GT, et al. Effect of Prenatal Supplementation With Vitamin D on Asthma or Recurrent Wheezing in Offspring by Age 3 Years: The VDAART Randomized Clinical Trial. *Jama*. 2016;315(4):362-70.
 13. Yepes-Nuñez JJ, Fiocchi A, Pawankar R, Cuello-Garcia C, Zhang Y, Morgano GP, et al. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Vitamin D. *The World Allergy Organization journal*. Forthcoming 2016.
 14. Yepes-Nunez JJ, Fiocchi A, Pawankar R, Cuello-Garcia CA, Zhang Y, Morgano GP, et al. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Vitamin D. *The World Allergy Organization journal*. 2016;9:17.
 15. Higgins JPT, Green S, (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: <http://www.cochrane-handbook.org>.
 16. Sterne JAC, Higgins JPT, Reeves BC on behalf of the development group for ACROBAT-NRSI. A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI), Version 1.0.0, 24 September 2014. Available from <http://www.riskofbias.info> [01 December 2014].
 17. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
 18. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Bmj*. 2008;336(7650):924-6.

19. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *Journal of clinical epidemiology*. 2011;64(4):407-15.
20. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *Journal of clinical epidemiology*. 2011;64(12):1283-93.
21. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *Journal of clinical epidemiology*. 2011;64(12):1294-302.
22. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *Journal of clinical epidemiology*. 2011;64(12):1303-10.
23. Schunemann HJ, Tugwell P, Reeves BC, Akl EA, Santesso N, Spencer FA, et al. Non-randomized studies as a source of complementary, sequential or replacement evidence for randomized controlled trials in systematic reviews on the effects of interventions. *Research synthesis methods*. 2013;4(1):49-62.
24. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Bmj*. 2009;339:b2535.
25. Goldring ST, Griffiths CJ, Martineau AR, Robinson S, Yu C, Poulton S, et al. Prenatal vitamin d supplementation and child respiratory health: a randomised controlled trial. *PloS one*. 2013;8(6):e66627.
26. Brooke OG, Brown IR, Bone CD, Carter ND, Cleeve HJ, Maxwell JD, et al. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. *British medical journal*. 1980;280(6216):751-4.
27. Hossain N, Kanani FH, Ramzan S, Kausar R, Ayaz S, Khanani R, et al. Obstetric and neonatal outcomes of maternal vitamin D supplementation: results of an open-label, randomized controlled trial of antenatal vitamin D supplementation in Pakistani women. *The Journal of clinical endocrinology and metabolism*. 2014;99(7):2448-55.

28. Roth DE, Al Mahmud A, Raqib R, Akhtar E, Perumal N, Pezzack B, et al. Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D3 supplementation in Bangladesh: the AViDD trial. *Nutrition journal*. 2013;12:47.
29. Roth DE, Perumal N, Al Mahmud A, Baqui AH. Maternal vitamin D3 supplementation during the third trimester of pregnancy: effects on infant growth in a longitudinal follow-up study in Bangladesh. *The Journal of pediatrics*. 2013;163(6):1605-11 e3.
30. Mallet E, Gugi B, Brunelle P, Henocq A, Basuyau JP, Lemeur H. Vitamin D supplementation in pregnancy: a controlled trial of two methods. *Obstetrics and gynecology*. 1986;68(3):300-4.
31. Yu CK, Sykes L, Sethi M, Teoh TG, Robinson S. Vitamin D deficiency and supplementation during pregnancy. *Clinical endocrinology*. 2009;70(5):685-90.
32. Sablok A, Thariani K, Batra A, Bharti R, Aggarwal AR, Kabi BC, et al. Supplementation of Vitamin D in pregnancy and its correlation with feto-maternal outcome. *Clinical endocrinology*. 2015; 83(4):536-41.
33. Rothberg AD, Pettifor JM, Cohen DF, Sonnendecker EW, Ross FP. Maternal-infant vitamin D relationships during breast-feeding. *The Journal of pediatrics*. 1982;101(4):500-3.
34. Alonso A, Rodriguez J, Carvajal I, Prieto MA, Rodriguez RM, Perez AM, et al. Prophylactic vitamin D in healthy infants: assessing the need. *Metabolism: clinical and experimental*. 2011;60(12):1719-25.
35. Chan GM, Roberts CC, Folland D, Jackson R. Growth and bone mineralization of normal breast-fed infants and the effects of lactation on maternal bone mineral status. *The American journal of clinical nutrition*. 1982;36(3):438-43.
36. Greer FR, Searcy JE, Levin RS, Steichen JJ, Steichen-Asche PS, Tsang RC. Bone mineral content and serum 25-hydroxyvitamin D concentrations in breast-fed infants with and without supplemental vitamin D: one-year follow-up. *The Journal of pediatrics*. 1982;100(6):919-22.
37. Ponnappakkam T, Bradford E, Gensure R. A treatment trial of vitamin D supplementation in breast-fed infants: universal supplementation is not necessary for rickets prevention in Southern Louisiana. *Clinical pediatrics*. 2010;49(11):1053-60.

38. Madar AA, Klepp KI, Meyer HE. Effect of free vitamin D(2) drops on serum 25-hydroxyvitamin D in infants with immigrant origin: a cluster randomized controlled trial. *European journal of clinical nutrition*. 2009;63(4):478-84.
39. Abrams SA, Hawthorne KM, Chen Z. Supplementation with 1000 IU vitamin D/d leads to parathyroid hormone suppression, but not increased fractional calcium absorption, in 4-8-y-old children: a double-blind randomized controlled trial. *The American journal of clinical nutrition*. 2013;97(1):217-23.
40. Guillemant J, Le HT, Maria A, Allemandou A, Peres G, Guillemant S. Wintertime vitamin D deficiency in male adolescents: effect on parathyroid function and response to vitamin D3 supplements. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2001;12(10):875-9.
41. Hower J, Knoll A, Ritzenthaler KL, Steiner C, Berwind R. Vitamin D fortification of growing up milk prevents decrease of serum 25-hydroxyvitamin D concentrations during winter: a clinical intervention study in Germany. *European journal of pediatrics*. 2013;172(12):1597-605.
42. Khadilkar AV, Sayyad MG, Sanwalka NJ, Bhandari DR, Naik S, Khadilkar VV, et al. Vitamin D supplementation and bone mass accrual in underprivileged adolescent Indian girls. *Asia Pacific journal of clinical nutrition*. 2010;19(4):465-72.
43. Lewis RD, Laing EM, Hill Gallant KM, Hall DB, McCabe GP, Hausman DB, et al. A randomized trial of vitamin D(3) supplementation in children: dose-response effects on vitamin D metabolites and calcium absorption. *The Journal of clinical endocrinology and metabolism*. 2013;98(12):4816-25.
44. Maalouf J, Nabulsi M, Vieth R, Kimball S, El-Rassi R, Mahfoud Z, et al. Short- and long-term safety of weekly high-dose vitamin D3 supplementation in school children. *The Journal of clinical endocrinology and metabolism*. 2008;93(7):2693-701.
45. Molgaard C, Larnkjaer A, Cashman KD, Lamberg-Allardt C, Jakobsen J, Michaelsen KF. Does vitamin D supplementation of healthy Danish Caucasian girls affect bone turnover and bone mineralization? *Bone*. 2010;46(2):432-9.

46. Rich-Edwards JW, Ganmaa D, Kleinman K, Sumberzul N, Holick MF, Lkhagvasuren T, et al. Randomized trial of fortified milk and supplements to raise 25-hydroxyvitamin D concentrations in schoolchildren in Mongolia. *The American journal of clinical nutrition*. 2011;94(2):578-84.
47. Rajakumar K, Moore CG, Yabes J, Olabopo F, Haralam MA, Comer D, et al. Effect of Vitamin D3 Supplementation in Black and in White Children: A Randomized, Placebo-Controlled Trial. *The Journal of clinical endocrinology and metabolism*. 2015; 100(8):3183-92.
48. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *The American journal of clinical nutrition*. 2010;91(5):1255-60.
49. Viljakainen HT, Natri AM, Karkkainen M, Huttunen MM, Palssa A, Jakobsen J, et al. A positive dose-response effect of vitamin D supplementation on site-specific bone mineral augmentation in adolescent girls: a double-blinded randomized placebo-controlled 1-year intervention. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2006;21(6):836-44.
50. Ward KA, Das G, Roberts SA, Berry JL, Adams JE, Rawer R, et al. A randomized, controlled trial of vitamin D supplementation upon musculoskeletal health in postmenarchal females. *The Journal of clinical endocrinology and metabolism*. 2010;95(10):4643-51.
51. Allen KJ, Koplin JJ, Ponsonby AL, Gurrin LC, Wake M, Vuillermin P, et al. Vitamin D insufficiency is associated with challenge-proven food allergy in infants. *The Journal of allergy and clinical immunology*. 2013;131(4):1109-16, 16 e1-6.
52. Anderson LN, Chen Y, Omand JA, Birken CS, Parkin PC, To T, et al. Vitamin D exposure during pregnancy, but not early childhood, is associated with risk of childhood wheezing. *Journal of developmental origins of health and disease*. 2015;6(4):308-16.
53. Bener A, Ehlayel MS, Tulic MK, Hamid Q. Vitamin D deficiency as a strong predictor of asthma in children. *International archives of allergy and immunology*. 2012;157(2):168-75.
54. Hypponen E, Sovio U, Wjst M, Patel S, Pekkanen J, Hartikainen AL, et al. Infant vitamin d supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. *Annals of the New York Academy of Sciences*. 2004;1037:84-95.

55. Back O, Blomquist HK, Hernell O, Stenberg B. Does vitamin D intake during infancy promote the development of atopic allergy? *Acta dermato-venereologica*. 2009;89(1):28-32.
56. Camargo CA, Jr., Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *The American journal of clinical nutrition*. 2007;85(3):788-95.
57. Devereux G, Litonjua AA, Turner SW, Craig LC, McNeill G, Martindale S, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. *The American journal of clinical nutrition*. 2007;85(3):853-9.
58. Erkkola M, Kaila M, Nwaru BI, Kronberg-Kippila C, Ahonen S, Nevalainen J, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*. 2009;39(6):875-82.
59. Miyake Y, Sasaki S, Tanaka K, Hirota Y. Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants. *Eur Respir J*. 2010;35(6):1228-34.
60. Nja F, Nystad W, Lodrup Carlsen KC, Hetlevik O, Carlsen KH. Effects of early intake of fruit or vegetables in relation to later asthma and allergic sensitization in school-age children. *Acta paediatrica*. 2005;94(2):147-54.
61. Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN, et al. Maternal vitamin D status during pregnancy and child outcomes. *European journal of clinical nutrition*. 2008;62(1):68-77.
62. Baiz N, Dargent-Molina P, Wark JD, Souberbielle JC, Annesi-Maesano I, Group EM-CCS. Cord serum 25-hydroxyvitamin D and risk of early childhood transient wheezing and atopic dermatitis. *The Journal of allergy and clinical immunology*. 2014;133(1):147-53.

Figure S1. Summary of Risk of Bias in *randomized control trials* for RCT.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abrams 2013	+	+	+	?	+	+	+
Alonso 2011	+	+	+	?	+	+	?
Brooke 1980	?	?	+	?	+	?	?
Chan 1982	?	?	?	?	?	?	?
Goldring 2013	+	+	+	+	+	+	+
Greer 1982	?	?	+	?	?	+	?
Guillemant 2001	?	?	?	?	?	+	?
Hossain 2014	?	?	+	?	+	+	+
Hower 2013	+	?	+	?	+	+	+
Khadilkar 2010	?	?	+	?	?	+	+
Lewis 2013	+	?	+	+	+	+	+
Maalouf 2008	+	+	+	?	?	?	+
Madar 2009	+	?	?	+	+	+	+
Mallet 1986	+	?	+	?	?	?	?
Mølgaard 2010	?	?	+	?	?	+	?
Ponnapakkam 2010	?	?	?	?	+	?	?
Rajakumar 2015	+	+	+	+	+	+	+
Rich Edwards 2011	+	?	+	?	?	+	?
Roth 2013 A	+	+	+	+	+	+	+
Roth 2013 B	+	+	+	?	+	+	+
Rothberg 1982	?	?	+	+	?	+	?
Sablok 2015	+	?	?	?	?	+	+
Urashima 2010	+	+	+	+	?	+	+
Vijakainen 2006	?	?	+	?	?	+	?
Ward 2010	+	+	+	+	?	+	+
Yu 2009	+	+	+	?	?	+	?

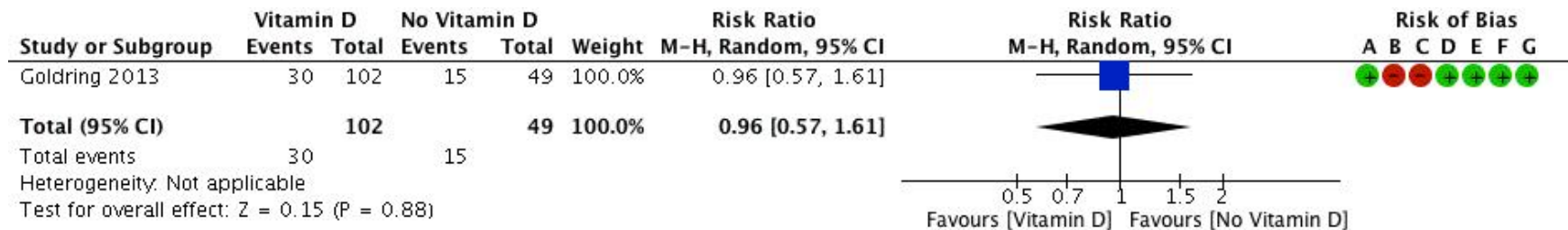
Figure S2. Forest plots of meta-analysis for each question

FOREST PLOTS OF COMPARISON VITAMIN D IN PREGNANT WOMEN

Question 1: Should supplementation of vitamin D vs. no such supplementation be used in pregnant women to prevent development of allergy in their children?

Randomized control trials

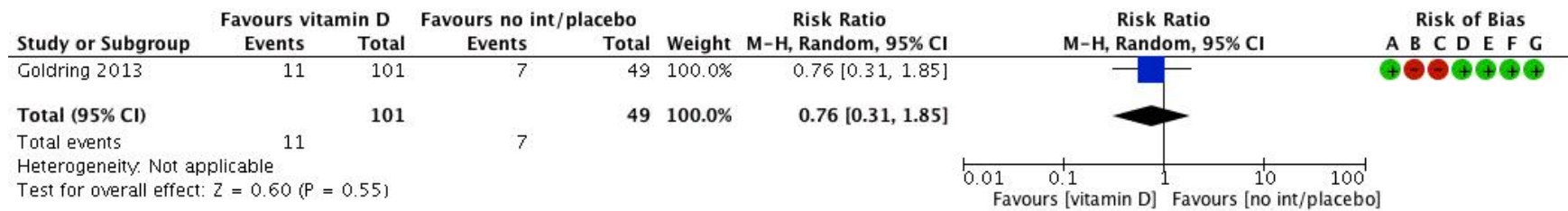
- Forest plot Vitamin D in pregnant women; outcome: Eczema



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

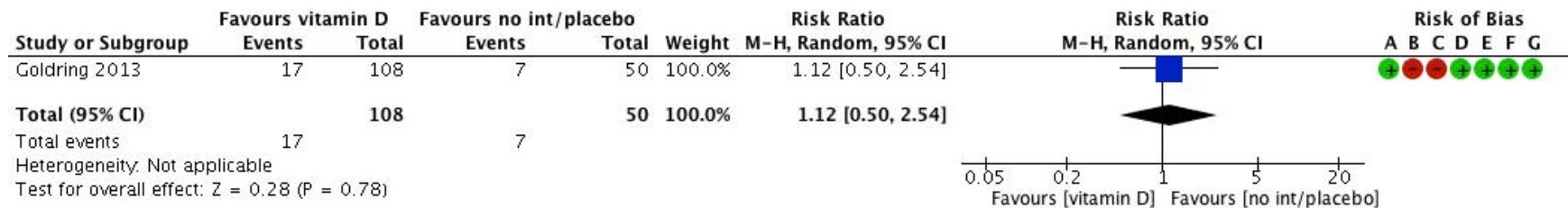
- Forest plot Vitamin D in pregnant women; outcome: Allergic rhinitis



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

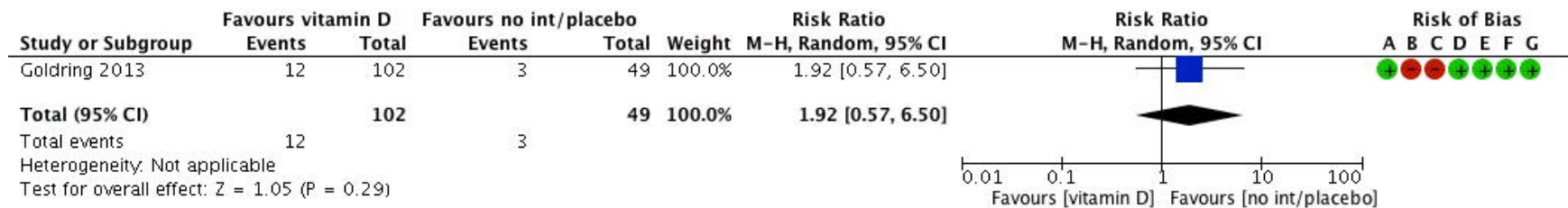
- Forest plot Vitamin D in pregnant women; outcome: Asthma/wheezing



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

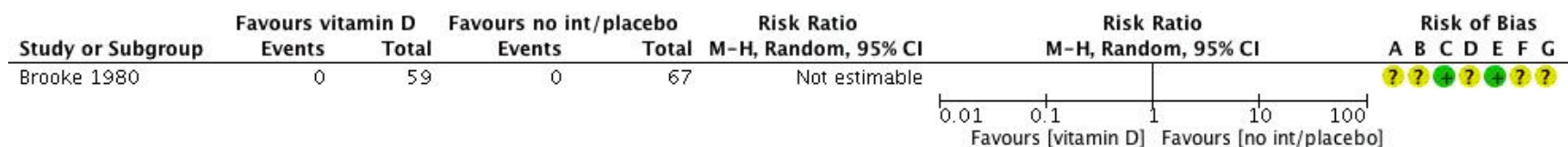
• Forest plot Vitamin D in pregnant women; outcome: Food allergy



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

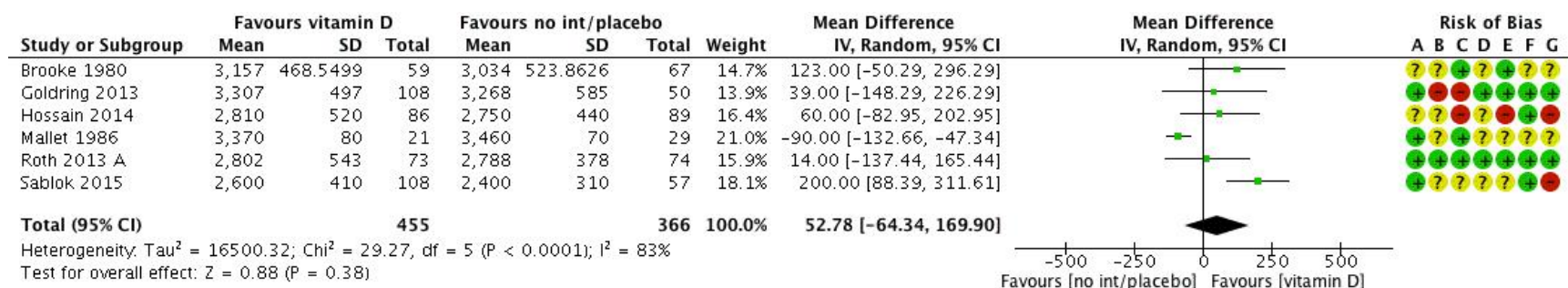
- Forest plot Vitamin D in pregnant women; outcome: Rickets



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

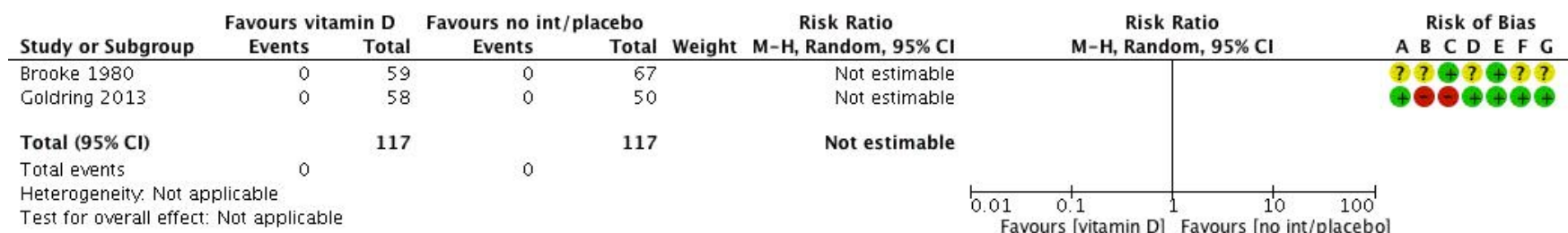
- Forest plot Vitamin D in pregnant women; outcome: Nutritional status (birth weight)



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

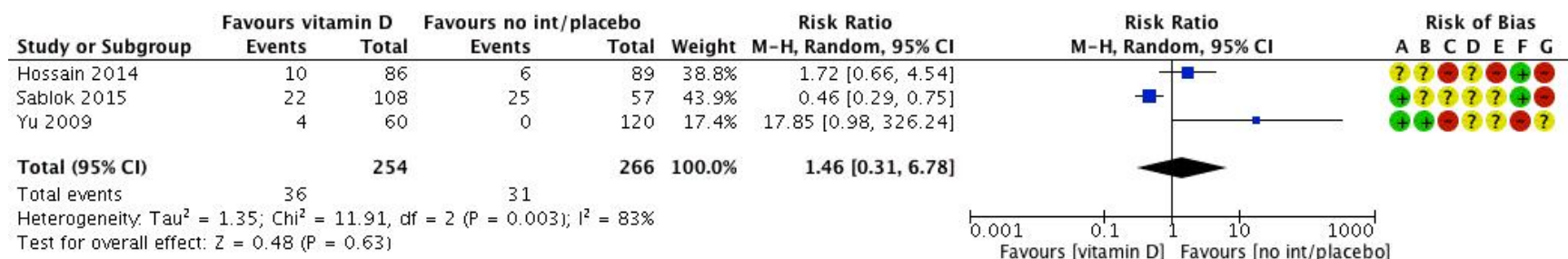
• Forest plot Vitamin D in pregnant women; outcome: Any adverse events (children)



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

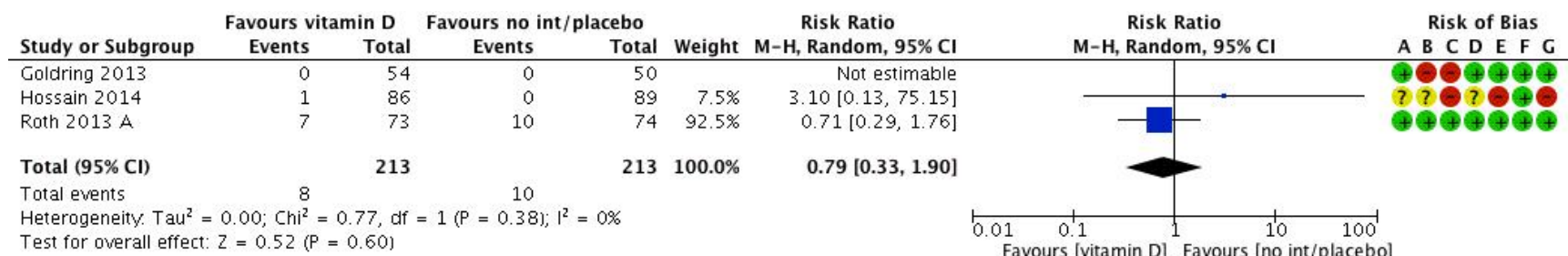
• Forest plot Vitamin D in pregnant women; outcome: Any adverse events (mother)



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

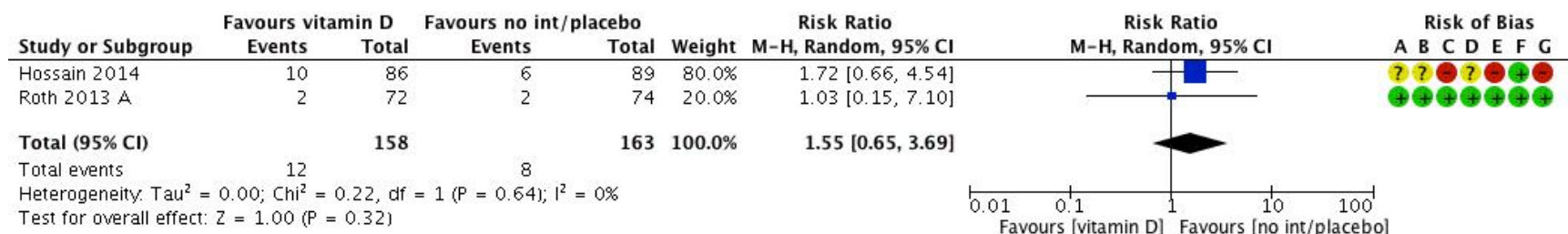
- Forest plot Vitamin D in pregnant women; outcome: Serious adverse events (children)



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

- Forest plot Vitamin D in pregnant women; outcome: Serious adverse events (mother)

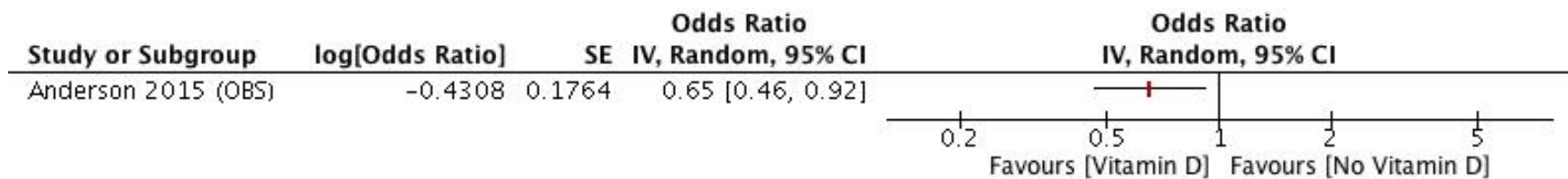


Risk of bias legend

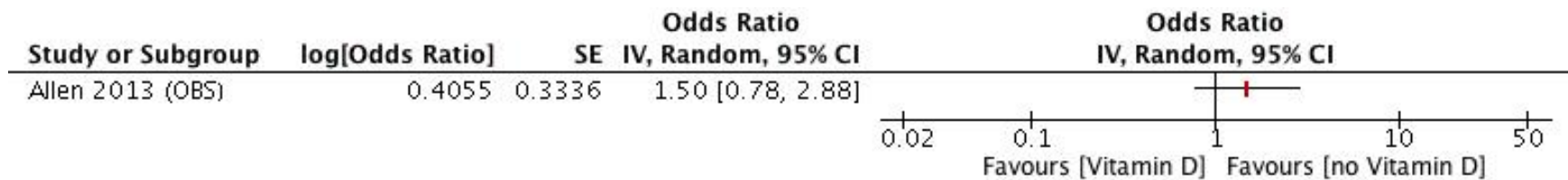
- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Observational studies

- Forest plot Vitamin D in pregnant women; outcome: Asthma/wheezing



- Forest plot Vitamin D in pregnant women; outcome: Food allergy

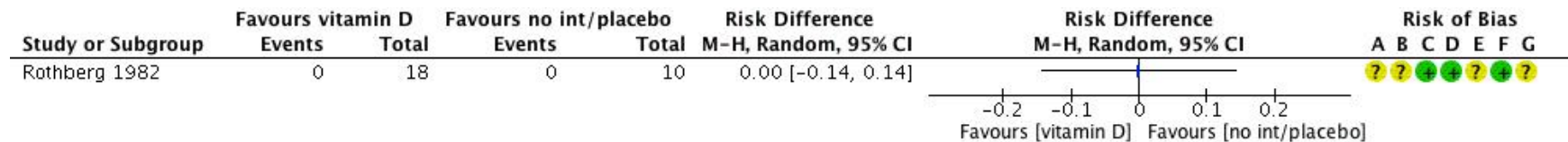


FOREST PLOTS OF COMPARISON VITAMIN D IN BREASTFEEDING MOTHERS

Question 2: Should supplementation of vitamin D vs. no such supplementation be used in breastfeeding mothers to prevent development of allergy in their children?

