National Allergy Centre of Excellence

Vitamin D for the prevention of food allergy and eczema: Protocol for a living systematic review

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Declaration of interests

SCD, DJP, RLP, KR, KPP, JJK and AJL have contributed as investigators to trials which may be eligible for inclusion in this review. Any review team members named as authors on reports identified for potential inclusion in this review will not be involved in screening, data extraction or quality appraisal for those studies.

Additional interests declared by members of the review team but deemed not to require management in relation to this review are described in **Appendix 1**.

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Introduction

Both eczema (atopic dermatitis) and food allergy are common conditions and major public health issues(2). Eczema is a chronic skin inflammatory disorder characterised by red, itchy, scaly and dry skin(3). Food allergy is an adverse immunologic response to a dietary protein, manifesting symptoms in the skin, gastrointestinal and respiratory tracts(4, 5). Both eczema and food allergy can occur at any age but more than half of the cases occur within the first year of life.(5) Globally, the prevalence of current eczema ranges from 0.9% to 22.5% in children aged 6 to 7 years and up to 24.6% in children aged 13 to 14 years(6). The prevalence of food allergy, based on oral food challenges (OFC), varies by region and ranges from 1% to 10% in infants and preschool children (7). Although for some, eczema and food allergies may resolve with increasing age, a large number of children have persistent eczema and food allergies through later childhood and adolescence(8). Eczema and food allergy frequently co-exist, and infants with early onset eczema are more prone to the development and persistence of food allergy(9-12). Both eczema and food allergy bring heavy clinical, social, psychological and economic burdens to the children and their families as well as the healthcare system(13-23). Currently, there is no cure for eczema or food allergies, so there is a need to identify strategies that are effective in preventing their occurrence.

It has been hypothesised that low levels of maternal and infant vitamin D may play an important role in the aetiology of eczema and food allergy.(24, 25) Vitamin D has two forms, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). More than 90% of the formation of vitamin D3 is triggered by skin sunlight exposure (UVB radiation)(26). However, due to the modern more indoor-centred lifestyle and increasing sun protection behaviours such as the use of sunscreen, vitamin D deficiency remains a global problem in all age groups, particularly in pregnant women and infants(27). Vitamin D can also be obtained from diet or supplements.(28-30) In some countries like Canada, Norway, Finland, Sweden and the United States, milk products are mandatorily or voluntarily fortified with vitamin D, while other countries, such as Australia, do not have formal public health fortification programs. Therefore, vitamin D supplementation may be required to maintain a sufficient vitamin D status. The recommended dose of vitamin D intake (from diet and/or supplementation) varies among countries and scientific societies, ranging from 400IU to 1000 IU per day(31). Pregnant women and other people at high risk of vitamin D deficiency may need a higher dose of vitamin D supplementation(32). Vitamin D influences the immune system both in utero and during the postnatal period(33, 34). The complex of vitamin D and its receptor (VDR) has been found to maintain the balance between Type 1 and Type 2 T helper cell (Th1/Th2) responses and suppress Th17. In addition, vitamin D can enhance the development and function of T regulatory cells (Tregs)(35) and inhibit the maturation and differentiation of dendritic cells (DCs)(36), promoting the production of anti-inflammatory cytokines like IL-10 by Tregs and DCs, thereby maintaining immune homeostasis and reducing inflammation. Vitamin D may inhibit the production of IgE, decrease skin inflammation and sensitisation, and ultimately reduce eczema and food allergy(37). As eczema and food allergy generally present in the first year of life, an adequate level of vitamin D during pregnancy and early life may be critical to reduce the occurrence and development of eczema and food allergy in the offspring(38, 39).

There is some evidence that vitamin D levels are associated with the risk of developing eczema and food allergy. Vitamin D deficiency and allergic diseases are more prevalent in areas further from the equator(40) (41) (42, 43). It has been suggested that latitude can serve as a proxy for UV light exposure, and that UVB inhibiting T cell responses and skin inflammation leads to lower prevalence of allergic disease closer to the equator(44). Our recent systematic review of six cohort studies showed that higher levels of cord blood vitamin D were consistently associated with reduced risk of eczema prevalence in early childhood(1). Since cord blood vitamin D levels are highly correlated with maternal vitamin D levels during pregnancy, especially in the third trimester (45, 46), it is possible that maternal vitamin D supplementation, leading to high levels of maternal vitamin D, may prevent the development of eczema in the offspring. However, our systematic review showed that existing observational studies have not observed an association between maternal vitamin D levels and eczema or food allergy risk in the offspring. As the measured vitamin D levels are largely determined by UV light exposure (47), the observed association between vitamin D levels and eczema/food allergy may be due to other effects of UV light(48), a possibility that observational studies cannot rule out. In contrast, outcomes of clinical trials may provide stronger evidence on the role of vitamin D supplementation in the aetiology of these conditions.