Randomized control trials

- Forest plot Vitamin D in breastfeeding women; outcome: Rickets

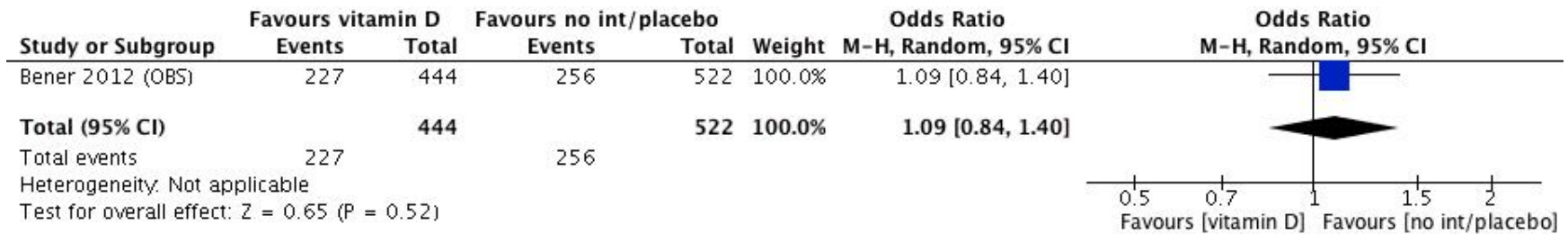


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

OBSERVATIONAL STUDIES

- Forest plot Vitamin D in breastfeeding women; outcome: Asthma



Risk of bias legend

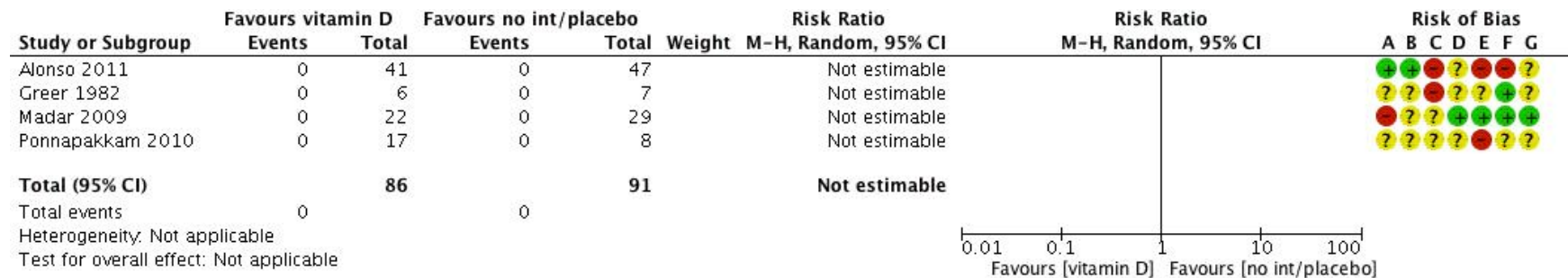
- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

FOREST PLOTS OF COMPARISON VITAMIN D IN INFANTS

Question 3: Should supplementation of vitamin D vs. no such supplementation be used in infants to prevent development of allergy?

Randomized control trials

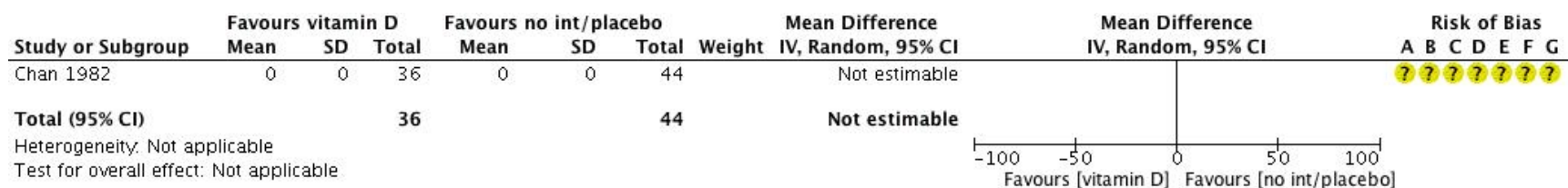
- Forest plot Vitamin D in infants; outcome: Rickets



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

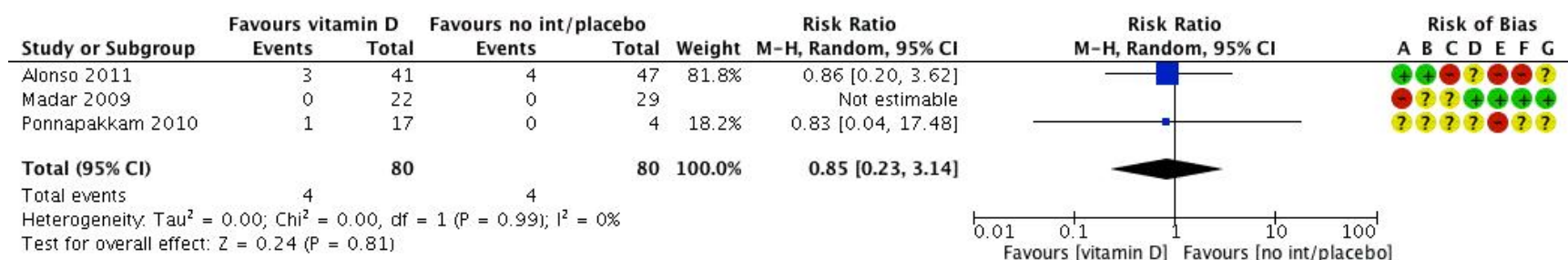
- Forest plot Vitamin D in infants; outcome: Nutritional status (weight at 1 year)



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

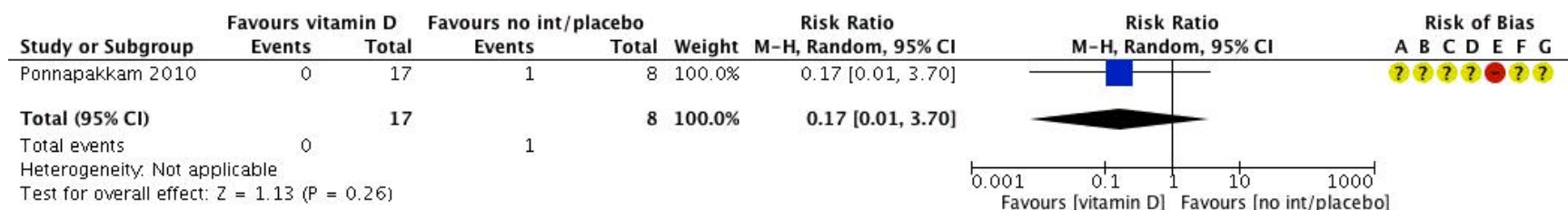
- Forest plot Vitamin D in infants; outcome: Any adverse events



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

- Forest plot Vitamin D in infants; outcome: Serious adverse events

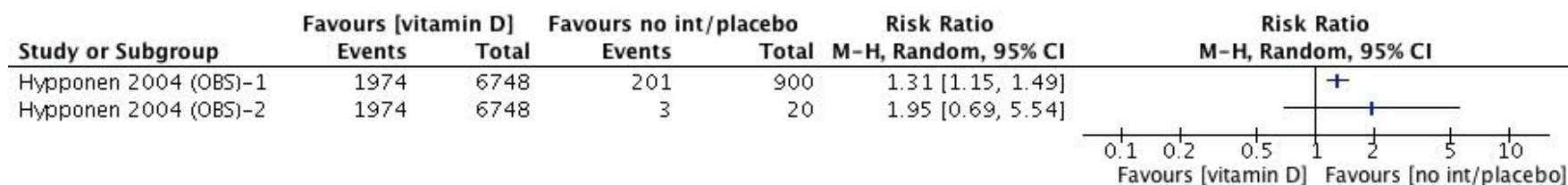


Risk of bias legend

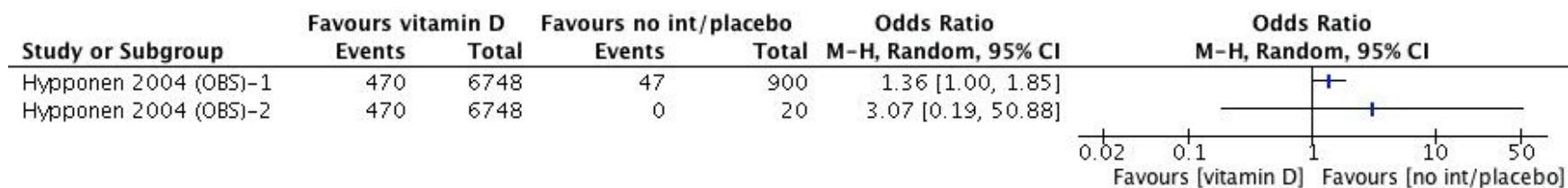
- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Observational studies

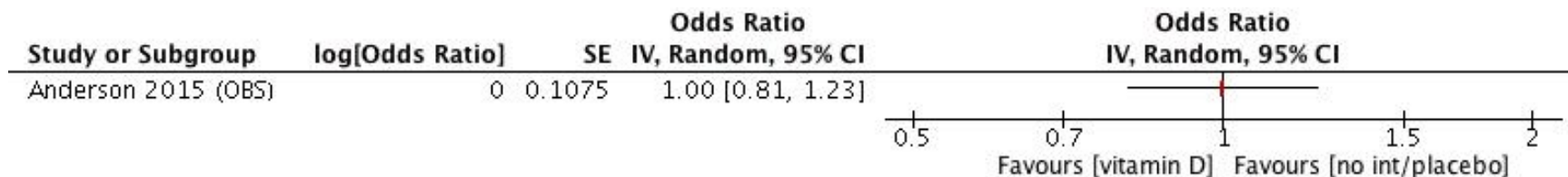
- Forest plot Vitamin D in infants; outcome: Allergic rhinitis



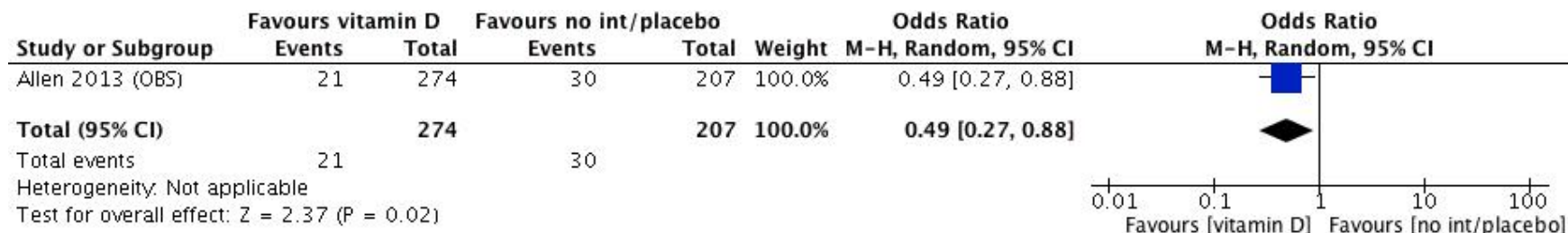
- Forest plot Vitamin D in infants; outcome: Asthma/wheezing Case-control



- Forest plot Vitamin D in infants; outcome: Asthma/wheezing Cohort



- Forest plot Vitamin D in infants; outcome: Food allergy

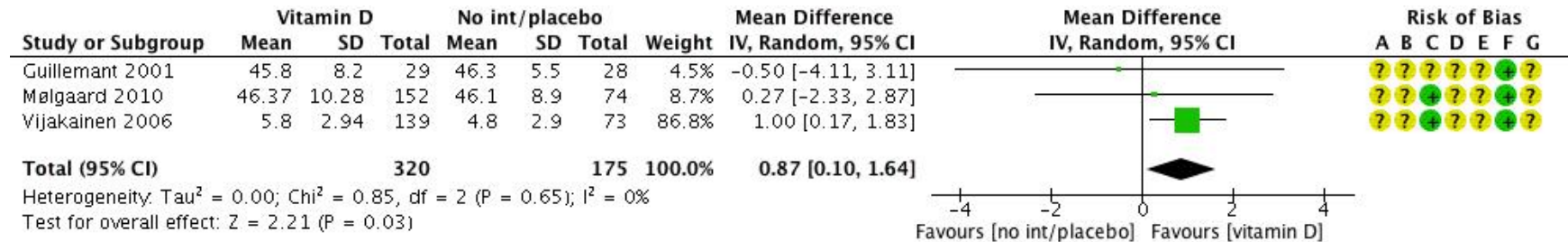


FOREST PLOTS OF COMPARISON VITAMIN D IN CHILDREN

Question 4: Should supplementation of vitamin D vs. no such supplementation be used in children to prevent development of allergy and other important outcomes?

Randomized control trials

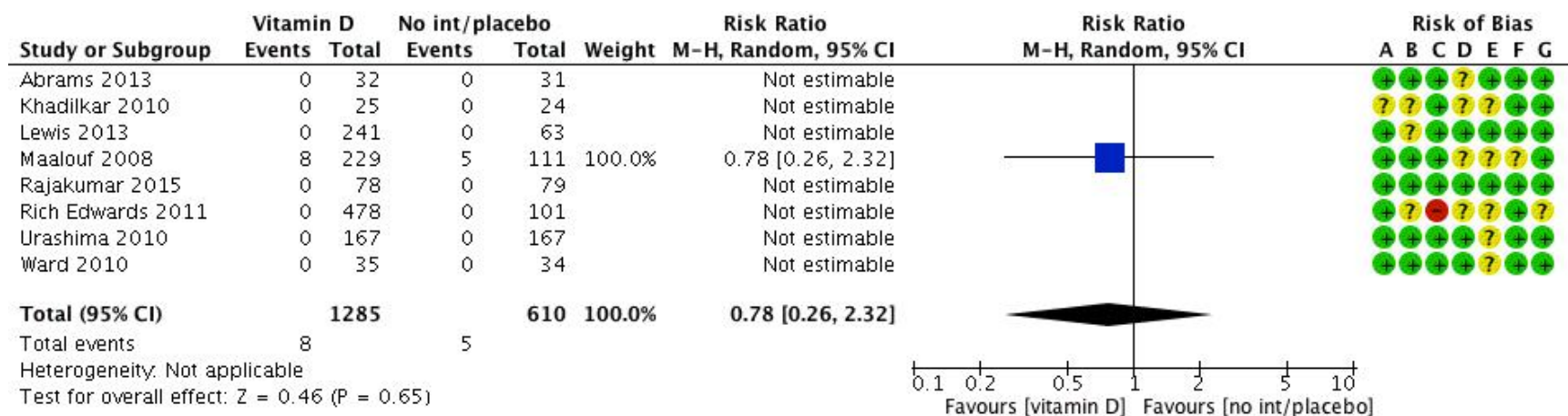
- Forest plot Vitamin D in children; outcome: nutritional status (weight)



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

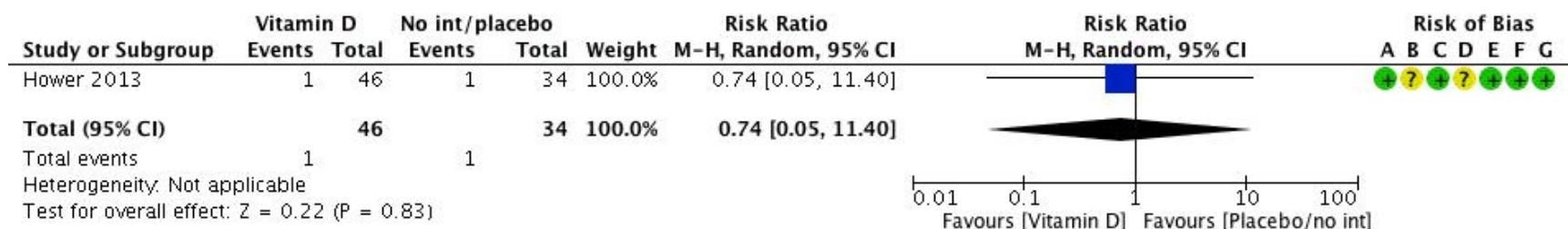
- Forest plot Vitamin D in children; outcome: any adverse events



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

- Forest plot Vitamin D in children; outcome: serious adverse events



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Table S1. Search strategies

Interface	Ovid	
Database	Medline	
Date of searching	January 30, 2016	
Study Types	Randomized control trials and observational studies [†]	
Limits	No limits	
Database strategy		
1	exp Vitamin D/	46990
2	hydroxyvitamin D.mp.	9536
3	1,25-dihydroxycholecalciferol.mp.	1125
4	24,25-dihydroxycholecalciferol.mp.	155
5	1,25-dihydroxyvitamin D3.mp.	4713
6	Vitamin D.tw.	43639
7	1 or 2 or 3 or 4 or 5 or 6	65198
8	exp Child/	1637039
9	exp Infant/	991473
10	Childhood.mp.	194126
11	Infant*.mp.	1083596
12	Infancy.tw.	40952
13	Baby.tw.	29822
14	Baby's.tw.	1767
15	Babies.tw.	30029
16	Neonat*.mp.	232911
17	Child*.mp.	2014319
18	Schoolchild*.tw.	11251
19	Schoolage*.tw.	60
20	School age*.tw.	15763
21	Kids.tw.	4276
22	Kid.tw.	1348
23	Toddler*.tw.	6943
24	exp Pediatrics/	48238
25	Pediatric*.mp.	243725
26	Paediatric*.mp.	45757
27	exp Schools/	93035
28	Kindergar*.tw.	4754
29	Primary school*.mp.	8699
30	exp Pregnancy/	778451
31	Pregnant Women/	5514
32	Gestation.mp.	96310
33	(pregnanc* or pregnant).mp.	844193
34	gravidity/ or postpartum period/ or pregnancy trimesters/	22478
35	(gravidity or peripartum period or postpartum period).mp.	27479

36	exp Breast Feeding/	30816
37	(breast feeding or breastfeeding).mp.	40802
38	Lactation/	34864
39	lactation.mp.	48150
40	Milk, Human/	16202
41	((human or breast) adj1 milk).mp.	22920
42	or/8-41	3318393
43	7 and 42	11604
44	exp animals/ not humans.sh.	4177874
45	43 not 44	10694
46	exp Hypersensitivity/	299314
47	hypersensitiv*.mp.	154466
48	allerg*.mp.	182301
49	anaphyla*.mp.	31973
50	asthma*.mp.	147962
51	wheez*.mp.	10884
52	eczema*.mp.	19485
53	dermatit*.mp.	77572
54	rhinit*.mp.	36427
55	hyperreactiv*.mp.	12121
56	(atopi* or atopy).mp.	38578
57	or/46-55	483374
58	45 and 57	538

[†]Case-control and cohort studies

Interface	Ovid	
Database	<i>Embase</i>	
Date of searching	January 30, 2016	
Study Types	Randomized control trials and observational studies [†]	
Limits	No limits	
Database strategy		
1	exp Vitamin D/	105925
2	hydroxyvitamin D.mp.	15624
3	1,25-dihydroxycholecalciferol.mp.	1334
4	24,25-dihydroxycholecalciferol.mp.	163
5	1,25-dihydroxyvitamin D3.mp.	6018
6	Vitamin D.tw.	62288
7	1 or 2 or 3 or 4 or 5 or 6	117168
8	exp Child/	2272928
9	exp Infant/	926161
10	Childhood.mp.	330316
11	Infant*.mp.	803451

12	Infancy.tw.	51760
13	Baby.tw.	40153
14	Baby's.tw.	2470
15	Babies.tw.	40269
16	Neonat*.mp.	279324
17	Child*.mp.	2270276
18	Schoolchild*.tw.	13113
19	Schoolage*.tw.	267
20	School age*.tw.	20183
21	Kids.tw.	5607
22	Kid.tw.	1858
23	Toddler*.tw.	9009
24	exp Pediatrics/	89907
25	Pediatric*.mp.	381375
26	Paediatric*.mp.	77246
27	exp Schools/	281779
28	Kindergar*.tw.	5745
29	Primary school*.mp.	115091
30	exp Pregnancy/	638165
31	Pregnant Women/	431318
32	Gestation.mp.	127611
33	(pregnanc* or pregnant).mp.	828937
34	gravity/ or postpartum period/ or pregnancy trimesters/	605720
35	(gravity or peripartum period or postpartum period).mp.	10771
36	exp Breast Feeding/	38888
37	(breast feeding or breastfeeding).mp.	48741
38	Lactation/	41982
39	lactation.mp.	52471
40	Milk, Human/	20880
41	((human or breast) adj1 milk).mp.	28541
42	or/8-41	3862110
43	7 and 42	21988
44	exp animals/ not humans.sh.	21055025
45	43 not 44	2362
46	exp Hypersensitivity/	514647
47	hypersensitiv*.mp.	157307
48	allerg*.mp.	304176
49	anaphyla*.mp.	56335
50	asthma*.mp.	242104
51	wheez*.mp.	23991
52	eczema*.mp.	37471
53	dermatit*.mp.	105183
54	rhinit*.mp.	49945
55	hyperreactiv*.mp.	17775

56	(atopi* or atopy).mp.	63796
57	or/46-55	714556
58	45 and 57	96

[†]Case-control and cohort studies

Database	<i>The Cochrane Library</i>	
Date of searching	January 30, 2016	
Study Types	Randomized control trials and observational studies*	
Limits	No limits	
Database strategy		
1	MeSH descriptor: [Vitamin D] explode all trees	2805
2	"vitamin D":ti,ab,kw	4621
3	hydroxyvitamin	1427
4	1,25-dihydroxycholecalciferol	59
5	1,25-dihydroxyvitamin D3	171
6	24,25-dihydroxycholecalciferol	9
7	#1 or #2 or #3 or #4 or #5 or #6	5685
8	MeSH descriptor: [Child] explode all trees	152
9	MeSH descriptor: [Infant] explode all trees	14330
10	Infant*	43342
11	Infancy	1655
12	Baby*	2871
13	Babies	3380
14	Neonat*	21029
15	Preterm*	7785
16	Newborn*	19707
17	Prematur*	15107
18	Postmatur*	35
19	Child*	106611
20	Schoolchild*	1062
21	School age*	52028
22	Kid	106
23	Kids*	503
24	Toddler*	948
25	Boy*	8480
26	Girl*	4732
27	MeSH descriptor: [Minors] explode all trees	8
28	Minors*	197
29	MeSH descriptor: [Pediatrics] explode all trees	608
30	Paediatric*	10981
31	Peadiatric*	42
32	MeSH descriptor: [Schools] explode all trees	1991

33	Preschool*	31280
34	Kindergar*	456
35	Primary school*	15081
36	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35	177870
37	MeSH descriptor: [Pregnancy] explode all trees	6296
38	MeSH descriptor: [Breast Feeding] explode all trees	1498
39	#36 or #37 or #38	180453
40	#7 and #39	1298

Table S2. Characteristics of included studies**1. PREGNANT WOMEN**

Study, Year	n	Population who received vitamin D	Type of vitamin D administered	Route of administration and forms	Doses of vitamin D administered	Time of administration of vitamin D	Time of follow-up for outcome(s)
<i>Randomized control trials</i>							
Brooke, 1980 (29)	126*	Pregnant women with 28 gestation weeks	Ergocalciferol	Oral (unreported)	1000 IU/day	Until delivery	At birth
Goldring, 2013 (25)	180*	Pregnant women at 27 weeks of gestation	Vitamin D3 (ergocalciferol)	Oral (tablets)	800 IU/day or 200000 UI (single dose)**	2 months (until delivery)	At 36 months
Hossain, 2014 (30)	200*	Pregnant women at 20 weeks of gestation	Vitamin D3 (Ergocalciferol)	Oral (liquid formulation)	4000 IU/day	Until delivery	At birth
Mallet, 1986 (52)	57*	Pregnant women at seven month	Vitamin D2	Unreported	1000 IU/day or 200000 IU (single dose)	Last trimester of pregnancy	At birth
Roth, 2013-A (31)	160*	Pregnant women with gestational age of 26 to < 30 weeks	Vitamin D3 (cholecalciferol)	Oral (liquid formulation)	35000 IU/week	3 months (last trimester of pregnancy)	At birth
Roth, 2013-B (28)	160*	Pregnant women with gestational age of 26 to < 30 weeks	Vitamin D3 (cholecalciferol)	Oral (liquid formulation)	35000 IU/week	3 months (last trimester of pregnancy)	One year after delivery
Sablok, 2015 (33)	180*	Pregnant women with gestational age at 14–20 weeks	Vitamin D (cholecalciferol)	Oral	Between 60000 IU to 480000 IU	Between second to third trimester of pregnancy	At birth
Yu, 2009 (32)	180*	Pregnant women with 27 gestation weeks	Vitamin D (Ergocalciferol or calciferol)	Oral	800 UI/day or 200000 IU (single dose)	Until delivery	At birth
<i>Observational studies</i>							
Allen, 2013 (27)	2252	Pregnant women	Maternal use of vitamin D supplement	Unreported	Unreported	During pregnancy	Infants with aged between 11 and 15 months
Anderson 2015 (26)	2478	Pregnant women	Maternal use of	Unreported	400 or 1000	During	Infants with aged

vitamin D supplement	IU/day	pregnancy	between 0 to 5 years
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2. BREASTFEEDING

Study, Year	n	Population who received vitamin D	Type of vitamin D administered	Route of administration and forms	Doses of vitamin D administered	Time of administration of vitamin D	Time of follow-up for outcome(s)
Randomized control trials							
Rothberg, 1982 (34)	60*	Breastfeeding mothers	Vitamin D	Unreported	500 IU or 1000 IU/day	6 weeks	At 6 weeks of age
Observational studies							
Bener, 2012 (24)	966	Breastfeeding mothers	Vitamin D supplementation	Unreported	Unreported	During breastfeeding	Children with different age group

3. INFANTS

[illegible]

Allen, 2013 (27)	2252	Infants	Vitamin D supplement	Unreported)	Unreported	During infancy	Infants with aged between 11 and 15 months
Anderson 2015 (26)	2478	Infants	Vitamin D supplement	Unreported	400 IU/day	During childhood	Infants with aged between 0 to 5 years
Hypponen, 2004 (35)	7648	Infants	Vitamin D supplement	Unreported	<2000 IU to >2000 IU‡	During the first year of life	At age 31 years

4. CHILDREN

Study, Year	n	Population who received vitamin D	Type of vitamin D administered	Route of administration and forms	Doses of vitamin D administered	Time of administration of vitamin D	Time of follow-up for outcome(s)
<i>Randomized control trials</i>							
Abrams, 2013 (53)	64*	Children between 4-8.9 years old	Vitamin D3	Oral	1000 IU/day	8 weeks	At the end of the trial (8 th week later)
Guillemant 2001 (41)	57*	Adolescents between 13 to 16 years old	Vitamin D3	Oral (phial of water-soluble oral solution)	100000 IU/3 times	18 months	At the end of the trial (18 months later)
Hower 2013 (44)	92*	Children between 2-6 years old	Vitamin D fortified milk	Oral	400 IU/day	8 months	At the end of the trial (8 months later)
Khadiolkar 2010 (54)	50*	Adolescents between 14 to 15 years old	Vitamin D2	Oral	300000/4 times	12 months	At the end of the trial (12 months later)
Lewis 2013 (55)	323*	Children between 9-13 years old	Vitamin D3	Oral (tablets)	400, 1000, 2000, or 4000 IU/day	12 weeks	At the end of the trial (12 weeks later)
Maalouf 2008 (56)	340*	Adolescents between 10 to 17 years old	Vitamin D3	Oral	1400 or 14000 UI/weekly	12 months	At the end of the trial (12 months later)
Mølgaard 2010 (42)	225*	Children between 11 to 12 years old	Vitamin D3	Oral	200 or 400 IU/day	12 months	At the end of the trial (12 months later)
Rich Edwards 2011 (57)	579	Children between 9 to 11 years old	Vitamin D3	Oral	13700 IU in one week or 300 IU/day	49 days	At the end of the trial

Rajakumar, 2015 (58)	157*	Children between 8 to 14 years old	Vitamin D3	Oral (tablets)	1000 IU/daily	6 months	At the end of the trial (6 months later)
Urashima 2010 (59)	430*	Children between 6 to 15 years old	Vitamin D3	Oral (tablets)	1200 IU/day	4 months	At the end of the trial (4 months later)
Vijakainen 2006 (43)	228	Adolescents between 11 to 12 years old	Vitamin D3	Oral	200 or 400 IU/day	12 months	At the end of the trial (12 months later)
Ward 2010 (60)	73*	Adolescents between 12 to 14 years old	Vitamin D 2 (ergocalciferol)	Oral	150000 IU/four times	12 months	At the end of the trial (12 months later)

*Patients randomized. **Results presented in metanalysis correspond to pooled data. Single oral dose was administered as cholecalciferol (oral bolus). ***Randomization was carried out at the health clinic level. [†] Two group of infants received vitamin D: one group started the vitamin D supplementation at birth and another group started at 2 months of age. [‡] The daily dose of vitamin D was calculated on the basis of concentration of vitamin D in the product used and the reported dosage (categorized as <50 µg, 50 µg, or >50 µg).

Table S3. Characteristics of excluded studies

Studies	Study was no RCT or Observational study †	Patients were not healthy §	Intervention was not vitamin D supplementation only ¶	Study did not report any of the outcomes of interest	Duplicate
Al-Shaar, 2014 (1)				•	
Ala-Houhala, 1988 (2)	•				
Ala-Houhala 1986 (3)	•				
Alyasin, 2011 (4)	•	•			
Allan, 2015 (5)			•		
Arabi, 2009 (6)				•	
Arikoglu, 2015 (7)			•		
Arshi, 2014 (8)		•			
Awasthi, 2014 (9)			•	•	
Bacharier, 2014 (10)	•				
Backström, 2000 (11)			•	•	
Backström, 1999 (12)			•	•	
Baek, 2014 (13)	•	•			
Baiz, 2014 (14)			•		
Bar Yoseph, 2015 (15)		•		•	
Baris, 2015 (16)		•		•	
Bechard, 2015 (17)		•	•	•	
Bird, 2014 (18)	•				
Brett, 2015 (19)			•		
Brehm, 2012 (20)	•				
Brehm, 2009 (21)	•				
Brehm, 2010 (22)		•	•		•
Camargo, 2012 (23)					

Camargo, 2011 (24)	•		
Camargo, 2007 (25)		•	
Carroll, 2011 (26)	•		
Cashman, 2011 (27)			•
Chawes, 2014 (28)		•	
Chawes 2016 (29)		•	
Cheng, 2005 (30)		•	
Cosenza, 2013 (31)		•	•
Delvin, 1986 (32)			•
Devereux, 2007 (33)		•	
Du, 2004 (34)		•	
Duhamel, 2000 (35)	•		
Erkkola, 2009 (36)		•	
Freishtat, 2010 (37)		•	
Gale, 2008 (38)		•	
Ganmaa, 2012 (39)		•	
Gentile, 2010 (40)	•		
Gergen, 2013 (41)		•	
Grant, 2014 (42)			•
Grant, 2015 (43)			•
Green, 2010 (44)		•	•
Greene, 2011 (45)		•	
Greer, 1981 (46)			•
Harvey, 2012 (47)	•		
Heimbeck, 2013 (48)		•	
Hibbs, 2015 (49)		•	

Hollams, 2011 (50)			•	
Hughes, 2011 (51)			•	
Ito, 2013 (52)			•	
Jacobs, 2011 (53)			•	
Jensen, 2015 (54)		•	•	•
Jones, 2012 (55)			•	
Kemp, 2013 (56)			•	
Khadgawat, 2013 (57)			•	
Kim, 2010 (58)	•			
Koistinen, 2014 (59)			•	
Krotrakulchai 2013, (60)	•			
Kull, 2006 (61)			•	
Lewis, 2012 (62)		•		
Li, 2015 (63)	•	•	•	•
Litonjua, 2014 (64) ‡			•	•
Litonjua, 2016 (65)			•	
Liu, 2011 (66)			•	
Liu, 2013 (67)		•	•	•
Ma, 2011 (68)			•	•
Madsen, 2013 (69)				•
Magnus, 2013 (70)			•	
Maguire, 2014 (71)	•			
Majak, 2011 (72)		•		
Marchisio, 2013 (73)		•		
Marya, 1981 (74)			•	
Maslova, 2013 (75)			•	

Maxwell, 1981 (76)	•		
Menon, 2012 (77)		•	
Meyer, 2015 (78)		•	•
Miller, 2015 (79)		•	•
Miyake, 2010 (80)		•	
Miyake, 2012 (81)		•	
Miyake, 2014 (82)		•	
Morales, 2012 (83)		•	
Mouratidou, 2013 (84)		•	
Moyer-Mileur, 2003 (85)		•	
Mullins, 2010 (86)	•		
Mullins, 2010 (87)	•		
Mullins, 2011 (88)	•		
Mullins, 2012 (89)		•	
Nissen, 2015 (90)			•
Norizoe, 2014 (91)		•	
Nwaru, 2010 (92)		•	
O'Connor, 2010 (93)			•
Oktaria, 2013 (94)	•		
Oliver, 2014 (95)	•		
Ozaydin, 2013 (96)		•	
Palmer, 2015 (97)		•	•
Persson, 2013 (98)		•	
Peters, 2015 (99)		•	
Pike, 2012 (100)		•	
Rajabbik, 2014 (101)	•		

Rochat, 2010 (102)			•
Rosser, 2014 (103)		•	•
Rothers, 2011 (104)		•	
Sacheck, 2015 (105)		•	
San, 2013 (106)		•	•
Sharief, 2011 (107)		•	
Sidbury, 2008 (108)	•		•
Stelmach, 2015 (109)		•	
Stenberg, 2014 (110)		•	
Strucinska, 2015 (111)		•	
Sun, 2011 (112)		•	•
Tolppanen, 2011 (113)		•	
Tolppanen, 2013 (114)		•	
Trilok-Kumar, 2015 (115)	•	•	
Tse, 2012 (116)	•	•	•
Tu, 2015 (117)	•		•
Uysalol, 2013 (118)	•		
van Oeffelen, 2011 (119)		•	
Venkataraman, 1992 (120)		•	
Visness, 2015 (121)	•	•	
Wagner, 2006 (122)		•	
Wagner 2013 (123)		•	
Wang, 2014 (124)		•	
Weisse, 2013 (125)		•	
Willers, 2007 (126)		•	
Wills, 2013 (127)		•	

Wjst, 2007 (128)	•	•	
Wu, 2012 (129)		•	
Yadav, 2014 (130)	•	•	
Yao, 2014 (131)	•	•	
Young, 2001 (132)		•	
Zhang, 2003 (133)			•
Zhang, 2014 (134)		•	
Zhong, 2013 (135)	•		
Zhu, 2005 (136)		•	
Zhu 2003 (137)			•
Zhu, 2008 (138)			•
Zittermann, 2004 (139)		•	•
Zoratti, 2013 (140)	•		
Zosky, 2014 (141)	•		

†Case-control or cohort studies. §Only for randomized control trial. ¶ Information about vitamin D supplementation was rejected if that was obtained by using any food frequency questionnaire. ‡This is a protocol of the RCT published by Litonjua 2016.

REFERENCES

1. Al-Shaar L, Mneimneh R, Nabulsi, Maalouf J, Fuleihan Gel H. Vitamin D3 dose requirement to raise 25-hydroxyvitamin D to desirable levels in adolescents: results from a randomized controlled trial. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2014;29(4):944-51.
2. Ala-Houhala M, Koskinen T, Parviainen MT, Visakorpi JK. 25-Hydroxyvitamin D and vitamin D in human milk: effects of supplementation and season. The American journal of clinical nutrition. 1988;48(4):1057-60.

3. Ala-Houhala M, Koskinen T, Terho A, Koivula T, Visakorpi J. Maternal compared with infant vitamin D supplementation. *Archives of disease in childhood*. 1986;61(12):1159-63.
4. Alyasin S, Momen T, Kashef S, Alipour A, Amin R. The relationship between serum 25 hydroxy vitamin d levels and asthma in children. *Allergy, asthma & immunology research*. 2011;3(4):251-5.
5. Allan KM, Prabhu N, Craig LCA, McNeill G, Kirby B, McLay J, et al. Maternal vitamin D and E intakes during pregnancy are associated with asthma in children. *Eur Respir J*. 2015;45(4):1027-36.
6. Arabi A, Zahed L, Mahfoud Z, El-Onsi L, Nabulsi M, Maalouf J, et al. Vitamin D receptor gene polymorphisms modulate the skeletal response to vitamin D supplementation in healthy girls. *Bone*. 2009;45(6):1091-7.
7. Arikoglu T, Kuyucu S, Karaismailoglu E, Batmaz SB, Balci S. The association of vitamin D, cathelicidin, and vitamin D binding protein with acute asthma attacks in children. *Allergy Asthma Proc*. 2015;36(4):51-8.
8. Arshi S, Fallahpour M, Nabavi M, Bemanian MH, Javad-Mousavi SA, Nojomi M, et al. The effects of vitamin D supplementation on airway functions in mild to moderate persistent asthma. *Ann Allergy Asthma Immunol*. 2014;113(4):404-9.
9. Awasthi S, Vikram K. Serum 25 hydroxy vitamin D insufficiency associated with bronchial asthma in Lucknow, India. *Indian journal of pediatrics*. 2014;81(7):644-9.
10. Bacharier LB. Vitamin D status at birth: an important and potentially modifiable determinant of atopic disease in childhood? *J Allergy Clin Immunol*. 2014;133(1):154-5.
11. Backstrom MC, Aine L, Maki R, Kuusela AL, Sievanen H, Koivisto AM, et al. Maturation of primary and permanent teeth in preterm infants. *Archives of disease in childhood Fetal and neonatal edition*. 2000;83(2):F104-8.

12. Backstrom MC, Maki R, Kuusela AL, Sievanen H, Koivisto AM, Koskinen M, et al. The long-term effect of early mineral, vitamin D, and breast milk intake on bone mineral status in 9- to 11-year-old children born prematurely. *Journal of pediatric gastroenterology and nutrition*. 1999;29(5):575-82.
13. Baek JH, Shin YH, Chung IH, Kim HJ, Yoo EG, Yoon JW, et al. The link between serum vitamin D level, sensitization to food allergens, and the severity of atopic dermatitis in infancy. *The Journal of pediatrics*. 2014;165(4):849-54 e1.
14. Baiz N, Dargent-Molina P, Wark JD, Souberbielle JC, Annesi-Maesano I, Group EM-CCS. Cord serum 25-hydroxyvitamin D and risk of early childhood transient wheezing and atopic dermatitis. *J Allergy Clin Immunol*. 2014;133(1):147-53.
15. Bar Yoseph R, Livnat G, Schnapp Z, Hakim F, Dabbah H, Goldbart A, et al. The effect of vitamin D on airway reactivity and inflammation in asthmatic children: A double-blind placebo-controlled trial. *Pediatric pulmonology*. 2015;50(8):747-53.
16. Baris S, Ozen A, Cagan H, Kiykim A, Tulunay A, Karakoc-Aydiner E. The effect of Vitamin D supplementation on subcutaneous allergen immunotherapy in house dust mite sensitive asthmatic children. *Turkish Journal of Immunology*. 2015; 3(2):54-63.
17. Bechard LJ, Gordon C, Feldman HA, Venick R, Gura K, Guinan EC, et al. Bone loss and vitamin D deficiency in children undergoing hematopoietic cell transplantation. *Pediatric blood & cancer*. 2015;62(4):687-92.
18. Bird JA, Wang J, Visness CM, Calatroni A, Sampson HA, Gruchalla R. Winter birth in inner-city asthmatic children is associated with increased food allergen sensitization risk. *J Allergy Clin Immunol*. 2014;134(2):490-2.
19. Brett N, Lavery P, Vanstone C, Maguire J, Rauch F, Weiler H. Vitamin D status and functional health outcomes: A randomized vitamin D dose-response trial in 28-Y olds. *FASEB journal*. 2015; 29(1 Meeting Abstracts).

20. Brehm JM, Acosta-Perez E, Klei L, Roeder K, Barmada M, Boutaoui N, et al. Vitamin D insufficiency and severe asthma exacerbations in Puerto Rican children. *American journal of respiratory and critical care medicine*. 2012;186(2):140-6.
21. Brehm JM, Celedon JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *American journal of respiratory and critical care medicine*. 2009;179(9):765-71.
22. Brehm JM, Schuemann B, Fuhlbrigge AL, Hollis BW, Strunk RC, Zeiger RS, et al. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. *J Allergy Clin Immunol*. 2010;126(1):52-8 e5.
23. Camargo CA, Jr., Ganmaa D, Frazier AL, Kirchberg FF, Stuart JJ, Kleinman K, et al. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. *Pediatrics*. 2012;130(3):e561-7.
24. Camargo CA, Jr., Ingham T, Wickens K, Thadhani R, Silvers KM, Epton MJ, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics*. 2011;127(1):e180-7.
25. Camargo CA, Jr., Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *The American journal of clinical nutrition*. 2007;85(3):788-95.
26. Carroll KN, Gebretsadik T, Larkin EK, Dupont WD, Liu Z, Driest S, et al. Relationship of maternal vitamin D level with maternal and infant respiratory disease. *American journal of obstetrics and gynecology*. 2011; 205(3):215.e1-.e7.
27. Cashman KD, FitzGerald AP, Viljakainen HT, Jakobsen J, Michaelsen KF, Lamberg-Allardt C, et al. Estimation of the dietary requirement for vitamin D in healthy adolescent white girls. *The American journal of clinical nutrition*. 2011;93(3):549-55.

28. Chawes BL, Bonnelykke K, Jensen PF, Schoos AM, Heickendorff L, Bisgaard H. Cord blood 25(OH)-vitamin D deficiency and childhood asthma, allergy and eczema: the COPSAC2000 birth cohort study. *PloS one*. 2014;9(6):e99856.
29. Chawes BL, Bonnelykke K, Stokholm J, Vissing NH, Bjarnadottir E, Schoos A-MM, et al. Effect of Vitamin D3 Supplementation During Pregnancy on Risk of Persistent Wheeze in the Offspring: A Randomized Clinical Trial. *Jama*. 2016;315(4):353-61.
30. Cheng S, Lyytikainen A, Kroger H, Lamberg-Allardt C, Alen M, Koistinen A, et al. Effects of calcium, dairy product, and vitamin D supplementation on bone mass accrual and body composition in 10-12-y-old girls: a 2-y randomized trial. *The American journal of clinical nutrition*. 2005;82(5):1115-26; quiz 47-8.
31. Cosenza L, Pezzella V, Nocerino R, Di Costanzo M, Coruzzo A, Passariello A, et al. Calcium and vitamin D intakes in children: a randomized controlled trial. *BMC pediatrics*. 2013;13:86.
32. Delvin EE, Salle BL, Glorieux FH, Adeleine P, David LS. Vitamin D supplementation during pregnancy: effect on neonatal calcium homeostasis. *The Journal of pediatrics*. 1986;109(2):328-34.
33. Devereux G, Litonjua AA, Turner SW, Craig LC, McNeill G, Martindale S, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. *The American journal of clinical nutrition*. 2007;85(3):853-9.
34. Du X, Zhu K, Trube A, Zhang Q, Ma G, Hu X, et al. School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10-12 years in Beijing. *The British journal of nutrition*. 2004;92(1):159-68.
35. Duhamel JF, Zeghoud F, Sempe M, Boudailliez B, Odievre M, Laurans M, et al. [Prevention of vitamin D deficiency in adolescents and pre-adolescents. An interventional multicenter study on the biological effect of repeated doses of 100,000 IU of vitamin D3]. *Archives de pediatrie : organe officiel de la Societe francaise de pediatrie*. 2000;7(2):148-53.

36. Erkkola M, Kaila M, Nwaru BI, Kronberg-Kippila C, Ahonen S, Nevalainen J, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*. 2009;39(6):875-82.
37. Freishtat RJ, Iqbal SF, Pillai DK, Klein CJ, Ryan LM, Benton AS, et al. High prevalence of vitamin D deficiency among inner-city African American youth with asthma in Washington, DC. *The Journal of pediatrics*. 2010;156(6):948-52.
38. Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN, et al. Maternal vitamin D status during pregnancy and child outcomes. *European journal of clinical nutrition*. 2008;62(1):68-77.
39. Ganmaa D, Giovannucci E, Bloom BR, Fawzi W, Burr W, Batbaatar D, et al. Vitamin D, tuberculin skin test conversion, and latent tuberculosis in Mongolian school-age children: a randomized, double-blind, placebo-controlled feasibility trial. *The American journal of clinical nutrition*. 2012;96(2):391-6.
40. Gentile DA, Patel A, Koehrsen JM, Skoner DP. Reduced Vitamin D Levels in Asthmatic Children. *Journal of Allergy and Clinical Immunology*. 2010;125(2, Supplement 1):AB47.
41. Gergen PJ, Teach SJ, Mitchell HE, Freishtat RF, Calatroni A, Matsui E, et al. Lack of a relation between serum 25-hydroxyvitamin D concentrations and asthma in adolescents. *The American journal of clinical nutrition*. 2013;97(6):1228-34.
42. Grant CC, Stewart AW, Scragg R, Milne T, Rowden J, Ekeroma A, et al. Vitamin D during pregnancy and infancy and infant serum 25-hydroxyvitamin D concentration. *Pediatrics*. 2014;133(1):e143-53.
43. Grant CC, Kaur S, Waymouth E, Mitchell EA, Scragg R, Ekeroma A, et al. Reduced primary care respiratory infection visits following pregnancy and infancy vitamin D supplementation: a randomised controlled trial. *Acta Paediatr*. 2015;104(4):396-404.

44. Green TJ, Skeaff CM, Rockell JE. Milk fortified with the current adequate intake for vitamin D (5 microg) increases serum 25-hydroxyvitamin D compared to control milk but is not sufficient to prevent a seasonal decline in young women. *Asia Pacific journal of clinical nutrition*. 2010;19(2):195-9.
45. Greene DA, Naughton GA. Calcium and vitamin-D supplementation on bone structural properties in peripubertal female identical twins: a randomised controlled trial. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2011;22(2):489-98.
46. Greer FR, Searcy JE, Levin RS, Steichen JJ, Asch PS, Tsang RC. Bone mineral content and serum 25-hydroxyvitamin D concentration in breast-fed infants with and without supplemental vitamin D. *The Journal of pediatrics*. 1981;98(5):696-701.
47. Harvey NC, Javaid K, Bishop N, Kennedy S, Papageorgiou AT, Fraser R, et al. MAVIDOS Maternal Vitamin D Osteoporosis Study: study protocol for a randomized controlled trial. The MAVIDOS Study Group. *Trials*. 2012;13:13.
48. Heimbeck I, Wjst M, Apfelbacher CJ. Low vitamin D serum level is inversely associated with eczema in children and adolescents in Germany. *Allergy*. 2013;68(7):906-10.
49. Hibbs AM, Babineau DC, Wang X, Redline S. Race differences in the association between multivitamin exposure and wheezing in preterm infants. *J Perinatol*. 2015;35(3):192-7.
50. Hollams EM, Hart PH, Holt BJ, Serralha M, Parsons F, de Klerk NH, et al. Vitamin D and atopy and asthma phenotypes in children: a longitudinal cohort study. *Eur Respir J*. 2011;38(6):1320-7.
51. Hughes AM, Lucas RM, Ponsonby AL, Chapman C, Coulthard A, Dear K, et al. The role of latitude, ultraviolet radiation exposure and vitamin D in childhood asthma and hayfever: an Australian multicenter study. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2011;22(3):327-33.

52. Ito Y, Adachi Y, Yoshida K, Akasawa A. No association between serum vitamin D status and the prevalence of allergic diseases in Japanese children. *International archives of allergy and immunology*. 2013;160(2):218-20.
53. Jacobs ZD, Dai H, Feldt M, Dinakar C. Relationship between serum 25-hydroxyvitamin D and IgE: National Health and Nutrition Examination Survey 2-year results. *Journal of Allergy and Clinical Immunology*. 2011;1):AB151.
54. Jensen ME, Mailhot G, Alos N, White JH, Rousseau E, Khamessan A. A vitamin D intervention in preschoolers with viral-induced asthma: A pilot randomised controlled trial (DIVA). *American journal of respiratory and critical care medicine*. 2015; 191(Meeting Abstracts):A3360.
55. Jones AP, Palmer D, Zhang G, Prescott SL. Cord blood 25-hydroxyvitamin D3 and allergic disease during infancy. *Pediatrics*. 2012;130(5):e1128-35.
56. Kemp AS, Ponsonby A-L, Pezic A, Cochrane JA, Dwyer T, Jones G. The influence of sun exposure in childhood and adolescence on atopic disease at adolescence. *Pediatric Allergy & Immunology*. 2013;24(5):493-500.
57. Khadgawat R, Marwaha RK, Garg MK, Ramot R, Oberoi AK, Sreenivas V, et al. Impact of vitamin D fortified milk supplementation on vitamin D status of healthy school children aged 10-14 years. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2013; 24(8):2335-43.
58. Kim MJ, Na B, No SJ, Han HS, Jeong EH, Lee W, et al. Nutritional status of vitamin D and the effect of vitamin D supplementation in Korean breast-fed infants. *Journal of Korean medical science*. 2010; 25(1):83-9.
59. Koistinen A, Turunen R, Vuorinen T, Soderlund-Venermo M, Camargo CA, Jr., Ruuskanen O, et al. Vitamin D, virus etiology, and atopy in first-time wheezing children in Finland. *Pediatric Allergy & Immunology*. 2014;25(8):834-7.