To date, four randomised controlled trials (RCTs) have explored the effect of maternal vitamin D supplementation during pregnancy on the primary prevention of eczema(49-53) or food allergy(53) in offspring, and only two trials investigated vitamin D supplementation during infancy for the prevention of

eczema and food allergy in childhood(54-56). These RCTs have not shown a consistent protective effect on offspring's eczema, and only three trials have examined food allergy as an outcome. The lack of observed effects may be due to a) lack of statistical power, b) the contamination of the control group as some trials gave 400IU/day of vitamin D to the control groups(49-51, 56), or c) the inclusion criteria with pregnant women or children with sufficient levels of vitamin D being included, when these individuals may not benefit from supplementation(52, 54, 55). Finally, there were significant differences in the interventions tested in these trials, with the vitamin D supplementation dose ranging from 400 IU (55, 57)to 4400 IU daily(50, 51), which may influence the impact of the supplementation. Therefore, the existing trial-based evidence is insufficient to make a recommendation on the routine use of vitamin D for the prevention of eczema or food allergy(1). There are some clinical trials(58) that are due to be published in the coming years, so it is important to review and synthesise the findings from these RCTs regularly so that they can be rapidly incorporated into public health guidelines.

Review questions

This Living Systematic Review (LSR) will examine RCT evidence to address the following questions:

1. Does maternal vitamin D supplementation during pregnancy influence the offspring's risk of developing eczema and/or food allergy?
2. Does maternal vitamin D supplementation during lactation influence the offspring's risk of developing eczema and/or food allergy?
3. Does vitamin D supplementation during infancy influence the risk that the infant will go on to develop eczema and/or food allergy?

Living mode

Vitamin D supplementation is safe, affordable and easy to implement, and despite the lack of recommendations on this topic in current Australian guidelines for the prevention of allergic disease, infant vitamin D supplementation for allergy prevention is making its way into community practice. A recent review and quality assessment of global guidelines for the prevention of atopic dermatitis and food allergy identified vitamin D supplementation in mothers and infants as a gap in current guidelines due to a lack of consistent data from high quality RCTs(59).

The most recent systematic review on this topic concluded that "further trials with maternal and infant supplementation are needed to confirm if vitamin D supplementation can effectively prevent eczema or food allergy in childhood," and Tham et al. have recommended future trials focusing on dosage, duration of use and targeted users(1, 59).

As such, the question of whether to encourage maternal and/or infant supplementation with vitamin D for the prevention of eczema and/or food allergy meets the criteria for a living systematic review (LSR)(60):

1. priority for decision making
2. certainty in the existing evidence is low
3. there is likely to be new research evidence

This protocol describes the establishment of a LSR to ensure that new evidence on this potential intervention can be efficiently synthesised to inform up-to-date guidelines and future research.

Methods

The protocol for this LSR has been developed and reported with reference to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement(61) and the PRISMA extension for LSR (PRISMA-LSR)(62), and will be registered with the International Prospective Register of Systematic Reviews (PROSPERO).

This LSR has been developed as an extension of the systematic review published by Zeng et al in 2023((1, 59). Whilst this baseline systematic review examined both RCT and observational studies, in order to ensure feasibility of the living approach and focus on the evidence that is most directly applicable to guidelines, only

the examination of RCT evidence will be transitioned to living mode. Changes to the methods from the baseline review are detailed in the **Changes to the methods** section below.

Living mode parameters

Searches will be conducted every 3 months. Unscheduled searches may be triggered by the LSR team becoming aware of the publication of an eligible RCT or on request from guideline developers. Following each new search, a summary document will be added to the Open Science Framework (OSF) Project for this living overview at doi:10.17605/OSF.IO/CWX7D, including a PRISMA-LSR flow diagram and summary text describing the most recent search results.

As the outcomes of interest for this review are currently based on evidence from at most four RCTs, each with very low to moderate certainty of evidence (GRADE), subsequent steps of the review ("full update" consisting of data extraction, risk of bias assessment, analysis, certainty of evidence assessment and publication) will be triggered by the identification of any new eligible RCT, or additional or discrepant relevant data from a previously included RCT via additional publications, corrections or retractions. These criteria will be re-evaluated by the review team following each full update.