60. Krobtrakulchai W, Praikanahok J, Visitsunthorn N, Vichyanond P, Manonukul K, Pratumvinit B, et al. The effect of vitamin d status on pediatric asthma at a university hospital, Thailand. *Allergy, asthma & immunology research*. 2013;5(5):289-94.
61. Kull I, Bergstrom A, Melen E, Lilja G, van Hage M, Pershagen G, et al. Early-life supplementation of vitamins A and D, in water-soluble form or in peanut oil, and allergic diseases during childhood. *J Allergy Clin Immunol*. 2006;118(6):1299-304.
62. Lewis E, Fernandez C, Nella A, Hopp R, Gallagher JC, Casale TB. Relationship of 25-hydroxyvitamin D and asthma control in children. *Annals of allergy, asthma & immunology*. 2012; 108(4):281-2.
63. Li R, Li M. [The immune regulation of vitamin D in children's allergic disease]. *Zhonghua Er Ke Za Zhi*. 2015;53(3):232-4.
64. Litonjua AA, Lange NE, Carey VJ, Brown S, Laranjo N, Harshfield BJ, et al. The Vitamin D Antenatal Asthma Reduction Trial (VDAART): rationale, design, and methods of a randomized, controlled trial of vitamin D supplementation in pregnancy for the primary prevention of asthma and allergies in children. *Contemp Clin Trials*. 2014;38(1):37-50.
65. Litonjua AA, Carey VJ, Laranjo N, Harshfield BJ, McElrath TF, O'Connor GT, et al. Effect of Prenatal Supplementation With Vitamin D on Asthma or Recurrent Wheezing in Offspring by Age 3 Years: The VDAART Randomized Clinical Trial. *Jama*. 2016;315(4):362-70.
66. Liu X, Wang G, Hong X, Wang D, Tsai HJ, Zhang S, et al. Gene-vitamin D interactions on food sensitization: a prospective birth cohort study. *Allergy*. 2011;66(11):1442-8.
67. Liu X, Arguelles L, Zhou Y, Wang G, Chen Q, Tsai HJ, et al. Longitudinal trajectory of vitamin D status from birth to early childhood in the development of food sensitization. *Pediatric research*. 2013;74(3):321-6.

68. Ma X-L, Zhen Y-F. [Serum levels of 25-(OH)D(3) and total IgE in children with asthma]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2011;13(7):551-3.
69. Madsen KH, Rasmussen LB, Andersen R, Molgaard C, Jakobsen J, Bjerrum PJ, et al. Randomized controlled trial of the effects of vitamin D-fortified milk and bread on serum 25-hydroxyvitamin D concentrations in families in Denmark during winter: The VitmaD study. *American journal of clinical nutrition*. 2013; 98(2):374-82.
70. Magnus MC, Stene LC, Nafstad P, Stigum H, London SJ, Nystad W. Prospective study of maternal mid-pregnancy 25-hydroxyvitamin D level and early childhood respiratory disorders. *Paediatric and perinatal epidemiology*. 2013; 27(6):532-41.
71. Maguire JL, Birken CS, Loeb MB, Mamdani M, Thorpe K, Hoch JS, et al. DO IT Trial: vitamin D Outcomes and Interventions in Toddlers - a TARGet Kids! randomized controlled trial. *BMC pediatrics*. 2014;14:37.
72. Majak P, Olszowiec-Chlebna M, Smejda K, Stelmach I. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. *Journal of allergy and clinical immunology*. 2011; 127(5):1294-6.
73. Marchisio P, Consonni D, Baggi E, Zampiero A, Bianchini S, Terranova L. Vitamin D Supplementation Reduces the Risk of Acute Otitis Media in Otitis-prone Children. *Pediatric infectious disease journal*. 2013; 32(10):1055-60.
74. Marya RK, Rathee S, Lata V, Mudgil S. Effects of vitamin D supplementation in pregnancy. *Gynecologic and obstetric investigation*. 1981; 12(3):155-61.
75. Maslova E, Hansen S, Jensen CB, Thorne-Lyman AL, Strom M, Olsen SF. Vitamin D intake in mid-pregnancy and child allergic disease - a prospective study in 44,825 Danish mother-child pairs. *BMC Pregnancy Childbirth*. 2013;13:199.
76. Maxwell JD, Ang L, Brooke OG, Brown IR. Vitamin D supplements enhance weight gain and nutritional status in pregnant Asians. *British journal of obstetrics and gynaecology*. 1981; 88(10):987-91.

77. Menon J, Maranda L, Nwosu BU. Serum 25-hydroxyvitamin D levels do not correlate with asthma severity in a case-controlled study of children and adolescents. *J Pediatr Endocrinol*. 2012;25(7-8):673-9.
78. Meyer R, De Koker C, Dziubak R, Skrapac A-K, Godwin H, Reeve K, et al. A practical approach to vitamin and mineral supplementation in food allergic children. *Clin Transl Allergy*. 2015;5:11.
79. Miller DR, Turner SW, Spiteri-Cornish D, Scaife AR, Danielian PJ, Devereux GS, et al. Maternal vitamin D and E intakes during early pregnancy are associated with airway epithelial cell responses in neonates. *Clinical & Experimental Allergy*. 2015;45(5):920-7.
80. Miyake Y, Sasaki S, Tanaka K, Hirota Y. Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants. *Eur Respir J*. 2010;35(6):1228-34.
81. Miyake Y, Tanaka K, Okubo H, Sasaki S, Arakawa M. Dairy food, calcium and vitamin D intake and prevalence of allergic disorders in pregnant Japanese women. *Int J Tuberc Lung Dis*. 2012;16(2):255-61.
82. Miyake Y, Tanaka K, Okubo H, Sasaki S, Arakawa M. Maternal consumption of dairy products, calcium, and vitamin D during pregnancy and infantile allergic disorders. *Ann Allergy Asthma Immunol*. 2014;113(1):82-7.
83. Morales E, Romieu I, Guerra S, Ballester F, Rebagliato M, Vioque J, et al. Maternal vitamin D status in pregnancy and risk of lower respiratory tract infections, wheezing, and asthma in offspring. *Epidemiology*. 2012;23(1):64-71.
84. Mouratidou T, Vicente-Rodriguez G, Gracia-Marco L, Huybrechts I, Sioen I, Widhalm K, et al. Associations of dietary calcium, vitamin D, milk intakes, and 25-hydroxyvitamin D with bone mass in Spanish adolescents: the HELENA study. *Journal of clinical densitometry*. 2013; 16(1):110-7.
85. Moyer-Mileur LJ, Xie B, Ball SD, Pratt T. Bone mass and density response to a 12-month trial of calcium and vitamin D supplement in preadolescent girls. *Journal of Musculoskeletal Neuronal Interactions*. 2003; 3(1):63-70.

86. Mullins RJ, Clark S, Katelaris C, Smith V, Solley G, Camargo CA. Season of birth and childhood food allergy in Australia: A role for ultraviolet radiation/vitamin D? *Internal Medicine Journal*. 2010;40:14-5.
87. Mullins RJ, Clark S, Camargo CA, Jr. Regional variation in infant hypoallergenic formula prescriptions in Australia. *Pediatric Allergy & Immunology*. 2010;21(2 Pt 2):e413-20.
88. Mullins RJ, Clark S, Katelaris C, Smith V, Solley G, Camargo CA, Jr. Season of birth and childhood food allergy in Australia. *Pediatric Allergy & Immunology*. 2011;22(6):583-9.
89. Mullins RJ, Clark S, Wiley V, Eyles D, Camargo CA, Jr. Neonatal vitamin D status and childhood peanut allergy: a pilot study. *Ann Allergy Asthma Immunol*. 2012;109(5):324-8.
90. Nissen J, Vogel U, Ravn-Haren G, Andersen EW, Madsen KH, Nexø BA, et al. Common variants in CYP2R1 and GC genes are both determinants of serum 25-hydroxyvitamin D concentrations after UVB irradiation and after consumption of vitamin D₃ -fortified bread and milk during winter in Denmark. *The American journal of clinical nutrition*. 2015; 101(1):218-27.
91. Norizoe C, Akiyama N, Segawa T, Tachimoto H, Mezawa H, Ida H, et al. Increased food allergy and vitamin D: Randomized, double-blind, placebo-controlled trial. *Pediatrics international*. 2014; 56(1):6-12.
92. Nwaru BI, Ahonen S, Kaila M, Erkkola M, Haapala A-M, Kronberg-Kippila C, et al. Maternal diet during pregnancy and allergic sensitization in the offspring by 5 yrs of age: a prospective cohort study. *Pediatric Allergy & Immunology*. 2010;21(1 Pt 1):29-37.
93. O'Connor E, Mølgaard C, Michaelsen KF, Jakobsen J, Cashman KD. Vitamin D-vitamin K interaction: effect of vitamin D supplementation on serum percentage undercarboxylated osteocalcin, a sensitive measure of vitamin K status, in Danish girls. *British journal of nutrition*. 2010; 104(8):1091-5.

94. Oktaria V, Dharmage SC, Burgess JA, Simpson JA, Morrison S, Giles GG, et al. Association between latitude and allergic diseases: a longitudinal study from childhood to middle-age. *Ann Allergy Asthma Immunol.* 2013;110(2):80-5.e1.
95. Oliver EM, Grimshaw KEC, Schoemaker AA, Keil T, McBride D, Sprickelman AB, et al. Dietary habits and supplement use in relation to national pregnancy recommendations: data from the EuroPrevall birth cohort. *Matern Child Health J.* 2014;18(10):2408-25.
96. Ozaydin E, Butun MF, Cakir BC, Kose G. The association between vitamin d status and recurrent wheezing. *Indian journal of pediatrics.* 2013;80(11):907-10.
97. Palmer DJ, Sullivan TR, Skeaff CM, Smithers LG, Makrides M, Team DOAF-u. Higher cord blood 25-hydroxyvitamin D concentrations reduce the risk of early childhood eczema: in children with a family history of allergic disease. *World Allergy Organiza.* 2015;8(1):28.
98. Persson K, Ohlund I, Nordstrom L, Winberg A, Ronmark E, West CE. Vitamin D deficiency at the Arctic Circle - a study in food-allergic adolescents and controls. *Acta Paediatr.* 2013;102(6):644-9.
99. Peters RL, Allen KJ, Dharmage SC, Lodge CJ, Koplin JJ, Ponsonby AL, et al. Differential factors associated with challenge-proven food allergy phenotypes in a population cohort of infants: a latent class analysis. *Clinical & Experimental Allergy.* 2015;45(5):953-63.
100. Pike KC, Inskip HM, Robinson S, Lucas JS, Cooper C, Harvey NC, et al. Maternal late-pregnancy serum 25-hydroxyvitamin D in relation to childhood wheeze and atopic outcomes. *Thorax.* 2012;67(11):950-6.
101. Rajabbik MH, Lotfi T, Alkhaled L, Fares M, El-Hajj Fuleihan G, Mroueh S, et al. Association between low vitamin D levels and the diagnosis of asthma in children: a systematic review of cohort studies. *Allergy Asthma Clin Immunol.* 2014;10(1):31.

102. Roachat MK, Ege MJ, Plabst D, Steinle J, Bitter S, Braun-Fahrlander C, et al. Maternal vitamin D intake during pregnancy increases gene expression of ILT3 and ILT4 in cord blood. *Clinical & Experimental Allergy*. 2010;40(5):786-94.
103. Rosser F, Brehm JM, Forno E, Acosta-Perez E, Kurland K, Canino G, et al. Proximity to a major road, vitamin D insufficiency, and severe asthma exacerbations in Puerto Rican children. *American Journal of Respiratory & Critical Care Medicine*. 2014;190(10):1190-3.
104. Rothers J, Wright AL, Stern DA, Halonen M, Camargo CA, Jr. Cord blood 25-hydroxyvitamin D levels are associated with aeroallergen sensitization in children from Tucson, Arizona. *J Allergy Clin Immunol*. 2011;128(5):1093-9.e1-5.
105. Sackeck JM, Rompay MI, Olson EM, Chomitz VR, Goodman E, Gordon CM, et al. Recruitment and retention of urban schoolchildren into a randomized double-blind vitamin D supplementation trial. *Clinical trials (London, England)*. 2015; 12(1 //) *National Institutes of Health*):45-53.
106. San T, Muluk NB, Cingi C. 1,25(OH)2D3 and specific IgE levels in children with recurrent tonsillitis, and allergic rhinitis. *Int J Pediatr Otorhinolaryngol*. 2013;77(9):1506-11.
107. Sharief S, Jariwala S, Kumar J, Muntner P, Melamed ML. Vitamin D levels and food and environmental allergies in the United States: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol*. 2011;127(5):1195-202.
108. Sidbury R, Sullivan AF, Thadhani RI, Camargo CA. Randomized controlled trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. *British journal of dermatology*. 2008; 159(1):245-7.
109. Stelmach I, Majak P, Jerzynska J, Podlecka D, Stelmach W, Polanska K, et al. Cord serum 25-hydroxyvitamin D correlates with early childhood viral-induced wheezing. *Respir Med*. 2015;109(1):38-43.

110. Stenberg Hammar K, Hedlin G, Konradsen JR, Nordlund B, Kull I, Giske CG, et al. Subnormal levels of vitamin D are associated with acute wheeze in young children. *Acta Paediatr.* 2014;103(8):856-61.
111. Strucinska M, Rowicka G, Riahi A. Profiles of selected nutrients affecting skin condition in children with atopic dermatitis. *Rocz Panstw Zakl Hig.* 2015;66(1):45-53.
112. Sun Q, Yang BL, Feng L, Chen QL, Liu YJ. Prospective study on effect of calcium and vitamin D fortified drinks on bone development in children. [Chinese]. *Journal of Jilin University Medicine Edition.* 2011; 37(5):959-64.
113. Tolppanen AM, Williams D, Henderson J, Lawlor DA. Serum 25-hydroxy-vitamin D and ionised calcium in relation to lung function and allergen skin tests. *European journal of clinical nutrition.* 2011;65(4):493-500.
114. Tolppanen A-M, Sayers A, Granell R, Fraser WD, Henderson J, Lawlor DA. Prospective association of 25-hydroxyvitamin d3 and d2 with childhood lung function, asthma, wheezing, and flexural dermatitis. *Epidemiology.* 2013;24(2):310-9.
115. Trilok-Kumar G, Kaur M, Rehman AM, Arora H, Rajput MM, Chugh R, et al. Effects of vitamin D supplementation in infancy on growth, bone parameters, body composition and gross motor development at age 3-6 years: Follow-up of a randomized controlled trial. *International journal of epidemiology.* 2015; 44(3):894-905.
116. Tse SM, Kelly HW, Litonjua AA, Natta ML, Weiss ST, Tantisira KG. Corticosteroid use and bone mineral accretion in children with asthma: effect modification by vitamin D. *The Journal of allergy and clinical immunology.* 2012; 130(1):53-60.e4.
117. Tu H, Flanders WD, Ahearn TU, Daniel CR, Gonzalez-Feliciano AG, Long Q, et al. Effects of calcium and vitamin D3 on transforming growth factors in rectal mucosa of sporadic colorectal adenoma patients: a randomized controlled trial. *Molecular carcinogenesis.* 2015; 54(4):270-80.

118. Uysalol M, Mutlu LC, Saracoglu GV, Karasu E, Guzel S, Kayaoglu S, et al. Childhood asthma and vitamin D deficiency in Turkey: is there cause and effect relationship between them? *Ital.* 2013;39:78.
119. van Oeffelen AAM, Bekkers MBM, Smit HA, Kerkhof M, Koppelman GH, Haveman-Nies A, et al. Serum micronutrient concentrations and childhood asthma: the PIAMA birth cohort study. *Pediatric Allergy & Immunology.* 2011;22(8):784-93.
120. Venkataraman PS, Luhar H, Neylan MJ. Bone mineral metabolism in full-term infants fed human milk, cow milk-based, and soy-based formulas. *American journal of diseases of children (1960).* 1992; 146(11):1302-5.
121. Visness CM, Sandel MT, O'Connor G, Gern JE, Jaffee KF, Wood RA, et al. Cord blood vitamin D concentrations are unrelated to atopy and wheeze in 2 diverse birth cohort studies. *J Allergy Clin Immunol.* 2015; 136(4):1108-10.e2.
122. Wagner CL, Hulse TC, Fanning D, Ebeling M, Hollis BW. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. *Breastfeeding medicine.* 2006; 1(2):59-70.
123. Wagner CL, McNeil R, Hamilton SA, Winkler J, Rodriguez Cook C, Warner G, et al. A randomized trial of vitamin D supplementation in 2 community health center networks in South Carolina. *American journal of obstetrics and gynecology.* 2013; 208(2):137.e1-13.
124. Wang SS, Hon KL, Kong AP-s, Pong HN-h, Wong GW-k, Leung TF. Vitamin D deficiency is associated with diagnosis and severity of childhood atopic dermatitis. *Pediatric Allergy & Immunology.* 2014;25(1):30-5.
125. Weisse K, Winkler S, Hirche F, Herberth G, Hinz D, Bauer M, et al. Maternal and newborn vitamin D status and its impact on food allergy development in the German LINA cohort study. *Allergy.* 2013;68(2):220-8.
126. Willers SM, Devereux G, Craig LCA, McNeill G, Wijga AH, Abou El-Magd W, et al. Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. *Thorax.* 2007;62(9):773-9.

127. Wills AK, Shaheen SO, Granell R, Henderson AJ, Fraser WD, Lawlor DA. Maternal 25-hydroxyvitamin D and its association with childhood atopic outcomes and lung function. *Clinical & Experimental Allergy*. 2013;43(10):1180-8.
128. Wjst M, Hypponen E. Vitamin D serum levels and allergic rhinitis. *Allergy*. 2007;62(9):1085-6.
129. Wu AC, Tantisira K, Li L, Fuhlbrigge AL, Weiss ST, Litonjua A. Effect of vitamin D and inhaled corticosteroid treatment on lung function in children. *American journal of respiratory and critical care medicine*. 2012; 186(6):508-13.
130. Yadav M, Mittal K. Effect of vitamin D supplementation on moderate to severe bronchial asthma. *Indian journal of pediatrics*. 2014; 81(7):650-4.
131. Yao T-C, Tu Y-L, Chang S-W, Tsai H-J, Gu P-W, Ning H-C, et al. Suboptimal vitamin D status in a population-based study of Asian children: prevalence and relation to allergic diseases and atopy. *PLoS ONE [Electronic Resource]*. 2014;9(6):e99105.
132. Young MW. The effectiveness of weekly iron and vitamin supplementation of Malawian preschool children [2]. *South African medical journal*. 2001; 91(1):49-50.
133. Zhang Q, Ma GS, Greenfield H, Du XQ, Zhu K, Fraser DR. Effects of fortified milk consumption on regional bone mineral accrual in Chinese girls. *Asia Pacific journal of clinical nutrition*. 2003; 12 Suppl:S46.
134. Zhang ZQ, Ma XM, Huang ZW, Yang XG, Chen YM, Su YX. Effects of milk salt supplementation on bone mineral gain in pubertal Chinese adolescents: A 2-year randomized, double-blind, controlled, dose-response trial. *Bone*. 2014; 65:69-76.
135. Zhong H, Zhou X-J, Hong J-G. [1,25-(OH)₂D₃ inhibits lipopolysaccharide-induced expression of interleukin-13 and interleukin-17 in cord blood CD4⁺T cells]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2013;15(9):763-6.

136. Zhu K, Du X, Cowell CT, Greenfield H, Blades B, Dobbins TA, et al. Effects of school milk intervention on cortical bone accretion and indicators relevant to bone metabolism in Chinese girls aged 10-12 y in Beijing. *American journal of clinical nutrition*. 2005; 81(5):1168-75.
137. Zhu K, Greenfield H, Du X, Zhang Q, Fraser DR. Effects of milk supplementation on cortical bone gain in Chinese girls aged 10-12 years. *Asia Pacific journal of clinical nutrition*. 2003; 12 Suppl:S47.
138. Zhu K, Greenfield H, Du X, Zhang Q, Ma G, Hu X, et al. Effects of two years' milk supplementation on size-corrected bone mineral density of Chinese girls. *Asia Pacific journal of clinical nutrition*. 2008; 17 Suppl 1:147-50.
139. Zittermann A, Dembinski J, Stehle P. Low vitamin D status is associated with low cord blood levels of the immunosuppressive cytokine interleukin-10. *Pediatric Allergy & Immunology*. 2004;15(3):242-6.
140. Zoratti EM, Wegienka G. Vitamin D concentration in newborn cord blood is correlated with maternal intake of supplemental vitamin D, and lower levels are associated with increased risk of the infant developing eczema. *Evid Based Nurs*. 2013;16(4):105-6.
141. Zosky GR, Hart PH, Whitehouse AJO, Kusel MM, Ang W, Foong RE, et al. Vitamin D deficiency at 16 to 20 weeks' gestation is associated with impaired lung function and asthma at 6 years of age. *Ann Am Thorac Soc*. 2014;11(4):571-7.

Table S4. Summary of Risk of Bias in *non-randomized studies*.

Allen 2013 (27)

Type of study: Case-control

Participants: Pregnancy women and infants

Experimental intervention: Vitamin D supplementation

Control intervention: No Vitamin D supplementation

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		<i>Bias due to confounding</i>	<i>Bias in selection of participants into the study</i>	<i>Bias in measurement of interventions</i>	<i>Bias due to departures from intended interventions</i>	<i>Bias due to missing data</i>	<i>Bias in measurement of outcomes</i>	<i>Bias in selection of the reported result</i>	
Food allergy	Benefit	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate	MODERATE

Anderson 2015 (26)

Type of study: Cohort

Participants: Pregnancy women and infants

Experimental intervention: Vitamin D supplementation

Control intervention: No Vitamin D supplementation

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		<i>Bias due to confounding</i>	<i>Bias in selection of participants into the study</i>	<i>Bias in measurement of interventions</i>	<i>Bias due to departures from intended interventions</i>	<i>Bias due to missing data</i>	<i>Bias in measurement of outcomes</i>	<i>Bias in selection of the reported result</i>	
Asthma/wheezing	Benefit	Low	Low	Moderate	Moderate	Low	Moderate	Moderate	MODERATE

Bener 2012 (24)

Type of study: Case-control

Participants: Breastfeeding women

Experimental intervention: Vitamin D supplementation

Control intervention: No Vitamin D supplementation

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		<i>Bias due to confounding</i>	<i>Bias in selection of participants into the study</i>	<i>Bias in measurement of interventions</i>	<i>Bias due to departures from intended interventions</i>	<i>Bias due to missing data</i>	<i>Bias in measurement of outcomes</i>	<i>Bias in selection of the reported result</i>	
Asthma	Benefit	Moderate	Serious ¹	Moderate	Serious ²	Low	Moderate	Moderate	MODERATE

1. Controls were sampled from a population that is unlikely to be representative of the population that gave rise to the cases; 2. Switches in treatment, co-interventions, or problems with implementation fidelity are apparent and are not adjusted for in the analyses.

Hypponen 2014 (35)

Type of study: Case-control

Participants: Infants

Experimental intervention: Vitamin D supplementation

Control intervention: Irregular or No Vitamin D supplementation

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		<i>Bias due to confounding</i>	<i>Bias in selection of participants into the study</i>	<i>Bias in measurement of interventions</i>	<i>Bias due to departures from intended interventions</i>	<i>Bias due to missing data</i>	<i>Bias in measurement of outcomes</i>	<i>Bias in selection of the reported result</i>	
Asthma	Benefit	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate	MODERATE
Allergic rhinitis	Benefit	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate	MODERATE

EVIDENCE PROFILE: PREGNANCY WOMEN

Date: January 19, 2015; updated January 30 2016

Setting: General population

Bibliography: Allen 2013 (1), Anderson 2015 (2), Brooke 1980 (3), Goldring 2013 (4) , Hossain 2014 (5), Mallet 1986 (6), Roth 2013 (7), Sablok (8), Yu 2009 (9)

Quality assessment							N ₂ of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	No vitamin D supplementation	Relative (95% CI)	Absolute (95% CI)		
Eczema (follow up: 3 years)												
1	randomised trials	serious ¹	not serious	not serious ²	very serious ³	none	30/102 (29.4%)	15/49 (30.6%)	RR 0.96 (0.57 to 1.61)	12 fewer per 1000 (from 132 fewer to 187 more)	VERY LOW	CRITICAL
								1.0% ⁴		0 fewer per 1000 (from 4 fewer to 6 more)		
Allergic rhinitis (follow up: 3 years)												
1	randomised trials	serious ¹	not serious	not serious ²	very serious ⁵	none	11/101 (10.9%)	7/49 (14.3%)	RR 0.76 (0.31 to 1.85)	34 fewer per 1000 (from 99 fewer to 121 more)	VERY LOW	CRITICAL
								14.6% ⁶		35 fewer per 1000 (from 101 fewer to 124 more)		
Asthma/wheezing (follow up: 3 years)												
1	randomised trials	serious ¹	not serious	not serious ²	very serious ⁷	none	17/108 (15.7%)	7/50 (14.0%)	RR 1.12 (0.50 to 2.54)	17 more per 1000 (from 70 fewer to 216 more)	VERY LOW	CRITICAL
								9.4% ⁸		11 more per 1000 (from 47 fewer to 145 more)		
Asthma/wheezing ⁹												
1	observational studies	not serious	not serious	not serious	serious ¹⁰	none	493/2478 (19.9%)	9.4% ⁸	OR 0.65 (0.46 to 0.92) ¹¹	31 fewer per 1000 (from 7 fewer to 48 fewer)	VERY LOW	CRITICAL
Food allergy (follow up: 3 years)												

Quality assessment							N: of patients		Effect		Quality	Importance
N: of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	No vitamin D supplementation	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious ¹	not serious	not serious ²	very serious ¹²	none	12/102 (11.8%)	3/49 (6.1%)	RR 1.92 (0.57 to 6.50)	56 more per 1000 (from 26 fewer to 337 more)	VERY LOW	CRITICAL
								3.3% ¹³		30 more per 1000 (from 14 fewer to 182 more)		
Food allergy												
1	observational studies	not serious	not serious	not serious	serious ¹⁴	none	27 cases 213 controls		OR 1.50 (0.78 to 2.88) ¹⁵	-	VERY LOW	CRITICAL
							-	3.3% ¹³		16 more per 1000 (from 7 fewer to 56 more)		
Rickets												
1	randomised trials	not serious	not serious	not serious	very serious ¹⁶	none	0/59 (0.0%)	0/67 (0.0%)	not estimable	-	LOW	CRITICAL
Nutritional status: birth weight (gr)												
6	randomised trials	not serious	not serious	not serious	serious ¹⁷	none	455	366	-	MD 52.78 more (64.34 fewer to 169.9 more)	MODERATE	CRITICAL
Any adverse events (children)												
2	randomised trials	not serious	not serious	not serious	very serious ¹⁶	none	0/117 (0.0%)	0/117 (0.0%)	not estimable	0 fewer per 1000 (from 20 more to 20 fewer)	LOW	CRITICAL
Any adverse events (mother) (assessed with: Preeclampsia)												
3	randomised trials	serious ¹⁸	not serious	not serious	very serious ¹⁹	none	36/254 (14.2%)	31/266 (11.7%)	RR 1.46 (0.31 to 6.78)	54 more per 1000 (from 80 fewer to 674 more)	VERY LOW	CRITICAL
Serious adverse events (children)												
3	randomised trials	not serious	not serious	not serious	very serious ²⁰	none	8/213 (3.8%)	10/213 (4.7%)	RR 0.79 (0.33 to 1.90)	10 fewer per 1000 (from 31 fewer to 42 more)	LOW	CRITICAL
Serious adverse events (mother)												
2	randomised trials	not serious	not serious	not serious	very serious ²¹	none	12/158 (7.6%)	8/163 (4.9%)	RR 1.55 (0.65 to 3.69)	27 more per 1000 (from 17 fewer to 132 more)	LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio; MD: Mean difference

1. Serious risk of bias. One study that carried large weight for the overall effect estimate rated as high risk of bias due to lack of concealment of allocation, and lack of blinding of participants and caregivers
2. Indirectness. One study assessed the effect of the intervention in 3-year-old children, which was measured in the development of eczema, asthma, allergic rhinitis, or food allergy. The effect of the intervention could be different in children over 3 years old or adults
3. Very serious imprecision. Wide confidence interval with only 45 events in total
4. Difference in anticipated absolute effect was calculated based on the range of prevalence of eczema in International Study for Asthma and Allergy in Childhood (ISAAC) Phase Three (1%) (10)
5. Very serious imprecision. Wide confidence interval with only 18 events in total
6. Difference in anticipated absolute effect was calculated based on the total global prevalence of rhinoconjunctivitis symptoms for the 13- to 14-year old children according with Phase Three ISAAC (14.6%) (11)
7. Very serious imprecision. Wide confidence interval with only 24 events in total
8. Difference in anticipated absolute effect was calculated based on the total global prevalence of asthma symptoms in the 6-7 year old children according with Phase Three ISAAC in 9.4% (12)
9. Wheezing was measured using the ISAAC questionnaire
10. Very serious imprecision. Wide confidence interval with only 128 events in total
11. Odds ratio adjusted by age, sex, body mass index (BMI), outdoor play, daycare attendance, birth weight and breastfeeding duration
12. Very serious imprecision. Wide confidence interval with only 15 events in total
13. Difference in anticipated absolute effect was calculated based on the prevalence of food allergy in the population as a result of food challenge tests to any food according with metanalysis of Rona et al. 2007 (13)
14. Very serious imprecision. Wide confidence interval with only 240 events in total
15. Odds ratio was adjusted by infant formula, history of egg consumption, infant history of eczema, age [in months] at Oral Food Challenge, infant's gender, duration of breastfeeding, infant consumption of fish, number of siblings, socioeconomic status, pet ownership, maternal use of vitamin D supplements during pregnancy, maternal smoking during pregnancy, family history of allergy, filaggrin null mutations, season of birth, and UVR at the month of birth
16. Very serious imprecision with no events in a small study
17. Very serious imprecision. Wide confidence interval crosses 0 from -64.34 to 169.9 g/s
18. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to selective outcome reporting in 4 out of 7 studies.
19. Very serious imprecision. Wide confidence interval with only 67 events in total
20. Very serious imprecision. Wide confidence interval with only 18 events in total
21. Very serious imprecision. Wide confidence interval with only 20 events in total

REFERENCES

1. Allen KJ, Koplin JJ, Ponsonby AL, Gurrin LC, Wake M, Vuillermin P, et al. Vitamin D insufficiency is associated with challenge-proven food allergy in infants. *The Journal of allergy and clinical immunology*. 2013;131(4):1109-16, 16 e1-6.
2. Anderson LN, Chen Y, Omand JA, Birken CS, Parkin PC, To T, et al. Vitamin D exposure during pregnancy, but not early childhood, is associated with risk of childhood wheezing. *Journal of developmental origins of health and disease*. 2015;6(4):308-16.
3. Brooke OG, Brown IR, Bone CD, Carter ND, Cleeve HJ, Maxwell JD, et al. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. *British medical journal*. 1980;280(6216):751-4.
4. Goldring ST, Griffiths CJ, Martineau AR, Robinson S, Yu C, Poulton S, et al. Prenatal vitamin d supplementation and child respiratory health: a randomised controlled trial. *PLoS one*. 2013;8(6):e66627.
5. Hossain N, Kanani FH, Ramzan S, Kausar R, Ayaz S, Khanani R, et al. Obstetric and neonatal outcomes of maternal vitamin D supplementation: results of an open-label, randomized controlled trial of antenatal vitamin D supplementation in Pakistani women. *The Journal of clinical endocrinology and metabolism*. 2014;99(7):2448-55.
6. Mallet E, Gugi B, Brunelle P, Henocq A, Basuyau JP, Lemeur H. Vitamin D supplementation in pregnancy: a controlled trial of two methods. *Obstetrics and gynecology*. 1986;68(3):300-4.

7. Roth DE, Al Mahmud A, Raqib R, Akhtar E, Perumal N, Pezzack B, et al. Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D3 supplementation in Bangladesh: the AVIDD trial. *Nutrition journal*. 2013;12:47.
8. Sablok A, Thariani K, Batra A, Bharti R, Aggarwal AR, Kabi BC, et al. Supplementation of Vitamin D in pregnancy and its correlation with feto-maternal outcome. *Clinical endocrinology*. 2015; 83(4):536-41.
9. Yu CK, Sykes L, Sethi M, Teoh TG, Robinson S. Vitamin D deficiency and supplementation during pregnancy. *Clin Endocrinol (Oxf)*. 2009;70(5):685-90.
10. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, Group IPTS. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *The Journal of allergy and clinical immunology*. 2009;124(6):1251-8 e23.
11. Ait-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J, et al. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy*. 2009;64(1):123-48.
12. Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2009;64(6):476-83.
13. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. *The Journal of allergy and clinical immunology*. 2007;120(3):638-46.

EVIDENCE PROFILE: *BREASTFEEDING WOMEN*

Authors: Juan José Yepes-Nuñez, Jan Brozek, Carlos Cuello-García, Yuan Zhang, Gian Paolo Morgano, Holger Schünemann

Date: January 19, 2015; updated January 30 2016

Question: Vitamin D versus no vitamin D supplementation in **breastfeeding women** for the prevention of allergy in their children and other important outcomes

Setting: General population

Bibliography: Bener 2012 (1), Rothberg 1982 (2)

Quality assessment							N of patients		Effect		Quality	Importance
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	No vitamin D supplementation	Relative (95% CI)	Absolute (95% CI)		
Eczema												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Allergic rhinitis												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Asthma/wheezing (follow-up: up to 16 years)												
1	observational studies	serious ¹	not serious	not serious ²	serious ³	none	483 cases 483 controls		OR 1.09 (0.84 to 1.40)	-	VERY LOW	CRITICAL
							-	9.4% ⁴		8 more per 1000 (from 14 fewer to 33 more)		
Food allergy												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Rickets (follow up: 6 weeks)												

Quality assessment							N of patients		Effect		Quality	Importance
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	No vitamin D supplementation	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious ⁵	not serious	not serious	very serious ₆	none	0/18 (0.0%)	0/10 (0.0%)	not estimable	0 fewer per 1000 (from 140 more to 140 fewer)	VERY LOW	CRITICAL
Any allergy												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Nutritional status												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Adverse events												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Severe adverse events												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL

CI: Confidence interval; OR: Odds ratio

1. Serious risk of bias. Controls were sampled from a population that is unlikely to be representative of the population from which cases were selected, and analysis was not adjusted for confounding factors
2. Indirectness. Over 80% of the children in the study had mild to severe vitamin D deficiency
3. Serious imprecision. Wide confidence interval with 483 events in total
4. Difference in anticipated absolute effect was calculated based on the total global prevalence of asthma symptoms in the 6-7 year old children according with Phase Three ISAAC in 9.4% (3)
5. Serious risk of bias. One study that carried large weight for the overall effect estimate rated as unclear risk of bias due to insufficient information about random sequence generation, allocation concealment, and incomplete outcome data
6. Very serious imprecision with no events in a small study

REFERENCE

1. Bener A, Ehlayel MS, Tulic MK, Hamid Q. Vitamin D deficiency as a strong predictor of asthma in children. International archives of allergy and immunology. 2012;157(2):168-75.
2. Rothberg AD, Pettifor JM, Cohen DF, Sonnendecker EW, Ross FP. Maternal-infant vitamin D relationships during breast-feeding. The Journal of pediatrics. 1982;101(4):500-3.

3. Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2009;64(6):476-83.

EVIDENCE PROFILE: *INFANTS*

Authors: Juan José Yepes-Nuñez, Jan Brozek, Carlos Cuello-García, Yuan Zhang, Gian Paolo Morgano, Holger Schünemann

Date: January 19, 2015; updated January 30 2016

Question: Vitamin D versus no vitamin D supplementation in **infants** for the prevention of allergy and other important outcomes

Setting: General population

Bibliography: Allen 2013 (1), Alonso 2011 (2), Anderson 2015 (3), Chan 1982 (4), Greer 1982 (5), Hypponen 2004 (6), Madar (7), Ponnappakkam (8):

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	no intervention/placebo	Relative (95% CI)	Absolute (95% CI)		
Eczema												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Allergic rhinitis (follow up: 31 years) ¹												
1	observational studies	serious ²	not serious	not serious	serious ³	none	1974/6748 (29.3%)	3/20 (15.0%)	RR 1.95 (0.69 to 5.54)	143 more per 1000 (from 47 fewer to 681 more)	VERY LOW	CRITICAL
								14.6% ⁴		139 more per 1000 (from 45 fewer to 663 more)		
Asthma/wheezing (follow up: 31 years) ¹												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	no intervention/placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious ²	not serious	not serious	serious ⁵	none	470/6748 (7.0%)	0/20 (0.0%)	RR 3.07 (0.19 to 50.88)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
								9.4% ⁶		195 more per 1000 (from 76 fewer to 1000 more)		
Asthma/wheezing (follow up: 72 months) ⁷												
1	observational studies	not serious	not serious	not serious	serious ⁸	none	493/2478 (19.9%)	9.4%	OR 1.00 (0.81 to 1.23)	0 fewer per 1000 (from 16 fewer to 19 more)	VERY LOW	CRITICAL
Food allergy (follow up: 1 years)												
1	observational studies	serious ⁹	not serious	serious ¹⁰	serious ¹¹	none	21/274 (7.7%)	30/207 (14.5%)	OR 0.49 (0.27 to 0.88)	68 fewer per 1000 (from 15 fewer to 101 fewer)	VERY LOW	CRITICAL
								3.3% ¹²		17 fewer per 1000 (from 4 fewer to 24 fewer)		
Rickets (follow up: range 2 months to 12 months)												
4	randomised trials	serious ¹³	not serious	serious ¹⁴	serious ¹⁵	none	0/86 (0.0%)	0/91 (0.0%)	not estimable	0 fewer per 1000 (from 40 more to 40 fewer)	VERY LOW	CRITICAL
Nutritional status (body weight in grams) (follow up: range 6 months to 12 months)												
1	randomised trials	serious ¹⁶	not serious	not serious	serious ¹⁷	none	36	44	-	0 (0 to 0)	LOW	CRITICAL
Any adverse events												
2	randomised trials	serious ¹⁸	not serious	not serious	serious ¹⁹	none	4/58 (6.9%)	4/51 (7.8%)	RR 0.85 (0.23 to 3.14)	12 fewer per 1000 (from 60 fewer to 168 more)	LOW	CRITICAL
Serious adverse events												
1	randomised trials	serious ²⁰	not serious	not serious	serious ²¹	none	0/17 (0.0%)	1/8 (12.5%)	RR 0.17 (0.01 to 3.70)	104 fewer per 1000 (from 124 fewer to 338 more)	LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio

1. Information corresponds to case control study, Hypponen 2004 (6)

2. Serious risk of bias. Criteria for diagnosis of asthma and allergic rhinitis were not provided, and results were not adjusted for confounding factors
3. Serious imprecision. Wide confidence interval with only 3 events in total
4. Difference in anticipated absolute effect was calculated based on the total global prevalence of rhinoconjunctivitis symptoms for the 13- to 14-year old children according with the International Study for Asthma and Allergy in Childhood (ISAAC) Phase Three (14.6%) (9)
5. Serious imprecision. Wide confidence interval with only 470 events in total and not no events in a small control group
6. Difference in anticipated absolute effect was calculated based on the total global prevalence of asthma symptoms in the 6-7 year old children according with Phase Three ISAAC (9.4%) (10)
7. Information corresponds to cohort study, Anderson 2015 (3)
8. Serious imprecision. Wide confidence interval
9. Serious risk of bias. Results were not adjusted for confounding factors
10. Serious indirectness. The outcome was measured after 1 year of life, which is likely a short frame time to reliably measure development of food allergy
11. Serious imprecision with only 51 events in total
12. Difference in anticipated absolute effect was calculated based on the prevalence of food allergy in the population as a result of food challenge tests to any food according with meta-analysis of Rona et al. 2007 (3.3%) (11)
13. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 2 out of 4 studies and incomplete outcome data in 2 out of 4 studies
14. Serious indirectness. Patients included in the study were follow-up from 2 to 12 months which is not long enough for assessing development of rickets
15. Serious imprecision. Wide confidence interval with no events among 177 children
16. Serious risk of bias. One study that carried large weight for the overall effect estimate rated as high risk of bias due to lack of random sequence generation
17. Serious imprecision. Mean weights were not significant different between patients who received vitamin D supplementation versus no vitamin D supplementation. Mean values was displayed in a graphic
18. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to incomplete outcome data in 2 out of 3 studies
19. Serious imprecision. Wide confidence interval with only 8 events in total
20. Serious risk of bias. One study that carried large weight for the overall effect estimate rated as high risk of bias due to incomplete outcome data
21. Serious imprecision. Wide confidence interval with only 1 events in total

REFERENCES

1. Allen KJ, Koplin JJ, Ponsonby AL, Gurrin LC, Wake M, Vuillermin P, et al. Vitamin D insufficiency is associated with challenge-proven food allergy in infants. *The Journal of allergy and clinical immunology*. 2013;131(4):1109-16, 16 e1-6.
2. Alonso A, Rodriguez J, Carvajal I, Prieto MA, Rodriguez RM, Perez AM, et al. Prophylactic vitamin D in healthy infants: assessing the need. *Metabolism: clinical and experimental*. 2011;60(12):1719-25.
3. Anderson LN, Chen Y, Omand JA, Birken CS, Parkin PC, To T, et al. Vitamin D exposure during pregnancy, but not early childhood, is associated with risk of childhood wheezing. *Journal of developmental origins of health and disease*. 2015;6(4):308-16.
4. Chan GM, Roberts CC, Folland D, Jackson R. Growth and bone mineralization of normal breast-fed infants and the effects of lactation on maternal bone mineral status. *The American journal of clinical nutrition*. 1982;36(3):438-43.
5. Greer FR, Searcy JE, Levin RS, Steichen JJ, Steichen-Asche PS, Tsang RC. Bone mineral content and serum 25-hydroxyvitamin D concentrations in breast-fed infants with and without supplemental vitamin D: one-year follow-up. *The Journal of pediatrics*. 1982;100(6):919-22.
6. Hypponen E, Sovio U, Wjst M, Patel S, Pekkanen J, Hartikainen AL, et al. Infant vitamin d supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. *Annals of the New York Academy of Sciences*. 2004;1037:84-95.
7. Madar AA, Klepp KI, Meyer HE. Effect of free vitamin D(2) drops on serum 25-hydroxyvitamin D in infants with immigrant origin: a cluster randomized controlled trial. *European journal of clinical nutrition*. 2009;63(4):478-84.
8. Ponnappakkam T, Bradford E, Gensure R. A treatment trial of vitamin D supplementation in breast-fed infants: universal supplementation is not necessary for rickets prevention in Southern Louisiana. *Clinical pediatrics*. 2010;49(11):1053-60.
9. Ait-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J, et al. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy*. 2009;64(1):123-48.

10. Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2009;64(6):476-83.
11. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. *The Journal of allergy and clinical immunology*. 2007;120(3):638-46.

EVIDENCE PROFILE: CHILDREN

Authors: Juan José Yepes-Nuñez, Jan Brozek, Carlos Cuello-García, Yuan Zhang, Gian Paolo Morgano, Holger Schünemann

Date: January 19, 2015; updated January 30 2016

Question: Vitamin D versus no vitamin D supplementation in **children** for the prevention of allergy and other important outcomes

Setting: General population

Bibliography: Abrams 2013 (1), Guillemant 2001 (2), Khadilkar 2010 (3), Lewis 2013 (4), Maalouf 2008 (5), Mølgaard 2010 (6), Rajakumar 2015 (7), Rich Edwards 2011 (8), Urashima 2010 (9), Viikainen 2006 (10), Ward 2010 (11)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	no intervention/placebo	Relative (95% CI)	Absolute (95% CI)		
Eczema												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Allergic rhinitis												

Quality assessment							N _o of patients		Effect		Quality	Importance
N _o of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	no intervention/placebo	Relative (95% CI)	Absolute (95% CI)		
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Asthma/wheezing												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Food allergy												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Rickets												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Nutritional status												
3	randomised trials	serious ¹	not serious	not serious	serious ²	none	320	175	-	MD 0.87 kg more (0.1 more to 1.64 more)	LOW	CRITICAL
Any adverse events												
8	randomised trials	not serious	not serious	not serious	serious ³	none	8/1285 (0.6%)	5/610 (0.8%)	RR 0.78 (0.26 to 2.32)	2 fewer per 1000 (from 6 fewer to 11 more)	MODERATE	CRITICAL
Serious adverse events												
1	randomised trials	serious ⁴	not serious	not serious	serious ⁵	none	1/46 (2.2%)	1/34 (2.9%)	RR 0.74 (0.05 to 11.40)	8 fewer per 1000 (from 28 fewer to 306 more)	LOW	CRITICAL

CI: Confidence interval; MD: Mean difference; RR: Risk ratio; OR: Odds ratio

1. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as unclear risk of bias due to insufficient information about random sequence generation, allocation concealment, blinding of outcome assessment, and incomplete outcome data in all studies
2. Serious imprecision. Wide confidence interval including only 495 patients in total
3. Serious imprecision. Wide confidence interval with only 13 events in total
4. Serious risk of bias. One study that carried large weight for the overall effect estimate rated as unclear risk of bias due to insufficient information about allocation concealment, and blinding of outcome assessment
5. Serious imprecision. Wide confidence interval with only 2 events in total

REFERENCES

1. Abrams SA, Hawthorne KM, Chen Z. Supplementation with 1000 IU vitamin D/d leads to parathyroid hormone suppression, but not increased fractional calcium absorption, in 4-8-y-old children: a double-blind randomized controlled trial. *The American journal of clinical nutrition*. 2013;97(1):217-23.
2. Guillemant J, Le HT, Maria A, Allemandou A, Peres G, Guillemant S. Wintertime vitamin D deficiency in male adolescents: effect on parathyroid function and response to vitamin D3 supplements. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2001;12(10):875-9.
3. Khadilkar AV, Sayyad MG, Sanwalka NJ, Bhandari DR, Naik S, Khadilkar VV, et al. Vitamin D supplementation and bone mass accrual in underprivileged adolescent Indian girls. *Asia Pacific journal of clinical nutrition*. 2010;19(4):465-72.
4. Lewis RD, Laing EM, Hill Gallant KM, Hall DB, McCabe GP, Hausman DB, et al. A randomized trial of vitamin D(3) supplementation in children: dose-response effects on vitamin D metabolites and calcium absorption. *The Journal of clinical endocrinology and metabolism*. 2013;98(12):4816-25.
5. Maalouf J, Nabulsi M, Vieth R, Kimball S, El-Rassi R, Mahfoud Z, et al. Short- and long-term safety of weekly high-dose vitamin D3 supplementation in school children. *The Journal of clinical endocrinology and metabolism*. 2008;93(7):2693-701.
6. Molgaard C, Larnkjaer A, Cashman KD, Lamberg-Allardt C, Jakobsen J, Michaelsen KF. Does vitamin D supplementation of healthy Danish Caucasian girls affect bone turnover and bone mineralization? *Bone*. 2010;46(2):432-9.
7. Rajakumar K, Moore CG, Yabes J, Olabopo F, Haralam MA, Comer D, et al. Effect of Vitamin D3 Supplementation in Black and in White Children: A Randomized, Placebo-Controlled Trial. *The Journal of clinical endocrinology and metabolism*. 2015;100(8):3183-92.
8. Rich-Edwards JW, Ganmaa D, Kleinman K, Sumberzul N, Holick MF, Lkhagvasuren T, et al. Randomized trial of fortified milk and supplements to raise 25-hydroxyvitamin D concentrations in schoolchildren in Mongolia. *The American journal of clinical nutrition*. 2011;94(2):578-84.
9. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *The American journal of clinical nutrition*. 2010;91(5):1255-60.
10. Viljakainen HT, Natri AM, Karkkainen M, Huttunen MM, Palssa A, Jakobsen J, et al. A positive dose-response effect of vitamin D supplementation on site-specific bone mineral augmentation in adolescent girls: a double-blinded randomized placebo-controlled 1-year intervention. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2006;21(6):836-44.
11. Ward KA, Das G, Roberts SA, Berry JL, Adams JE, Rawer R, et al. A randomized, controlled trial of vitamin D supplementation upon musculoskeletal health in postmenarchal females. *The Journal of clinical endocrinology and metabolism*. 2010;95(10):4643-51.

Table S1. Search strategies

Interface	Ovid	
Database	Medline	
Date of searching	January 30, 2016	
Study Types	Randomized control trials and observational studies [†]	
Limits	No limits	
Database strategy		
1	exp Vitamin D/	46990
2	hydroxyvitamin D.mp.	9536
3	1,25-dihydroxycholecalciferol.mp.	1125
4	24,25-dihydroxycholecalciferol.mp.	155
5	1,25-dihydroxyvitamin D3.mp.	4713
6	Vitamin D.tw.	43639
7	1 or 2 or 3 or 4 or 5 or 6	65198
8	exp Child/	1637039
9	exp Infant/	991473
10	Childhood.mp.	194126
11	Infant*.mp.	1083596
12	Infancy.tw.	40952
13	Baby.tw.	29822
14	Baby's.tw.	1767
15	Babies.tw.	30029
16	Neonat*.mp.	232911
17	Child*.mp.	2014319
18	Schoolchild*.tw.	11251
19	Schoolage*.tw.	60
20	School age*.tw.	15763
21	Kids.tw.	4276
22	Kid.tw.	1348
23	Toddler*.tw.	6943
24	exp Pediatrics/	48238
25	Pediatric*.mp.	243725
26	Paediatric*.mp.	45757
27	exp Schools/	93035
28	Kindergar*.tw.	4754
29	Primary school*.mp.	8699
30	exp Pregnancy/	778451
31	Pregnant Women/	5514
32	Gestation.mp.	96310
33	(pregnanc* or pregnant).mp.	844193
34	gravidity/ or postpartum period/ or pregnancy trimesters/	22478
35	(gravidity or peripartum period or postpartum period).mp.	27479

36	exp Breast Feeding/	30816
37	(breast feeding or breastfeeding).mp.	40802
38	Lactation/	34864
39	lactation.mp.	48150
40	Milk, Human/	16202
41	((human or breast) adj1 milk).mp.	22920
42	or/8-41	3318393
43	7 and 42	11604
44	exp animals/ not humans.sh.	4177874
45	43 not 44	10694
46	exp Hypersensitivity/	299314
47	hypersensitiv*.mp.	154466
48	allerg*.mp.	182301
49	anaphyla*.mp.	31973
50	asthma*.mp.	147962
51	wheez*.mp.	10884
52	eczema*.mp.	19485
53	dermatit*.mp.	77572
54	rhinit*.mp.	36427
55	hyperreactiv*.mp.	12121
56	(atopi* or atopy).mp.	38578
57	or/46-55	483374
58	45 and 57	538

[†]Case-control and cohort studies

Interface	Ovid	
Database	<i>Embase</i>	
Date of searching	January 30, 2016	
Study Types	Randomized control trials and observational studies [†]	
Limits	No limits	
Database strategy		
1	exp Vitamin D/	105925
2	hydroxyvitamin D.mp.	15624
3	1,25-dihydroxycholecalciferol.mp.	1334
4	24,25-dihydroxycholecalciferol.mp.	163
5	1,25-dihydroxyvitamin D3.mp.	6018
6	Vitamin D.tw.	62288
7	1 or 2 or 3 or 4 or 5 or 6	117168
8	exp Child/	2272928
9	exp Infant/	926161
10	Childhood.mp.	330316
11	Infant*.mp.	803451

12	Infancy.tw.	51760
13	Baby.tw.	40153
14	Baby's.tw.	2470
15	Babies.tw.	40269
16	Neonat*.mp.	279324
17	Child*.mp.	2270276
18	Schoolchild*.tw.	13113
19	Schoolage*.tw.	267
20	School age*.tw.	20183
21	Kids.tw.	5607
22	Kid.tw.	1858
23	Toddler*.tw.	9009
24	exp Pediatrics/	89907
25	Pediatric*.mp.	381375
26	Paediatric*.mp.	77246
27	exp Schools/	281779
28	Kindergar*.tw.	5745
29	Primary school*.mp.	115091
30	exp Pregnancy/	638165
31	Pregnant Women/	431318
32	Gestation.mp.	127611
33	(pregnanc* or pregnant).mp.	828937
34	gravity/ or postpartum period/ or pregnancy trimesters/	605720
35	(gravity or peripartum period or postpartum period).mp.	10771
36	exp Breast Feeding/	38888
37	(breast feeding or breastfeeding).mp.	48741
38	Lactation/	41982
39	lactation.mp.	52471
40	Milk, Human/	20880
41	((human or breast) adj1 milk).mp.	28541
42	or/8-41	3862110
43	7 and 42	21988
44	exp animals/ not humans.sh.	21055025
45	43 not 44	2362
46	exp Hypersensitivity/	514647
47	hypersensitiv*.mp.	157307
48	allerg*.mp.	304176
49	anaphyla*.mp.	56335
50	asthma*.mp.	242104
51	wheez*.mp.	23991
52	eczema*.mp.	37471
53	dermatit*.mp.	105183
54	rhinit*.mp.	49945
55	hyperreactiv*.mp.	17775

56	(atopi* or atopy).mp.	63796
57	or/46-55	714556
58	45 and 57	96

[†]Case-control and cohort studies

Database	<i>The Cochrane Library</i>	
Date of searching	January 30, 2016	
Study Types	Randomized control trials and observational studies*	
Limits	No limits	
Database strategy		
1	MeSH descriptor: [Vitamin D] explode all trees	2805
2	"vitamin D":ti,ab,kw	4621
3	hydroxyvitamin	1427
4	1,25-dihydroxycholecalciferol	59
5	1,25-dihydroxyvitamin D3	171
6	24,25-dihydroxycholecalciferol	9
7	#1 or #2 or #3 or #4 or #5 or #6	5685
8	MeSH descriptor: [Child] explode all trees	152
9	MeSH descriptor: [Infant] explode all trees	14330
10	Infant*	43342
11	Infancy	1655
12	Baby*	2871
13	Babies	3380
14	Neonat*	21029
15	Preterm*	7785
16	Newborn*	19707
17	Prematur*	15107
18	Postmatur*	35
19	Child*	106611
20	Schoolchild*	1062
21	School age*	52028
22	Kid	106
23	Kids*	503
24	Toddler*	948
25	Boy*	8480
26	Girl*	4732
27	MeSH descriptor: [Minors] explode all trees	8
28	Minors*	197
29	MeSH descriptor: [Pediatrics] explode all trees	608
30	Paediatric*	10981
31	Peadiatric*	42
32	MeSH descriptor: [Schools] explode all trees	1991

33	Preschool*	31280
34	Kindergar*	456
35	Primary school*	15081
36	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35	177870
37	MeSH descriptor: [Pregnancy] explode all trees	6296
38	MeSH descriptor: [Breast Feeding] explode all trees	1498
39	#36 or #37 or #38	180453
40	#7 and #39	1298

Table S2. Characteristics of included studies**1. PREGNANT WOMEN**

Study, Year	n	Population who received vitamin D	Type of vitamin D administered	Route of administration and forms	Doses of vitamin D administered	Time of administration of vitamin D	Time of follow-up for outcome(s)
<i>Randomized control trials</i>							
Brooke, 1980 (29)	126*	Pregnant women with 28 gestation weeks	Ergocalciferol	Oral (unreported)	1000 IU/day	Until delivery	At birth
Goldring, 2013 (25)	180*	Pregnant women at 27 weeks of gestation	Vitamin D3 (ergocalciferol)	Oral (tablets)	800 IU/day or 200000 UI (single dose)**	2 months (until delivery)	At 36 months
Hossain, 2014 (30)	200*	Pregnant women at 20 weeks of gestation	Vitamin D3 (Ergocalciferol)	Oral (liquid formulation)	4000 IU/day	Until delivery	At birth
Mallet, 1986 (52)	57*	Pregnant women at seven month	Vitamin D2	Unreported	1000 IU/day or 200000 IU (single dose)	Last trimester of pregnancy	At birth
Roth, 2013-A (31)	160*	Pregnant women with gestational age of 26 to < 30 weeks	Vitamin D3 (cholecalciferol)	Oral (liquid formulation)	35000 IU/week	3 months (last trimester of pregnancy)	At birth
Roth, 2013-B (28)	160*	Pregnant women with gestational age of 26 to < 30 weeks	Vitamin D3 (cholecalciferol)	Oral (liquid formulation)	35000 IU/week	3 months (last trimester of pregnancy)	One year after delivery
Sablok, 2015 (33)	180*	Pregnant women with gestational age at 14–20 weeks	Vitamin D (cholecalciferol)	Oral	Between 60000 IU to 480000 IU	Between second to third trimester of pregnancy	At birth
Yu, 2009 (32)	180*	Pregnant women with 27 gestation weeks	Vitamin D (Ergocalciferol or calciferol)	Oral	800 UI/day or 200000 IU (single dose)	Until delivery	At birth
<i>Observational studies</i>							
Allen, 2013 (27)	2252	Pregnant women	Maternal use of vitamin D supplement	Unreported	Unreported	During pregnancy	Infants with aged between 11 and 15 months
Anderson 2015 (26)	2478	Pregnant women	Maternal use of	Unreported	400 or 1000	During	Infants with aged

vitamin D supplement	IU/day	pregnancy	between 0 to 5 years
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2. BREASTFEEDING

Study, Year	n	Population who received vitamin D	Type of vitamin D administered	Route of administration and forms	Doses of vitamin D administered	Time of administration of vitamin D	Time of follow-up for outcome(s)
Randomized control trials							
Rothberg, 1982 (34)	60*	Breastfeeding mothers	Vitamin D	Unreported	500 IU or 1000 IU/day	6 weeks	At 6 weeks of age
Observational studies							
Bener, 2012 (24)	966	Breastfeeding mothers	Vitamin D supplementation	Unreported	Unreported	During breastfeeding	Children with different age group

3. INFANTS

[illegible]

Allen, 2013 (27)	2252	Infants	Vitamin D supplement	Unreported)	Unreported	During infancy	Infants with aged between 11 and 15 months
Anderson 2015 (26)	2478	Infants	Vitamin D supplement	Unreported	400 IU/day	During childhood	Infants with aged between 0 to 5 years
Hypponen, 2004 (35)	7648	Infants	Vitamin D supplement	Unreported	<2000 IU to >2000 IU‡	During the first year of life	At age 31 years

4. CHILDREN

Study, Year	n	Population who received vitamin D	Type of vitamin D administered	Route of administration and forms	Doses of vitamin D administered	Time of administration of vitamin D	Time of follow-up for outcome(s)
Randomized control trials							
Abrams, 2013 (53)	64*	Children between 4-8.9 years old	Vitamin D3	Oral	1000 IU/day	8 weeks	At the end of the trial (8 th week later)
Guillemant 2001 (41)	57*	Adolescents between 13 to 16 years old	Vitamin D3	Oral (phial of water-soluble oral solution)	100000 IU/3 times	18 months	At the end of the trial (18 months later)
Hower 2013 (44)	92*	Children between 2-6 years old	Vitamin D fortified milk	Oral	400 IU/day	8 months	At the end of the trial (8 months later)
Khadiolkar 2010 (54)	50*	Adolescents between 14 to 15 years old	Vitamin D2	Oral	300000/4 times	12 months	At the end of the trial (12 months later)
Lewis 2013 (55)	323*	Children between 9-13 years old	Vitamin D3	Oral (tablets)	400, 1000, 2000, or 4000 IU/day	12 weeks	At the end of the trial (12 weeks later)
Maalouf 2008 (56)	340*	Adolescents between 10 to 17 years old	Vitamin D3	Oral	1400 or 14000 UI/weekly	12 months	At the end of the trial (12 months later)
Mølgaard 2010 (42)	225*	Children between 11 to 12 years old	Vitamin D3	Oral	200 or 400 IU/day	12 months	At the end of the trial (12 months later)
Rich Edwards 2011 (57)	579	Children between 9 to 11 years old	Vitamin D3	Oral	13700 IU in one week or 300 IU/day	49 days	At the end of the trial

Rajakumar, 2015 (58)	157*	Children between 8 to 14 years old	Vitamin D3	Oral (tablets)	1000 IU/daily	6 months	At the end of the trial (6 months later)
Urashima 2010 (59)	430*	Children between 6 to 15 years old	Vitamin D3	Oral (tablets)	1200 IU/day	4 months	At the end of the trial (4 months later)
Vijakainen 2006 (43)	228	Adolescents between 11 to 12 years old	Vitamin D3	Oral	200 or 400 IU/day	12 months	At the end of the trial (12 months later)
Ward 2010 (60)	73*	Adolescents between 12 to 14 years old	Vitamin D 2 (ergocalciferol)	Oral	150000 IU/four times	12 months	At the end of the trial (12 months later)

*Patients randomized. **Results presented in metanalysis correspond to pooled data. Single oral dose was administered as cholecalciferol (oral bolus). ***Randomization was carried out at the health clinic level. [†] Two group of infants received vitamin D: one group started the vitamin D supplementation at birth and another group started at 2 months of age. [‡] The daily dose of vitamin D was calculated on the basis of concentration of vitamin D in the product used and the reported dosage (categorized as <50 µg, 50 µg, or >50 µg).

Table S3. Characteristics of excluded studies

Studies	Study was no RCT or Observational study †	Patients were not healthy §	Intervention was not vitamin D supplementation only ¶	Study did not report any of the outcomes of interest	Duplicate
Al-Shaar, 2014 (1)				•	
Ala-Houhala, 1988 (2)	•				
Ala-Houhala 1986 (3)	•				
Alyasin, 2011 (4)	•	•			
Allan, 2015 (5)			•		
Arabi, 2009 (6)				•	
Arikoglu, 2015 (7)			•		
Arshi, 2014 (8)		•			
Awasthi, 2014 (9)			•	•	
Bacharier, 2014 (10)	•				
Backström, 2000 (11)			•	•	
Backström, 1999 (12)			•	•	
Baek, 2014 (13)	•	•			
Baiz, 2014 (14)			•		
Bar Yoseph, 2015 (15)		•		•	
Baris, 2015 (16)		•		•	
Bechard, 2015 (17)		•	•	•	
Bird, 2014 (18)	•				
Brett, 2015 (19)			•		
Brehm, 2012 (20)	•				
Brehm, 2009 (21)	•				
Brehm, 2010 (22)		•	•		•
Camargo, 2012 (23)					

Camargo, 2011 (24)	•		
Camargo, 2007 (25)		•	
Carroll, 2011 (26)	•		
Cashman, 2011 (27)			•
Chawes, 2014 (28)		•	
Chawes 2016 (29)		•	
Cheng, 2005 (30)		•	
Cosenza, 2013 (31)		•	•
Delvin, 1986 (32)			•
Devereux, 2007 (33)		•	
Du, 2004 (34)		•	
Duhamel, 2000 (35)	•		
Erkkola, 2009 (36)		•	
Freishtat, 2010 (37)		•	
Gale, 2008 (38)		•	
Ganmaa, 2012 (39)		•	
Gentile, 2010 (40)	•		
Gergen, 2013 (41)		•	
Grant, 2014 (42)			•
Grant, 2015 (43)			•
Green, 2010 (44)		•	•
Greene, 2011 (45)		•	
Greer, 1981 (46)			•
Harvey, 2012 (47)	•		
Heimbeck, 2013 (48)		•	
Hibbs, 2015 (49)		•	

Hollams, 2011 (50)			•	
Hughes, 2011 (51)			•	
Ito, 2013 (52)			•	
Jacobs, 2011 (53)			•	
Jensen, 2015 (54)		•	•	•
Jones, 2012 (55)			•	
Kemp, 2013 (56)			•	
Khadgawat, 2013 (57)			•	
Kim, 2010 (58)	•			
Koistinen, 2014 (59)			•	
Krotrakulchai 2013, (60)	•			
Kull, 2006 (61)			•	
Lewis, 2012 (62)		•		
Li, 2015 (63)	•	•	•	•
Litonjua, 2014 (64) ‡			•	•
Litonjua, 2016 (65)			•	
Liu, 2011 (66)			•	
Liu, 2013 (67)		•	•	•
Ma, 2011 (68)			•	•
Madsen, 2013 (69)				•
Magnus, 2013 (70)			•	
Maguire, 2014 (71)	•			
Majak, 2011 (72)		•		
Marchisio, 2013 (73)		•		
Marya, 1981 (74)			•	
Maslova, 2013 (75)			•	

Maxwell, 1981 (76)	•		
Menon, 2012 (77)		•	
Meyer, 2015 (78)		•	•
Miller, 2015 (79)		•	•
Miyake, 2010 (80)		•	
Miyake, 2012 (81)		•	
Miyake, 2014 (82)		•	
Morales, 2012 (83)		•	
Mouratidou, 2013 (84)		•	
Moyer-Mileur, 2003 (85)		•	
Mullins, 2010 (86)	•		
Mullins, 2010 (87)	•		
Mullins, 2011 (88)	•		
Mullins, 2012 (89)		•	
Nissen, 2015 (90)			•
Norizoe, 2014 (91)		•	
Nwaru, 2010 (92)		•	
O'Connor, 2010 (93)			•
Oktaria, 2013 (94)	•		
Oliver, 2014 (95)	•		
Ozaydin, 2013 (96)		•	
Palmer, 2015 (97)		•	•
Persson, 2013 (98)		•	
Peters, 2015 (99)		•	
Pike, 2012 (100)		•	
Rajabbik, 2014 (101)	•		

Rochat, 2010 (102)			•
Rosser, 2014 (103)		•	•
Rothers, 2011 (104)		•	
Sacheck, 2015 (105)		•	
San, 2013 (106)		•	•
Sharief, 2011 (107)		•	
Sidbury, 2008 (108)	•		•
Stelmach, 2015 (109)		•	
Stenberg, 2014 (110)		•	
Strucinska, 2015 (111)		•	
Sun, 2011 (112)		•	•
Tolppanen, 2011 (113)		•	
Tolppanen, 2013 (114)		•	
Trilok-Kumar, 2015 (115)	•	•	
Tse, 2012 (116)	•	•	•
Tu, 2015 (117)	•		•
Uysalol, 2013 (118)	•		
van Oeffelen, 2011 (119)		•	
Venkataraman, 1992 (120)		•	
Visness, 2015 (121)	•	•	
Wagner, 2006 (122)		•	
Wagner 2013 (123)		•	
Wang, 2014 (124)		•	
Weisse, 2013 (125)		•	
Willers, 2007 (126)		•	
Wills, 2013 (127)		•	

Wjst, 2007 (128)	•	•	
Wu, 2012 (129)		•	
Yadav, 2014 (130)	•	•	
Yao, 2014 (131)	•	•	
Young, 2001 (132)		•	
Zhang, 2003 (133)			•
Zhang, 2014 (134)		•	
Zhong, 2013 (135)	•		
Zhu, 2005 (136)		•	
Zhu 2003 (137)			•
Zhu, 2008 (138)			•
Zittermann, 2004 (139)		•	•
Zoratti, 2013 (140)	•		
Zosky, 2014 (141)	•		

†Case-control or cohort studies. §Only for randomized control trial. ¶ Information about vitamin D supplementation was rejected if that was obtained by using any food frequency questionnaire. ‡This is a protocol of the RCT published by Litonjua 2016.

REFERENCES

1. Al-Shaar L, Mneimneh R, Nabulsi, Maalouf J, Fuleihan Gel H. Vitamin D3 dose requirement to raise 25-hydroxyvitamin D to desirable levels in adolescents: results from a randomized controlled trial. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2014;29(4):944-51.
2. Ala-Houhala M, Koskinen T, Parviainen MT, Visakorpi JK. 25-Hydroxyvitamin D and vitamin D in human milk: effects of supplementation and season. The American journal of clinical nutrition. 1988;48(4):1057-60.

3. Ala-Houhala M, Koskinen T, Terho A, Koivula T, Visakorpi J. Maternal compared with infant vitamin D supplementation. *Archives of disease in childhood*. 1986;61(12):1159-63.
4. Alyasin S, Momen T, Kashef S, Alipour A, Amin R. The relationship between serum 25 hydroxy vitamin d levels and asthma in children. *Allergy, asthma & immunology research*. 2011;3(4):251-5.
5. Allan KM, Prabhu N, Craig LCA, McNeill G, Kirby B, McLay J, et al. Maternal vitamin D and E intakes during pregnancy are associated with asthma in children. *Eur Respir J*. 2015;45(4):1027-36.
6. Arabi A, Zahed L, Mahfoud Z, El-Onsi L, Nabulsi M, Maalouf J, et al. Vitamin D receptor gene polymorphisms modulate the skeletal response to vitamin D supplementation in healthy girls. *Bone*. 2009;45(6):1091-7.
7. Arikoglu T, Kuyucu S, Karaismailoglu E, Batmaz SB, Balci S. The association of vitamin D, cathelicidin, and vitamin D binding protein with acute asthma attacks in children. *Allergy Asthma Proc*. 2015;36(4):51-8.
8. Arshi S, Fallahpour M, Nabavi M, Bemanian MH, Javad-Mousavi SA, Nojomi M, et al. The effects of vitamin D supplementation on airway functions in mild to moderate persistent asthma. *Ann Allergy Asthma Immunol*. 2014;113(4):404-9.
9. Awasthi S, Vikram K. Serum 25 hydroxy vitamin D insufficiency associated with bronchial asthma in Lucknow, India. *Indian journal of pediatrics*. 2014;81(7):644-9.
10. Bacharier LB. Vitamin D status at birth: an important and potentially modifiable determinant of atopic disease in childhood? *J Allergy Clin Immunol*. 2014;133(1):154-5.
11. Backstrom MC, Aine L, Maki R, Kuusela AL, Sievanen H, Koivisto AM, et al. Maturation of primary and permanent teeth in preterm infants. *Archives of disease in childhood Fetal and neonatal edition*. 2000;83(2):F104-8.

12. Backstrom MC, Maki R, Kuusela AL, Sievanen H, Koivisto AM, Koskinen M, et al. The long-term effect of early mineral, vitamin D, and breast milk intake on bone mineral status in 9- to 11-year-old children born prematurely. *Journal of pediatric gastroenterology and nutrition*. 1999;29(5):575-82.
13. Baek JH, Shin YH, Chung IH, Kim HJ, Yoo EG, Yoon JW, et al. The link between serum vitamin D level, sensitization to food allergens, and the severity of atopic dermatitis in infancy. *The Journal of pediatrics*. 2014;165(4):849-54 e1.
14. Baiz N, Dargent-Molina P, Wark JD, Souberbielle JC, Annesi-Maesano I, Group EM-CCS. Cord serum 25-hydroxyvitamin D and risk of early childhood transient wheezing and atopic dermatitis. *J Allergy Clin Immunol*. 2014;133(1):147-53.
15. Bar Yoseph R, Livnat G, Schnapp Z, Hakim F, Dabbah H, Goldbart A, et al. The effect of vitamin D on airway reactivity and inflammation in asthmatic children: A double-blind placebo-controlled trial. *Pediatric pulmonology*. 2015;50(8):747-53.
16. Baris S, Ozen A, Cagan H, Kiykim A, Tulunay A, Karakoc-Aydiner E. The effect of Vitamin D supplementation on subcutaneous allergen immunotherapy in house dust mite sensitive asthmatic children. *Turkish Journal of Immunology*. 2015; 3(2):54-63.
17. Bechard LJ, Gordon C, Feldman HA, Venick R, Gura K, Guinan EC, et al. Bone loss and vitamin D deficiency in children undergoing hematopoietic cell transplantation. *Pediatric blood & cancer*. 2015;62(4):687-92.
18. Bird JA, Wang J, Visness CM, Calatroni A, Sampson HA, Gruchalla R. Winter birth in inner-city asthmatic children is associated with increased food allergen sensitization risk. *J Allergy Clin Immunol*. 2014;134(2):490-2.
19. Brett N, Lavery P, Vanstone C, Maguire J, Rauch F, Weiler H. Vitamin D status and functional health outcomes: A randomized vitamin D dose-response trial in 28-Y olds. *FASEB journal*. 2015; 29(1 Meeting Abstracts).

20. Brehm JM, Acosta-Perez E, Klei L, Roeder K, Barmada M, Boutaoui N, et al. Vitamin D insufficiency and severe asthma exacerbations in Puerto Rican children. *American journal of respiratory and critical care medicine*. 2012;186(2):140-6.
21. Brehm JM, Celedon JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *American journal of respiratory and critical care medicine*. 2009;179(9):765-71.
22. Brehm JM, Schuemann B, Fuhlbrigge AL, Hollis BW, Strunk RC, Zeiger RS, et al. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. *J Allergy Clin Immunol*. 2010;126(1):52-8 e5.
23. Camargo CA, Jr., Ganmaa D, Frazier AL, Kirchberg FF, Stuart JJ, Kleinman K, et al. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. *Pediatrics*. 2012;130(3):e561-7.
24. Camargo CA, Jr., Ingham T, Wickens K, Thadhani R, Silvers KM, Epton MJ, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics*. 2011;127(1):e180-7.
25. Camargo CA, Jr., Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *The American journal of clinical nutrition*. 2007;85(3):788-95.
26. Carroll KN, Gebretsadik T, Larkin EK, Dupont WD, Liu Z, Driest S, et al. Relationship of maternal vitamin D level with maternal and infant respiratory disease. *American journal of obstetrics and gynecology*. 2011; 205(3):215.e1-.e7.
27. Cashman KD, FitzGerald AP, Viljakainen HT, Jakobsen J, Michaelsen KF, Lamberg-Allardt C, et al. Estimation of the dietary requirement for vitamin D in healthy adolescent white girls. *The American journal of clinical nutrition*. 2011;93(3):549-55.

28. Chawes BL, Bonnelykke K, Jensen PF, Schoos AM, Heickendorff L, Bisgaard H. Cord blood 25(OH)-vitamin D deficiency and childhood asthma, allergy and eczema: the COPSAC2000 birth cohort study. *PloS one*. 2014;9(6):e99856.
29. Chawes BL, Bonnelykke K, Stokholm J, Vissing NH, Bjarnadottir E, Schoos A-MM, et al. Effect of Vitamin D3 Supplementation During Pregnancy on Risk of Persistent Wheeze in the Offspring: A Randomized Clinical Trial. *Jama*. 2016;315(4):353-61.
30. Cheng S, Lyytikainen A, Kroger H, Lamberg-Allardt C, Alen M, Koistinen A, et al. Effects of calcium, dairy product, and vitamin D supplementation on bone mass accrual and body composition in 10-12-y-old girls: a 2-y randomized trial. *The American journal of clinical nutrition*. 2005;82(5):1115-26; quiz 47-8.
31. Cosenza L, Pezzella V, Nocerino R, Di Costanzo M, Coruzzo A, Passariello A, et al. Calcium and vitamin D intakes in children: a randomized controlled trial. *BMC pediatrics*. 2013;13:86.
32. Delvin EE, Salle BL, Glorieux FH, Adeleine P, David LS. Vitamin D supplementation during pregnancy: effect on neonatal calcium homeostasis. *The Journal of pediatrics*. 1986;109(2):328-34.
33. Devereux G, Litonjua AA, Turner SW, Craig LC, McNeill G, Martindale S, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. *The American journal of clinical nutrition*. 2007;85(3):853-9.
34. Du X, Zhu K, Trube A, Zhang Q, Ma G, Hu X, et al. School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10-12 years in Beijing. *The British journal of nutrition*. 2004;92(1):159-68.
35. Duhamel JF, Zeghoud F, Sempe M, Boudailliez B, Odievre M, Laurans M, et al. [Prevention of vitamin D deficiency in adolescents and pre-adolescents. An interventional multicenter study on the biological effect of repeated doses of 100,000 IU of vitamin D3]. *Archives de pediatrie : organe officiel de la Societe francaise de pediatrie*. 2000;7(2):148-53.

36. Erkkola M, Kaila M, Nwaru BI, Kronberg-Kippila C, Ahonen S, Nevalainen J, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*. 2009;39(6):875-82.
37. Freishtat RJ, Iqbal SF, Pillai DK, Klein CJ, Ryan LM, Benton AS, et al. High prevalence of vitamin D deficiency among inner-city African American youth with asthma in Washington, DC. *The Journal of pediatrics*. 2010;156(6):948-52.
38. Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN, et al. Maternal vitamin D status during pregnancy and child outcomes. *European journal of clinical nutrition*. 2008;62(1):68-77.
39. Ganmaa D, Giovannucci E, Bloom BR, Fawzi W, Burr W, Batbaatar D, et al. Vitamin D, tuberculin skin test conversion, and latent tuberculosis in Mongolian school-age children: a randomized, double-blind, placebo-controlled feasibility trial. *The American journal of clinical nutrition*. 2012;96(2):391-6.
40. Gentile DA, Patel A, Koehrsen JM, Skoner DP. Reduced Vitamin D Levels in Asthmatic Children. *Journal of Allergy and Clinical Immunology*. 2010;125(2, Supplement 1):AB47.
41. Gergen PJ, Teach SJ, Mitchell HE, Freishtat RF, Calatroni A, Matsui E, et al. Lack of a relation between serum 25-hydroxyvitamin D concentrations and asthma in adolescents. *The American journal of clinical nutrition*. 2013;97(6):1228-34.
42. Grant CC, Stewart AW, Scragg R, Milne T, Rowden J, Ekeroma A, et al. Vitamin D during pregnancy and infancy and infant serum 25-hydroxyvitamin D concentration. *Pediatrics*. 2014;133(1):e143-53.
43. Grant CC, Kaur S, Waymouth E, Mitchell EA, Scragg R, Ekeroma A, et al. Reduced primary care respiratory infection visits following pregnancy and infancy vitamin D supplementation: a randomised controlled trial. *Acta Paediatr*. 2015;104(4):396-404.

44. Green TJ, Skeaff CM, Rockell JE. Milk fortified with the current adequate intake for vitamin D (5 microg) increases serum 25-hydroxyvitamin D compared to control milk but is not sufficient to prevent a seasonal decline in young women. *Asia Pacific journal of clinical nutrition*. 2010;19(2):195-9.
45. Greene DA, Naughton GA. Calcium and vitamin-D supplementation on bone structural properties in peripubertal female identical twins: a randomised controlled trial. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2011;22(2):489-98.
46. Greer FR, Searcy JE, Levin RS, Steichen JJ, Asch PS, Tsang RC. Bone mineral content and serum 25-hydroxyvitamin D concentration in breast-fed infants with and without supplemental vitamin D. *The Journal of pediatrics*. 1981;98(5):696-701.
47. Harvey NC, Javaid K, Bishop N, Kennedy S, Papageorgiou AT, Fraser R, et al. MAVIDOS Maternal Vitamin D Osteoporosis Study: study protocol for a randomized controlled trial. The MAVIDOS Study Group. *Trials*. 2012;13:13.
48. Heimbeck I, Wjst M, Apfelbacher CJ. Low vitamin D serum level is inversely associated with eczema in children and adolescents in Germany. *Allergy*. 2013;68(7):906-10.
49. Hibbs AM, Babineau DC, Wang X, Redline S. Race differences in the association between multivitamin exposure and wheezing in preterm infants. *J Perinatol*. 2015;35(3):192-7.
50. Hollams EM, Hart PH, Holt BJ, Serralha M, Parsons F, de Klerk NH, et al. Vitamin D and atopy and asthma phenotypes in children: a longitudinal cohort study. *Eur Respir J*. 2011;38(6):1320-7.
51. Hughes AM, Lucas RM, Ponsonby AL, Chapman C, Coulthard A, Dear K, et al. The role of latitude, ultraviolet radiation exposure and vitamin D in childhood asthma and hayfever: an Australian multicenter study. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2011;22(3):327-33.

52. Ito Y, Adachi Y, Yoshida K, Akasawa A. No association between serum vitamin D status and the prevalence of allergic diseases in Japanese children. *International archives of allergy and immunology*. 2013;160(2):218-20.
53. Jacobs ZD, Dai H, Feldt M, Dinakar C. Relationship between serum 25-hydroxyvitamin D and IgE: National Health and Nutrition Examination Survey 2-year results. *Journal of Allergy and Clinical Immunology*. 2011;1):AB151.
54. Jensen ME, Mailhot G, Alos N, White JH, Rousseau E, Khamessan A. A vitamin D intervention in preschoolers with viral-induced asthma: A pilot randomised controlled trial (DIVA). *American journal of respiratory and critical care medicine*. 2015; 191(Meeting Abstracts):A3360.
55. Jones AP, Palmer D, Zhang G, Prescott SL. Cord blood 25-hydroxyvitamin D3 and allergic disease during infancy. *Pediatrics*. 2012;130(5):e1128-35.
56. Kemp AS, Ponsonby A-L, Pezic A, Cochrane JA, Dwyer T, Jones G. The influence of sun exposure in childhood and adolescence on atopic disease at adolescence. *Pediatric Allergy & Immunology*. 2013;24(5):493-500.
57. Khadgawat R, Marwaha RK, Garg MK, Ramot R, Oberoi AK, Sreenivas V, et al. Impact of vitamin D fortified milk supplementation on vitamin D status of healthy school children aged 10-14 years. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2013; 24(8):2335-43.
58. Kim MJ, Na B, No SJ, Han HS, Jeong EH, Lee W, et al. Nutritional status of vitamin D and the effect of vitamin D supplementation in Korean breast-fed infants. *Journal of Korean medical science*. 2010; 25(1):83-9.
59. Koistinen A, Turunen R, Vuorinen T, Soderlund-Venermo M, Camargo CA, Jr., Ruuskanen O, et al. Vitamin D, virus etiology, and atopy in first-time wheezing children in Finland. *Pediatric Allergy & Immunology*. 2014;25(8):834-7.

60. Krobtrakulchai W, Praikanahok J, Visitsunthorn N, Vichyanond P, Manonukul K, Pratumvinit B, et al. The effect of vitamin d status on pediatric asthma at a university hospital, Thailand. *Allergy, asthma & immunology research*. 2013;5(5):289-94.
61. Kull I, Bergstrom A, Melen E, Lilja G, van Hage M, Pershagen G, et al. Early-life supplementation of vitamins A and D, in water-soluble form or in peanut oil, and allergic diseases during childhood. *J Allergy Clin Immunol*. 2006;118(6):1299-304.
62. Lewis E, Fernandez C, Nella A, Hopp R, Gallagher JC, Casale TB. Relationship of 25-hydroxyvitamin D and asthma control in children. *Annals of allergy, asthma & immunology*. 2012; 108(4):281-2.
63. Li R, Li M. [The immune regulation of vitamin D in children's allergic disease]. *Zhonghua Er Ke Za Zhi*. 2015;53(3):232-4.
64. Litonjua AA, Lange NE, Carey VJ, Brown S, Laranjo N, Harshfield BJ, et al. The Vitamin D Antenatal Asthma Reduction Trial (VDAART): rationale, design, and methods of a randomized, controlled trial of vitamin D supplementation in pregnancy for the primary prevention of asthma and allergies in children. *Contemp Clin Trials*. 2014;38(1):37-50.
65. Litonjua AA, Carey VJ, Laranjo N, Harshfield BJ, McElrath TF, O'Connor GT, et al. Effect of Prenatal Supplementation With Vitamin D on Asthma or Recurrent Wheezing in Offspring by Age 3 Years: The VDAART Randomized Clinical Trial. *Jama*. 2016;315(4):362-70.
66. Liu X, Wang G, Hong X, Wang D, Tsai HJ, Zhang S, et al. Gene-vitamin D interactions on food sensitization: a prospective birth cohort study. *Allergy*. 2011;66(11):1442-8.
67. Liu X, Arguelles L, Zhou Y, Wang G, Chen Q, Tsai HJ, et al. Longitudinal trajectory of vitamin D status from birth to early childhood in the development of food sensitization. *Pediatric research*. 2013;74(3):321-6.

68. Ma X-L, Zhen Y-F. [Serum levels of 25-(OH)D(3) and total IgE in children with asthma]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2011;13(7):551-3.
69. Madsen KH, Rasmussen LB, Andersen R, Molgaard C, Jakobsen J, Bjerrum PJ, et al. Randomized controlled trial of the effects of vitamin D-fortified milk and bread on serum 25-hydroxyvitamin D concentrations in families in Denmark during winter: The VitmaD study. *American journal of clinical nutrition*. 2013; 98(2):374-82.
70. Magnus MC, Stene LC, Nafstad P, Stigum H, London SJ, Nystad W. Prospective study of maternal mid-pregnancy 25-hydroxyvitamin D level and early childhood respiratory disorders. *Paediatric and perinatal epidemiology*. 2013; 27(6):532-41.
71. Maguire JL, Birken CS, Loeb MB, Mamdani M, Thorpe K, Hoch JS, et al. DO IT Trial: vitamin D Outcomes and Interventions in Toddlers - a TARGet Kids! randomized controlled trial. *BMC pediatrics*. 2014;14:37.
72. Majak P, Olszowiec-Chlebna M, Smejda K, Stelmach I. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. *Journal of allergy and clinical immunology*. 2011; 127(5):1294-6.
73. Marchisio P, Consonni D, Baggi E, Zampiero A, Bianchini S, Terranova L. Vitamin D Supplementation Reduces the Risk of Acute Otitis Media in Otitis-prone Children. *Pediatric infectious disease journal*. 2013; 32(10):1055-60.
74. Marya RK, Rathee S, Lata V, Mudgil S. Effects of vitamin D supplementation in pregnancy. *Gynecologic and obstetric investigation*. 1981; 12(3):155-61.
75. Maslova E, Hansen S, Jensen CB, Thorne-Lyman AL, Strom M, Olsen SF. Vitamin D intake in mid-pregnancy and child allergic disease - a prospective study in 44,825 Danish mother-child pairs. *BMC Pregnancy Childbirth*. 2013;13:199.
76. Maxwell JD, Ang L, Brooke OG, Brown IR. Vitamin D supplements enhance weight gain and nutritional status in pregnant Asians. *British journal of obstetrics and gynaecology*. 1981; 88(10):987-91.

77. Menon J, Maranda L, Nwosu BU. Serum 25-hydroxyvitamin D levels do not correlate with asthma severity in a case-controlled study of children and adolescents. *J Pediatr Endocrinol*. 2012;25(7-8):673-9.
78. Meyer R, De Koker C, Dziubak R, Skrapac A-K, Godwin H, Reeve K, et al. A practical approach to vitamin and mineral supplementation in food allergic children. *Clin Transl Allergy*. 2015;5:11.
79. Miller DR, Turner SW, Spiteri-Cornish D, Scaife AR, Danielian PJ, Devereux GS, et al. Maternal vitamin D and E intakes during early pregnancy are associated with airway epithelial cell responses in neonates. *Clinical & Experimental Allergy*. 2015;45(5):920-7.
80. Miyake Y, Sasaki S, Tanaka K, Hirota Y. Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants. *Eur Respir J*. 2010;35(6):1228-34.
81. Miyake Y, Tanaka K, Okubo H, Sasaki S, Arakawa M. Dairy food, calcium and vitamin D intake and prevalence of allergic disorders in pregnant Japanese women. *Int J Tuberc Lung Dis*. 2012;16(2):255-61.
82. Miyake Y, Tanaka K, Okubo H, Sasaki S, Arakawa M. Maternal consumption of dairy products, calcium, and vitamin D during pregnancy and infantile allergic disorders. *Ann Allergy Asthma Immunol*. 2014;113(1):82-7.
83. Morales E, Romieu I, Guerra S, Ballester F, Rebagliato M, Vioque J, et al. Maternal vitamin D status in pregnancy and risk of lower respiratory tract infections, wheezing, and asthma in offspring. *Epidemiology*. 2012;23(1):64-71.
84. Mouratidou T, Vicente-Rodriguez G, Gracia-Marco L, Huybrechts I, Sioen I, Widhalm K, et al. Associations of dietary calcium, vitamin D, milk intakes, and 25-hydroxyvitamin D with bone mass in Spanish adolescents: the HELENA study. *Journal of clinical densitometry*. 2013; 16(1):110-7.
85. Moyer-Mileur LJ, Xie B, Ball SD, Pratt T. Bone mass and density response to a 12-month trial of calcium and vitamin D supplement in preadolescent girls. *Journal of Musculoskeletal Neuronal Interactions*. 2003; 3(1):63-70.

86. Mullins RJ, Clark S, Katelaris C, Smith V, Solley G, Camargo CA. Season of birth and childhood food allergy in Australia: A role for ultraviolet radiation/vitamin D? *Internal Medicine Journal*. 2010;40:14-5.
87. Mullins RJ, Clark S, Camargo CA, Jr. Regional variation in infant hypoallergenic formula prescriptions in Australia. *Pediatric Allergy & Immunology*. 2010;21(2 Pt 2):e413-20.
88. Mullins RJ, Clark S, Katelaris C, Smith V, Solley G, Camargo CA, Jr. Season of birth and childhood food allergy in Australia. *Pediatric Allergy & Immunology*. 2011;22(6):583-9.
89. Mullins RJ, Clark S, Wiley V, Eyles D, Camargo CA, Jr. Neonatal vitamin D status and childhood peanut allergy: a pilot study. *Ann Allergy Asthma Immunol*. 2012;109(5):324-8.
90. Nissen J, Vogel U, Ravn-Haren G, Andersen EW, Madsen KH, Nexø BA, et al. Common variants in CYP2R1 and GC genes are both determinants of serum 25-hydroxyvitamin D concentrations after UVB irradiation and after consumption of vitamin D₃ -fortified bread and milk during winter in Denmark. *The American journal of clinical nutrition*. 2015; 101(1):218-27.
91. Norizoe C, Akiyama N, Segawa T, Tachimoto H, Mezawa H, Ida H, et al. Increased food allergy and vitamin D: Randomized, double-blind, placebo-controlled trial. *Pediatrics international*. 2014; 56(1):6-12.
92. Nwaru BI, Ahonen S, Kaila M, Erkkola M, Haapala A-M, Kronberg-Kippila C, et al. Maternal diet during pregnancy and allergic sensitization in the offspring by 5 yrs of age: a prospective cohort study. *Pediatric Allergy & Immunology*. 2010;21(1 Pt 1):29-37.
93. O'Connor E, Mølgaard C, Michaelsen KF, Jakobsen J, Cashman KD. Vitamin D-vitamin K interaction: effect of vitamin D supplementation on serum percentage undercarboxylated osteocalcin, a sensitive measure of vitamin K status, in Danish girls. *British journal of nutrition*. 2010; 104(8):1091-5.

94. Oktaria V, Dharmage SC, Burgess JA, Simpson JA, Morrison S, Giles GG, et al. Association between latitude and allergic diseases: a longitudinal study from childhood to middle-age. *Ann Allergy Asthma Immunol.* 2013;110(2):80-5.e1.
95. Oliver EM, Grimshaw KEC, Schoemaker AA, Keil T, McBride D, Sprickelman AB, et al. Dietary habits and supplement use in relation to national pregnancy recommendations: data from the EuroPrevall birth cohort. *Matern Child Health J.* 2014;18(10):2408-25.
96. Ozaydin E, Butun MF, Cakir BC, Kose G. The association between vitamin d status and recurrent wheezing. *Indian journal of pediatrics.* 2013;80(11):907-10.
97. Palmer DJ, Sullivan TR, Skeaff CM, Smithers LG, Makrides M, Team DOAF-u. Higher cord blood 25-hydroxyvitamin D concentrations reduce the risk of early childhood eczema: in children with a family history of allergic disease. *World Allergy Organiza.* 2015;8(1):28.
98. Persson K, Ohlund I, Nordstrom L, Winberg A, Ronmark E, West CE. Vitamin D deficiency at the Arctic Circle - a study in food-allergic adolescents and controls. *Acta Paediatr.* 2013;102(6):644-9.
99. Peters RL, Allen KJ, Dharmage SC, Lodge CJ, Koplin JJ, Ponsonby AL, et al. Differential factors associated with challenge-proven food allergy phenotypes in a population cohort of infants: a latent class analysis. *Clinical & Experimental Allergy.* 2015;45(5):953-63.
100. Pike KC, Inskip HM, Robinson S, Lucas JS, Cooper C, Harvey NC, et al. Maternal late-pregnancy serum 25-hydroxyvitamin D in relation to childhood wheeze and atopic outcomes. *Thorax.* 2012;67(11):950-6.
101. Rajabbik MH, Lotfi T, Alkhaled L, Fares M, El-Hajj Fuleihan G, Mroueh S, et al. Association between low vitamin D levels and the diagnosis of asthma in children: a systematic review of cohort studies. *Allergy Asthma Clin Immunol.* 2014;10(1):31.

102. Roachat MK, Ege MJ, Plabst D, Steinle J, Bitter S, Braun-Fahrlander C, et al. Maternal vitamin D intake during pregnancy increases gene expression of ILT3 and ILT4 in cord blood. *Clinical & Experimental Allergy*. 2010;40(5):786-94.
103. Rosser F, Brehm JM, Forno E, Acosta-Perez E, Kurland K, Canino G, et al. Proximity to a major road, vitamin D insufficiency, and severe asthma exacerbations in Puerto Rican children. *American Journal of Respiratory & Critical Care Medicine*. 2014;190(10):1190-3.
104. Rothers J, Wright AL, Stern DA, Halonen M, Camargo CA, Jr. Cord blood 25-hydroxyvitamin D levels are associated with aeroallergen sensitization in children from Tucson, Arizona. *J Allergy Clin Immunol*. 2011;128(5):1093-9.e1-5.
105. Sackeck JM, Rompay MI, Olson EM, Chomitz VR, Goodman E, Gordon CM, et al. Recruitment and retention of urban schoolchildren into a randomized double-blind vitamin D supplementation trial. *Clinical trials (London, England)*. 2015; 12(1 //) *National Institutes of Health*):45-53.
106. San T, Muluk NB, Cingi C. 1,25(OH)2D3 and specific IgE levels in children with recurrent tonsillitis, and allergic rhinitis. *Int J Pediatr Otorhinolaryngol*. 2013;77(9):1506-11.
107. Sharief S, Jariwala S, Kumar J, Muntner P, Melamed ML. Vitamin D levels and food and environmental allergies in the United States: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol*. 2011;127(5):1195-202.
108. Sidbury R, Sullivan AF, Thadhani RI, Camargo CA. Randomized controlled trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. *British journal of dermatology*. 2008; 159(1):245-7.
109. Stelmach I, Majak P, Jerzynska J, Podlecka D, Stelmach W, Polanska K, et al. Cord serum 25-hydroxyvitamin D correlates with early childhood viral-induced wheezing. *Respir Med*. 2015;109(1):38-43.

110. Stenberg Hammar K, Hedlin G, Konradsen JR, Nordlund B, Kull I, Giske CG, et al. Subnormal levels of vitamin D are associated with acute wheeze in young children. *Acta Paediatr.* 2014;103(8):856-61.
111. Strucinska M, Rowicka G, Riahi A. Profiles of selected nutrients affecting skin condition in children with atopic dermatitis. *Rocz Panstw Zakl Hig.* 2015;66(1):45-53.
112. Sun Q, Yang BL, Feng L, Chen QL, Liu YJ. Prospective study on effect of calcium and vitamin D fortified drinks on bone development in children. [Chinese]. *Journal of Jilin University Medicine Edition.* 2011; 37(5):959-64.
113. Tolppanen AM, Williams D, Henderson J, Lawlor DA. Serum 25-hydroxy-vitamin D and ionised calcium in relation to lung function and allergen skin tests. *European journal of clinical nutrition.* 2011;65(4):493-500.
114. Tolppanen A-M, Sayers A, Granell R, Fraser WD, Henderson J, Lawlor DA. Prospective association of 25-hydroxyvitamin d3 and d2 with childhood lung function, asthma, wheezing, and flexural dermatitis. *Epidemiology.* 2013;24(2):310-9.
115. Trilok-Kumar G, Kaur M, Rehman AM, Arora H, Rajput MM, Chugh R, et al. Effects of vitamin D supplementation in infancy on growth, bone parameters, body composition and gross motor development at age 3-6 years: Follow-up of a randomized controlled trial. *International journal of epidemiology.* 2015; 44(3):894-905.
116. Tse SM, Kelly HW, Litonjua AA, Natta ML, Weiss ST, Tantisira KG. Corticosteroid use and bone mineral accretion in children with asthma: effect modification by vitamin D. *The Journal of allergy and clinical immunology.* 2012; 130(1):53-60.e4.
117. Tu H, Flanders WD, Ahearn TU, Daniel CR, Gonzalez-Feliciano AG, Long Q, et al. Effects of calcium and vitamin D3 on transforming growth factors in rectal mucosa of sporadic colorectal adenoma patients: a randomized controlled trial. *Molecular carcinogenesis.* 2015; 54(4):270-80.

118. Uysalol M, Mutlu LC, Saracoglu GV, Karasu E, Guzel S, Kayaoglu S, et al. Childhood asthma and vitamin D deficiency in Turkey: is there cause and effect relationship between them? *Ital.* 2013;39:78.
119. van Oeffelen AAM, Bekkers MBM, Smit HA, Kerkhof M, Koppelman GH, Haveman-Nies A, et al. Serum micronutrient concentrations and childhood asthma: the PIAMA birth cohort study. *Pediatric Allergy & Immunology.* 2011;22(8):784-93.
120. Venkataraman PS, Luhar H, Neylan MJ. Bone mineral metabolism in full-term infants fed human milk, cow milk-based, and soy-based formulas. *American journal of diseases of children (1960).* 1992; 146(11):1302-5.
121. Visness CM, Sandel MT, O'Connor G, Gern JE, Jaffee KF, Wood RA, et al. Cord blood vitamin D concentrations are unrelated to atopy and wheeze in 2 diverse birth cohort studies. *J Allergy Clin Immunol.* 2015; 136(4):1108-10.e2.
122. Wagner CL, Hulse TC, Fanning D, Ebeling M, Hollis BW. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. *Breastfeeding medicine.* 2006; 1(2):59-70.
123. Wagner CL, McNeil R, Hamilton SA, Winkler J, Rodriguez Cook C, Warner G, et al. A randomized trial of vitamin D supplementation in 2 community health center networks in South Carolina. *American journal of obstetrics and gynecology.* 2013; 208(2):137.e1-13.
124. Wang SS, Hon KL, Kong AP-s, Pong HN-h, Wong GW-k, Leung TF. Vitamin D deficiency is associated with diagnosis and severity of childhood atopic dermatitis. *Pediatric Allergy & Immunology.* 2014;25(1):30-5.
125. Weisse K, Winkler S, Hirche F, Herberth G, Hinz D, Bauer M, et al. Maternal and newborn vitamin D status and its impact on food allergy development in the German LINA cohort study. *Allergy.* 2013;68(2):220-8.
126. Willers SM, Devereux G, Craig LCA, McNeill G, Wijga AH, Abou El-Magd W, et al. Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. *Thorax.* 2007;62(9):773-9.

127. Wills AK, Shaheen SO, Granell R, Henderson AJ, Fraser WD, Lawlor DA. Maternal 25-hydroxyvitamin D and its association with childhood atopic outcomes and lung function. *Clinical & Experimental Allergy*. 2013;43(10):1180-8.
128. Wjst M, Hypponen E. Vitamin D serum levels and allergic rhinitis. *Allergy*. 2007;62(9):1085-6.
129. Wu AC, Tantisira K, Li L, Fuhlbrigge AL, Weiss ST, Litonjua A. Effect of vitamin D and inhaled corticosteroid treatment on lung function in children. *American journal of respiratory and critical care medicine*. 2012; 186(6):508-13.
130. Yadav M, Mittal K. Effect of vitamin D supplementation on moderate to severe bronchial asthma. *Indian journal of pediatrics*. 2014; 81(7):650-4.
131. Yao T-C, Tu Y-L, Chang S-W, Tsai H-J, Gu P-W, Ning H-C, et al. Suboptimal vitamin D status in a population-based study of Asian children: prevalence and relation to allergic diseases and atopy. *PLoS ONE [Electronic Resource]*. 2014;9(6):e99105.
132. Young MW. The effectiveness of weekly iron and vitamin supplementation of Malawian preschool children [2]. *South African medical journal*. 2001; 91(1):49-50.
133. Zhang Q, Ma GS, Greenfield H, Du XQ, Zhu K, Fraser DR. Effects of fortified milk consumption on regional bone mineral accrual in Chinese girls. *Asia Pacific journal of clinical nutrition*. 2003; 12 Suppl:S46.
134. Zhang ZQ, Ma XM, Huang ZW, Yang XG, Chen YM, Su YX. Effects of milk salt supplementation on bone mineral gain in pubertal Chinese adolescents: A 2-year randomized, double-blind, controlled, dose-response trial. *Bone*. 2014; 65:69-76.
135. Zhong H, Zhou X-J, Hong J-G. [1,25-(OH)₂D₃ inhibits lipopolysaccharide-induced expression of interleukin-13 and interleukin-17 in cord blood CD4⁺T cells]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2013;15(9):763-6.

136. Zhu K, Du X, Cowell CT, Greenfield H, Blades B, Dobbins TA, et al. Effects of school milk intervention on cortical bone accretion and indicators relevant to bone metabolism in Chinese girls aged 10-12 y in Beijing. *American journal of clinical nutrition*. 2005; 81(5):1168-75.
137. Zhu K, Greenfield H, Du X, Zhang Q, Fraser DR. Effects of milk supplementation on cortical bone gain in Chinese girls aged 10-12 years. *Asia Pacific journal of clinical nutrition*. 2003; 12 Suppl:S47.
138. Zhu K, Greenfield H, Du X, Zhang Q, Ma G, Hu X, et al. Effects of two years' milk supplementation on size-corrected bone mineral density of Chinese girls. *Asia Pacific journal of clinical nutrition*. 2008; 17 Suppl 1:147-50.
139. Zittermann A, Dembinski J, Stehle P. Low vitamin D status is associated with low cord blood levels of the immunosuppressive cytokine interleukin-10. *Pediatric Allergy & Immunology*. 2004;15(3):242-6.
140. Zoratti EM, Wegienka G. Vitamin D concentration in newborn cord blood is correlated with maternal intake of supplemental vitamin D, and lower levels are associated with increased risk of the infant developing eczema. *Evid Based Nurs*. 2013;16(4):105-6.
141. Zosky GR, Hart PH, Whitehouse AJO, Kusel MM, Ang W, Foong RE, et al. Vitamin D deficiency at 16 to 20 weeks' gestation is associated with impaired lung function and asthma at 6 years of age. *Ann Am Thorac Soc*. 2014;11(4):571-7.

Table S4. Summary of Risk of Bias in *non-randomized studies*.

Allen 2013 (27)

Type of study: Case-control

Participants: Pregnancy women and infants

Experimental intervention: Vitamin D supplementation

Control intervention: No Vitamin D supplementation

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		<i>Bias due to confounding</i>	<i>Bias in selection of participants into the study</i>	<i>Bias in measurement of interventions</i>	<i>Bias due to departures from intended interventions</i>	<i>Bias due to missing data</i>	<i>Bias in measurement of outcomes</i>	<i>Bias in selection of the reported result</i>	
Food allergy	Benefit	Moderate	Moderate	Moderate	Moderate	Low	Moderate	Moderate	MODERATE

Anderson 2015 (26)

Type of study: Cohort

Participants: Pregnancy women and infants

Experimental intervention: Vitamin D supplementation

Control intervention: No Vitamin D supplementation

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		<i>Bias due to confounding</i>	<i>Bias in selection of participants into the study</i>	<i>Bias in measurement of interventions</i>	<i>Bias due to departures from intended interventions</i>	<i>Bias due to missing data</i>	<i>Bias in measurement of outcomes</i>	<i>Bias in selection of the reported result</i>	
Asthma/wheezing	Benefit	Low	Low	Moderate	Moderate	Low	Moderate	Moderate	MODERATE

Bener 2012 (24)

Type of study: Case-control

Participants: Breastfeeding women

Experimental intervention: Vitamin D supplementation

Control intervention: No Vitamin D supplementation

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		<i>Bias due to confounding</i>	<i>Bias in selection of participants into the study</i>	<i>Bias in measurement of interventions</i>	<i>Bias due to departures from intended interventions</i>	<i>Bias due to missing data</i>	<i>Bias in measurement of outcomes</i>	<i>Bias in selection of the reported result</i>	
Asthma	Benefit	Moderate	Serious ¹	Moderate	Serious ²	Low	Moderate	Moderate	MODERATE

1. Controls were sampled from a population that is unlikely to be representative of the population that gave rise to the cases; 2. Switches in treatment, co-interventions, or problems with implementation fidelity are apparent and are not adjusted for in the analyses.

Hypponen 2014 (35)

Type of study: Case-control

Participants: Infants

Experimental intervention: Vitamin D supplementation

Control intervention: Irregular or No Vitamin D supplementation

Outcome	Benefit or harm of intervention	Domains							Overall Risk of Bias
		<i>Bias due to confounding</i>	<i>Bias in selection of participants into the study</i>	<i>Bias in measurement of interventions</i>	<i>Bias due to departures from intended interventions</i>	<i>Bias due to missing data</i>	<i>Bias in measurement of outcomes</i>	<i>Bias in selection of the reported result</i>	
Asthma	Benefit	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate	MODERATE
Allergic rhinitis	Benefit	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Moderate	MODERATE

Table S5. EVIDENCE PROFILES

EVIDENCE PROFILE: PREGNANCY WOMEN

Authors: Juan José Yepes-Nuñez, Jan Brozek, Carlos Cuello-García, Yuan Zhang, Gian Paolo Morgano, Holger Schünemann

Date: January 19, 2015; updated January 30 2016

Question: Vitamin D versus no vitamin D supplementation in **pregnant women** for the prevention of allergy in their children and other important outcomes

Setting: General population

Bibliography: Allen 2013 (1), Anderson 2015 (2), Brooke 1980 (3), Goldring 2013 (4) , Hossain 2014 (5), Mallet 1986 (6), Roth 2013 (7), Sablok (8), Yu 2009 (9)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	No vitamin D supplementation	Relative (95% CI)	Absolute (95% CI)		
Eczema (follow up: 3 years)												
1	randomised trials	serious ¹	not serious	not serious ²	very serious ³	none	30/102 (29.4%)	15/49 (30.6%)	RR 0.96 (0.57 to 1.61)	12 fewer per 1000 (from 132 fewer to 187 more)	VERY LOW	CRITICAL
								1.0% ⁴		0 fewer per 1000 (from 4 fewer to 6 more)		
Allergic rhinitis (follow up: 3 years)												
1	randomised trials	serious ¹	not serious	not serious ²	very serious ⁵	none	11/101 (10.9%)	7/49 (14.3%)	RR 0.76 (0.31 to 1.85)	34 fewer per 1000 (from 99 fewer to 121 more)	VERY LOW	CRITICAL
								14.6% ⁶		35 fewer per 1000 (from 101 fewer to 124 more)		
Asthma/wheezing (follow up: 3 years)												
1	randomised trials	serious ¹	not serious	not serious ²	very serious ⁷	none	17/108 (15.7%)	7/50 (14.0%)	RR 1.12 (0.50 to 2.54)	17 more per 1000 (from 70 fewer to 216 more)	VERY LOW	CRITICAL
								9.4% ⁸		11 more per 1000 (from 47 fewer to 145 more)		
Asthma/wheezing ⁹												
1	observational studies	not serious	not serious	not serious	serious ¹⁰	none	493/2478 (19.9%)	9.4% ⁸	OR 0.65 (0.46 to 0.92) ¹¹	31 fewer per 1000 (from 7 fewer to 48 fewer)	VERY LOW	CRITICAL
Food allergy (follow up: 3 years)												

Quality assessment							N:of patients		Effect		Quality	Importance
N:of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	No vitamin D supplementation	Relative (95%CI)	Absolute (95%CI)		
1	randomised trials	serious ¹	not serious	not serious ²	very serious ¹²	none	12/102 (11.8%)	3/49 (6.1%)	RR 1.92 (0.57 to 6.50)	56 more per 1000 (from 26 fewer to 337 more)	VERY LOW	CRITICAL
								3.3% ¹³		30 more per 1000 (from 14 fewer to 182 more)		
Food allergy												
1	observational studies	not serious	not serious	not serious	serious ¹⁴	none	27 cases 213 controls		OR 1.50 (0.78 to 2.88) ¹⁵	-	VERY LOW	CRITICAL
							-	3.3% ¹³		16 more per 1000 (from 7 fewer to 56 more)		
Rickets												
1	randomised trials	not serious	not serious	not serious	very serious ¹⁶	none	0/59 (0.0%)	0/67 (0.0%)	not estimable	-	LOW	CRITICAL
Nutritional status: birth weight (gr)												
6	randomised trials	not serious	not serious	not serious	serious ¹⁷	none	455	366	-	MD 52.78 more (64.34 fewer to 169.9 more)	MODERATE	CRITICAL
Any adverse events (children)												
2	randomised trials	not serious	not serious	not serious	very serious ¹⁸	none	0/117 (0.0%)	0/117 (0.0%)	not estimable	0 fewer per 1000 (from 20 more to 20 fewer)	LOW	CRITICAL
Any adverse events (mother) (assessed with: Preeclampsia)												
3	randomised trials	serious ¹⁸	not serious	not serious	very serious ¹⁹	none	36/254 (14.2%)	31/266 (11.7%)	RR 1.46 (0.31 to 6.78)	54 more per 1000 (from 80 fewer to 674 more)	VERY LOW	CRITICAL
Serious adverse events (children)												
3	randomised trials	not serious	not serious	not serious	very serious ²⁰	none	8/213 (3.8%)	10/213 (4.7%)	RR 0.79 (0.33 to 1.90)	10 fewer per 1000 (from 31 fewer to 42 more)	LOW	CRITICAL
Serious adverse events (mother)												
2	randomised trials	not serious	not serious	not serious	very serious ²¹	none	12/158 (7.6%)	8/163 (4.9%)	RR 1.55 (0.65 to 3.69)	27 more per 1000 (from 17 fewer to 132 more)	LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio; MD: Mean difference

1. Serious risk of bias. One study that carried large weight for the overall effect estimate rated as high risk of bias due to lack of concealment of allocation, and lack of blinding of participants and caregivers
2. Indirectness. One study assessed the effect of the intervention in 3-year-old children, which was measured in the development of eczema, asthma, allergic rhinitis, or food allergy. The effect of the intervention could be different in children over 3 years old or adults
3. Very serious imprecision. Wide confidence interval with only 45 events in total
4. Difference in anticipated absolute effect was calculated based on the range of prevalence of eczema in International Study for Asthma and Allergy in Childhood (ISAAC) Phase Three (1%) (10)
5. Very serious imprecision. Wide confidence interval with only 18 events in total
6. Difference in anticipated absolute effect was calculated based on the total global prevalence of rhinoconjunctivitis symptoms for the 13- to 14-year old children according with Phase Three ISAAC (14.6%) (11)
7. Very serious imprecision. Wide confidence interval with only 24 events in total
8. Difference in anticipated absolute effect was calculated based on the total global prevalence of asthma symptoms in the 6-7 year old children according with Phase Three ISAAC in 9.4% (12)
9. Wheezing was measured using the ISAAC questionnaire
10. Very serious imprecision. Wide confidence interval with only 128 events in total
11. Odds ratio adjusted by age, sex, body mass index (BMI), outdoor play, daycare attendance, birth weight and breastfeeding duration
12. Very serious imprecision. Wide confidence interval with only 15 events in total
13. Difference in anticipated absolute effect was calculated based on the prevalence of food allergy in the population as a result of food challenge tests to any food according with metanalysis of Rona et al. 2007 (13)
14. Very serious imprecision. Wide confidence interval with only 240 events in total
15. Odds ratio was adjusted by infant formula, history of egg consumption, infant history of eczema, age [in months] at Oral Food Challenge, infant's gender, duration of breastfeeding, infant consumption of fish, number of siblings, socioeconomic status, pet ownership, maternal use of vitamin D supplements during pregnancy, maternal smoking during pregnancy, family history of allergy, filaggrin null mutations, season of birth, and UVR at the month of birth
16. Very serious imprecision with no events in a small study
17. Very serious imprecision. Wide confidence interval crosses 0 from -64.34 to 169.9 grs
18. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to selective outcome reporting in 4 out of 7 studies.
19. Very serious imprecision. Wide confidence interval with only 67 events in total
20. Very serious imprecision. Wide confidence interval with only 18 events in total
21. Very serious imprecision. Wide confidence interval with only 20 events in total

REFERENCES

1. Allen KJ, Koplin JJ, Ponsonby AL, Gurrin LC, Wake M, Vuillermin P, et al. Vitamin D insufficiency is associated with challenge-proven food allergy in infants. *The Journal of allergy and clinical immunology*. 2013;131(4):1109-16, 16 e1-6.
2. Anderson LN, Chen Y, Omand JA, Birken CS, Parkin PC, To T, et al. Vitamin D exposure during pregnancy, but not early childhood, is associated with risk of childhood wheezing. *Journal of developmental origins of health and disease*. 2015;6(4):308-16.
3. Brooke OG, Brown IR, Bone CD, Carter ND, Cleeve HJ, Maxwell JD, et al. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. *British medical journal*. 1980;280(6216):751-4.
4. Goldring ST, Griffiths CJ, Martineau AR, Robinson S, Yu C, Poulton S, et al. Prenatal vitamin d supplementation and child respiratory health: a randomised controlled trial. *PLoS one*. 2013;8(6):e66627.
5. Hossain N, Karani FH, Ramzan S, Kausar R, Ayaz S, Khanani R, et al. Obstetric and neonatal outcomes of maternal vitamin D supplementation: results of an open-label, randomized controlled trial of antenatal vitamin D supplementation in Pakistani women. *The Journal of clinical endocrinology and metabolism*. 2014;99(7):2448-55.
6. Mallet E, Gugi B, Brunelle P, Henocq A, Basuyau JP, Lemeur H. Vitamin D supplementation in pregnancy: a controlled trial of two methods. *Obstetrics and gynecology*. 1986;68(3):300-4.
7. Roth DE, Al Mahmud A, Raqib R, Akhtar E, Perumal N, Pezzack B, et al. Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D3 supplementation in Bangladesh: the AVIDD trial. *Nutrition journal*. 2013;12:47.
8. Sablok A, Thariani K, Batra A, Bharti R, Aggarwal AR, Kabi BC, et al. Supplementation of Vitamin D in pregnancy and its correlation with feto-maternal outcome. *Clinical endocrinology*. 2015; 83(4):536-41.
9. Yu CK, Sykes L, Sethi M, Teoh TG, Robinson S. Vitamin D deficiency and supplementation during pregnancy. *Clin Endocrinol (Oxf)*. 2009;70(5):685-90.

10. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, Group IPTS. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *The Journal of allergy and clinical immunology*. 2009;124(6):1251-8 e23.
11. Ait-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J, et al. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy*. 2009;64(1):123-48.
12. Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2009;64(6):476-83.
13. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. *The Journal of allergy and clinical immunology*. 2007;120(3):638-46.

EVIDENCE PROFILE: BREASTFEEDING WOMEN

Authors: Juan José Yepes-Nuñez, Jan Brozek, Carlos Cuello-García, Yuan Zhang, Gian Paolo Morgano, Holger Schünemann

Date: January 19, 2015; updated January 30 2016

Question: Vitamin D versus no vitamin D supplementation in **breastfeeding women** for the prevention of allergy in their children and other important outcomes

Setting: General population

Bibliography: Bener 2012 (1), Rothberg 1982 (2)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	No vitamin D supplementation	Relative (95% CI)	Absolute (95% CI)		
Eczema												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Allergic rhinitis												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Asthma/wheezing (follow-up: up to 16 years)												
1	observational studies	serious ¹	not serious	not serious ²	serious ³	none	483 cases 483 controls		OR 1.09 (0.84 to 1.40)	-	VERY LOW	CRITICAL
							-	9.4% ⁴		8 more per 1000 (from 14 fewer to 33 more)		
Food allergy												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Rickets (follow up: 6 weeks)												
1	randomised trials	serious ⁵	not serious	not serious	very serious ⁶	none	0/18 (0.0%)	0/10 (0.0%)	not estimable	0 fewer per 1000 (from 140 more to 140 fewer)	VERY LOW	CRITICAL
Any allergy												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Nutritional status												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Adverse events												

Quality assessment							N _e of patients		Effect		Quality	Importance
N _e of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	No vitamin D supplementation	Relative (95% CI)	Absolute (95% CI)		
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Severe adverse events												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL

CI: Confidence interval; OR: Odds ratio

1. Serious risk of bias. Controls were sampled from a population that is unlikely to be representative of the population from which cases were selected, and analysis was not adjusted for confounding factors
2. Indirectness. Over 80% of the children in the study had mild to severe vitamin D deficiency
3. Serious imprecision. Wide confidence interval with 483 events in total
4. Difference in anticipated absolute effect was calculated based on the total global prevalence of asthma symptoms in the 6-7 year old children according with Phase Three ISAAC in 9.4%(3)
5. Serious risk of bias. One study that carried large weight for the overall effect estimate rated as unclear risk of bias due to insufficient information about random sequence generation, allocation concealment, and incomplete outcome data
6. Very serious imprecision with no events in a small study

REFERENCE

1. Bener A, Ehlayel MS, Tulic MK, Hamid Q. Vitamin D deficiency as a strong predictor of asthma in children. International archives of allergy and immunology. 2012;157(2):168-75.
2. Rothberg AD, Pettifor JM, Cohen DF, Sonnendecker EW, Ross FP. Maternal-infant vitamin D relationships during breast-feeding. The Journal of pediatrics. 1982;101(4):500-3.
3. Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax. 2009;64(6):476-83.

EVIDENCE PROFILE: INFANTS

Authors: Juan José Yepes-Nuñez, Jan Brozek, Carlos Cuello-García, Yuan Zhang, Gian Paolo Morgano, Holger Schünemann

Date: January 19, 2015; updated January 30 2016

Question: Vitamin D versus no vitamin D supplementation in **infants** for the prevention of allergy and other important outcomes

Setting: General population

Bibliography: Allen 2013 (1), Alonso 2011 (2), Anderson 2015 (3), Chan 1982 (4), Greer 1982 (5), Hyppönen 2004 (6), Madar (7), Ponnappakkam (8):

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	no intervention/placebo	Relative (95% CI)	Absolute (95% CI)		
Eczema												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Allergic rhinitis (follow up: 31 years) ¹												
1	observational studies	serious ²	not serious	not serious	serious ³	none	1974/6748 (29.3%)	3/20 (15.0%)	RR 1.95 (0.69 to 5.54)	143 more per 1000 (from 47 fewer to 681 more)	VERY LOW	CRITICAL
								14.6% ⁴		139 more per 1000 (from 45 fewer to 663 more)		
Asthma/wheezing (follow up: 31 years) ¹												
1	observational studies	serious ²	not serious	not serious	serious ⁵	none	470/6748 (7.0%)	0/20 (0.0%)	RR 3.07 (0.19 to 50.88)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	CRITICAL
								9.4% ⁶		195 more per 1000 (from 76 fewer to 1000 more)		
Asthma/wheezing (follow up: 72 months) ⁷												
1	observational studies	not serious	not serious	not serious	serious ⁸	none	493/2478 (19.9%)	9.4%	OR 1.00 (0.81 to 1.23)	0 fewer per 1000 (from 16 fewer to 19 more)	VERY LOW	CRITICAL
Food allergy (follow up: 1 years)												
1	observational studies	serious ⁹	not serious	serious ¹⁰	serious ¹¹	none	21/274 (7.7%)	30/207 (14.5%)	OR 0.49 (0.27 to 0.88)	68 fewer per 1000 (from 15 fewer to 101 fewer)	VERY LOW	CRITICAL
								3.3% ¹²		17 fewer per 1000 (from 4 fewer to 24 fewer)		
Rickets (follow up: range 2 months to 12 months)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	no intervention/placebo	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	serious ¹³	not serious	serious ¹⁴	serious ¹⁵	none	0/86 (0.0%)	0/91 (0.0%)	not estimable	0 fewer per 1000 (from 40 more to 40 fewer)	VERY LOW	CRITICAL
Nutritional status (body weight in grams) (follow up: range 6 months to 12 months)												
1	randomised trials	serious ¹⁶	not serious	not serious	serious ¹⁷	none	36	44	-	0 (0 to 0)	LOW	CRITICAL
Any adverse events												
2	randomised trials	serious ¹⁸	not serious	not serious	serious ¹⁹	none	4/58 (6.9%)	4/51 (7.8%)	RR 0.85 (0.23 to 3.14)	12 fewer per 1000 (from 60 fewer to 168 more)	LOW	CRITICAL
Serious adverse events												
1	randomised trials	serious ²⁰	not serious	not serious	serious ²¹	none	0/17 (0.0%)	1/8 (12.5%)	RR 0.17 (0.01 to 3.70)	104 fewer per 1000 (from 124 fewer to 338 more)	LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio

- Information corresponds to case control study, Hypponen 2004 (6)
- Serious risk of bias. Criteria for diagnosis of asthma and allergic rhinitis were not provided, and results were not adjusted for confounding factors
- Serious imprecision. Wide confidence interval with only 3 events in total
- Difference in anticipated absolute effect was calculated based on the total global prevalence of rhinoconjunctivitis symptoms for the 13- to 14-year old children according with the International Study for Asthma and Allergy in Childhood (ISAAC) Phase Three (14.6%) (9)
- Serious imprecision. Wide confidence interval with only 470 events in total and not no events in a small control group
- Difference in anticipated absolute effect was calculated based on the total global prevalence of asthma symptoms in the 6-7 year old children according with Phase Three ISAAC (9.4%) (10)
- Information corresponds to cohort study, Anderson 2015 (3)
- Serious imprecision. Wide confidence interval
- Serious risk of bias. Results were not adjusted for confounding factors
- Serious indirectness. The outcome was measured after 1 year of life, which is likely a short frame time to reliably measure development of food allergy
- Serious imprecision with only 51 events in total
- Difference in anticipated absolute effect was calculated based on the prevalence of food allergy in the population as a result of food challenge tests to any food according with meta-analysis of Rona et al. 2007 (3.3%) (11)
- Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to lack of blinding in 2 out of 4 studies and incomplete outcome data in 2 out of 4 studies
- Serious indirectness. Patients included in the study were follow-up from 2 to 12 months which is not long enough for assessing development of rickets
- Serious imprecision. Wide confidence interval with no events among 177 children
- Serious risk of bias. One study that carried large weight for the overall effect estimate rated as high risk of bias due to lack of random sequence generation
- Serious imprecision. Mean weights were not significant different between patients who received vitamin D supplementation versus no vitamin D supplementation. Mean values was displayed in a graphic
- Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as high risk of bias due to incomplete outcome data in 2 out of 3 studies
- Serious imprecision. Wide confidence interval with only 8 events in total
- Serious risk of bias. One study that carried large weight for the overall effect estimate rated as high risk of bias due to incomplete outcome data
- Serious imprecision. Wide confidence interval with only 1 events in total

REFERENCES

1. Allen KJ, Koplin JJ, Ponsonby AL, Gurrin LC, Wake M, Vuillermin P, et al. Vitamin D insufficiency is associated with challenge-proven food allergy in infants. *The Journal of allergy and clinical immunology*. 2013;131(4):1109-16, 16 e1-6.
2. Alonso A, Rodriguez J, Carvajal I, Prieto MA, Rodriguez RM, Perez AM, et al. Prophylactic vitamin D in healthy infants: assessing the need. *Metabolism: clinical and experimental*. 2011;60(12):1719-25.
3. Anderson LN, Chen Y, Omand JA, Birken CS, Parkin PC, To T, et al. Vitamin D exposure during pregnancy, but not early childhood, is associated with risk of childhood wheezing. *Journal of developmental origins of health and disease*. 2015;6(4):308-16.
4. Chan GM, Roberts CC, Folland D, Jackson R. Growth and bone mineralization of normal breast-fed infants and the effects of lactation on maternal bone mineral status. *The American journal of clinical nutrition*. 1982;36(3):438-43.
5. Greer FR, Searcy JE, Levin RS, Steichen JJ, Steichen-Asche PS, Tsang RC. Bone mineral content and serum 25-hydroxyvitamin D concentrations in breast-fed infants with and without supplemental vitamin D: one-year follow-up. *The Journal of pediatrics*. 1982;100(6):919-22.
6. Hypponen E, Sovio U, Wjst M, Patel S, Pekkanen J, Hartikainen AL, et al. Infant vitamin d supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. *Annals of the New York Academy of Sciences*. 2004;1037:84-95.
7. Madar AA, Klepp KI, Meyer HE. Effect of free vitamin D(2) drops on serum 25-hydroxyvitamin D in infants with immigrant origin: a cluster randomized controlled trial. *European journal of clinical nutrition*. 2009;63(4):478-84.
8. Ponnappakkam T, Bradford E, Gensure R. A treatment trial of vitamin D supplementation in breast-fed infants: universal supplementation is not necessary for rickets prevention in Southern Louisiana. *Clinical pediatrics*. 2010;49(11):1053-60.
9. Ait-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J, et al. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy*. 2009;64(1):123-48.
10. Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2009;64(6):476-83.
11. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. *The Journal of allergy and clinical immunology*. 2007;120(3):638-46.

EVIDENCE PROFILE: *CHILDREN*

Authors: Juan José Yepes-Nuñez, Jan Brozek, Carlos Cuello-García, Yuan Zhang, Gian Paolo Morgano, Holger Schünemann

Date: January 19, 2015; updated January 30 2016

Question: Vitamin D versus no vitamin D supplementation in **children** for the prevention of allergy and other important outcomes

Setting: General population

Bibliography: Abrams 2013 (1), Guillemant 2001 (2), Khadilkar 2010 (3), Lewis 2013 (4), Maalouf 2008 (5), Mølgaard 2010 (6), Rajakumar 2015 (7), Rich Edwards 2011 (8), Urashima 2010 (9), Vjakainen 2006 (10), Ward 2010 (11)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	no intervention/placebo	Relative (95% CI)	Absolute (95% CI)		
Eczema												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Allergic rhinitis												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Asthma/wheezing												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Food allergy												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Rickets												
0	-	-	-	-	-	-	-	-	not estimable	-	-	CRITICAL
Nutritional status												
3	randomised trials	serious ¹	not serious	not serious	serious ²	none	320	175	-	MD 0.87 kg more (0.1 more to 1.64 more)	LOW	CRITICAL
Any adverse events												
8	randomised trials	not serious	not serious	not serious	serious ³	none	8/1285 (0.6%)	5/610 (0.8%)	RR 0.78 (0.26 to 2.32)	2 fewer per 1000 (from 6 fewer to 11 more)	MODERATE	CRITICAL
Serious adverse events												
1	randomised trials	serious ⁴	not serious	not serious	serious ⁵	none	1/46 (2.2%)	1/34 (2.9%)	RR 0.74 (0.05 to 11.40)	8 fewer per 1000 (from 28 fewer to 306 more)	LOW	CRITICAL

CI: Confidence interval; MD: Mean difference; RR: Risk ratio; OR: Odds ratio

1. Serious risk of bias. Studies that carried large weight for the overall effect estimate rated as unclear risk of bias due to insufficient information about random sequence generation, allocation concealment, blinding of outcome assessment, and incomplete outcome data in all studies
2. Serious imprecision. Wide confidence interval including only 495 patients in total
3. Serious imprecision. Wide confidence interval with only 13 events in total
4. Serious risk of bias. One study that carried large weight for the overall effect estimate rated as unclear risk of bias due to insufficient information about allocation concealment, and blinding of outcome assessment
5. Serious imprecision. Wide confidence interval with only 2 events in total

REFERENCES

1. Abrams SA, Hawthorne KM, Chen Z. Supplementation with 1000 IU vitamin D/d leads to parathyroid hormone suppression, but not increased fractional calcium absorption, in 4-8-y-old children: a double-blind randomized controlled trial. *The American journal of clinical nutrition*. 2013;97(1):217-23.
2. Guillemant J, Le HT, Maria A, Allemandou A, Peres G, Guillemant S. Wintertime vitamin D deficiency in male adolescents: effect on parathyroid function and response to vitamin D3 supplements. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2001;12(10):875-9.
3. Khadilkar AV, Sayyad MG, Sanwalka NJ, Bhandari DR, Naik S, Khadilkar VV, et al. Vitamin D supplementation and bone mass accrual in underprivileged adolescent Indian girls. *Asia Pacific journal of clinical nutrition*. 2010;19(4):465-72.
4. Lewis RD, Laing EM, Hill Gallant KM, Hall DB, McCabe GP, Hausman DB, et al. A randomized trial of vitamin D(3) supplementation in children: dose-response effects on vitamin D metabolites and calcium absorption. *The Journal of clinical endocrinology and metabolism*. 2013;98(12):4816-25.
5. Maalouf J, Nabulsi M, Vieth R, Kimball S, El-Rassi R, Mahfoud Z, et al. Short- and long-term safety of weekly high-dose vitamin D3 supplementation in school children. *The Journal of clinical endocrinology and metabolism*. 2008;93(7):2693-701.
6. Molgaard C, Larnkjaer A, Cashman KD, Lamberg-Allardt C, Jakobsen J, Michaelsen KF. Does vitamin D supplementation of healthy Danish Caucasian girls affect bone turnover and bone mineralization? *Bone*. 2010;46(2):432-9.
7. Rajakumar K, Moore CG, Yabes J, Olabopo F, Haralam MA, Comer D, et al. Effect of Vitamin D3 Supplementation in Black and in White Children: A Randomized, Placebo-Controlled Trial. *The Journal of clinical endocrinology and metabolism*. 2015;100(8):3183-92.
8. Rich-Edwards JW, Ganmaa D, Kleinman K, Sumberzul N, Holick MF, Lkhagvasuren T, et al. Randomized trial of fortified milk and supplements to raise 25-hydroxyvitamin D concentrations in schoolchildren in Mongolia. *The American journal of clinical nutrition*. 2011;94(2):578-84.
9. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *The American journal of clinical nutrition*. 2010;91(5):1255-60.
10. Viljakainen HT, Natri AM, Karkkainen M, Huttunen MM, Palssa A, Jakobsen J, et al. A positive dose-response effect of vitamin D supplementation on site-specific bone mineral augmentation in adolescent girls: a double-blinded randomized placebo-controlled 1-year intervention. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*. 2006;21(6):836-44.
11. Ward KA, Das G, Roberts SA, Berry JL, Adams JE, Rawer R, et al. A randomized, controlled trial of vitamin D supplementation upon musculoskeletal health in postmenarchal females. *The Journal of clinical endocrinology and metabolism*. 2010;95(10):4643-51.