The appropriateness of the living review approach (search frequency, review questions, search strategy, eligibility criteria and data extraction) will be reassessed by the review team on at least an annual basis. The review will be retired from living mode based on consensus amongst the review team or when required resources become unavailable.

Knowledge user involvement

Key stakeholders in this living review include those responsible for the development and dissemination of guidance for allergy prevention, the intended recipients of this guidance, and those designing and conducting future research on this topic.

Knowledge users consulted in the development of this protocol include representatives from the Australasian Society of Clinical Immunology and Allergy (ASCIA), the National Allergy Council (NAC), Allergy & Anaphylaxis Australia (A&AA), the Centre for Food Allergy Research (CFAR) and the National Allergy Centre of Excellence (NACE).

Knowledge users will be consulted during each reassessment of the living review approach, and prior to the dissemination of results from any full update of the review.

Eligibility criteria

Table 1: Eligibility criteria

	Inclusion criteria	Exclusion criteria
Publication type	Peer-reviewed publications	Publications that do not report original data Conference abstracts Preprints
Publication language	All languages	
Publication date	For **Update 1.1**: from inception to present For future updates: since last search update	
Study type	Randomised controlled trials	Other study designs, including quasi-randomised controlled trials, non-randomised controlled trials

Table 1: Eligibility criteria (continued)

	Inclusion criteria	Exclusion criteria
Setting	All settings	
Population	Pregnant and/or breastfeeding women, at the time of intervention: - Any maternal age - Any stage of pregnancy AND/OR breastfeeding - Any (including unknown) risk/diagnosis/family history of allergic disease Infants[a], at the time of intervention: - Any (including unknown) risk or family history of allergic disease - Any diagnosis of allergic disease other than the target condition [a]Infancy as defined by the study, or 0-12 months of age if not specified	
Intervention	Maternal and/or infant supplementation with vitamin D	Behavioural interventions targeting increased vitamin D exposure Complex interventions that include differences in vitamin D exposure coupled with other differences between the treatment groups Interventions with the aim of treating existing allergic conditions, rather than preventing the development of eczema or food allergy
Comparator	No vitamin D supplementation (including placebo) Varying dosage of vitamin D supplementation, when the only difference between groups is level of vitamin D in the supplement	

Table 1: Eligibility criteria (continued)

	Inclusion criteria	Exclusion criteria
Outcome	Eczema or food allergy in offspring (maternal intervention) or individual (infant intervention) Outcomes assessed at any age and defined as: Eczema - (i) (parental report of) doctor-diagnosed eczema, or assessed by (ii) International Study of Asthma and Allergies in Children (ISAAC) criteria(63), (iii) Hanifin & Rajka criteria(64) or (iv) the UK Working Party's diagnostic criteria(65) Food allergy - (i) positive oral food challenge, and/or (ii) clinical history and evidence of sensitisation to the trigger allergen (positive skin prick test or sIgE), and/or (iii) (parental report of) doctor-diagnosed food allergy Safety outcomes as reported by the study	Non-IgE-mediated food allergies or intolerances, non-eczematous skin conditions Outcomes assessed prior to intervention

Search strategy

We will search the PubMed, Embase (Elsevier) and Cochrane Library (Wiley) Central Register of Controlled Trials (CENTRAL) databases for original articles, with searches for **Update 1.1** including articles published from inception to present, and future updates restricted to articles published since the date of the last search. In addition, we will conduct an annual search of the following registries to identify RCTs in progress which might meet the eligibility criteria for this review: ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and the Australian New Zealand Clinical Trials Registry (ANZCTR).

The search strategies for this living review were developed by a health sciences librarian (GV). The PubMed search was adapted from the baseline review(1) and underwent peer review (DH) using the Peer Review of Electronic Search Strategies (PRESS) checklist(66) before translation to additional databases. Full search strategies and modifications from the baseline searches are reported in **Appendix 2**.

Search strategies will be reviewed and updated on an annual basis in consultation with a health sciences librarian.

Study selection

Search results will be uploaded to Endnote(67) for removal of duplicates, then remaining records will be uploaded to Covidence(68) for removal of previously unidentified duplicates. All screening, both title and abstract and full text review, will be conducted in Covidence by two independent reviewers. Discrepancies between reviewers will be resolved through discussion, with involvement of a third reviewer if necessary.

Results for each search update will be documented using a PRISMA-LSR Flow Diagram(62).

Data extraction

Following each search update data extraction will be conducted independently by two members of the review team using a pre-piloted extraction form in Excel. Data to be extracted will include study characteristics, participant eligibility criteria, timing and method of vitamin D intervention (pregnancy, lactation, or infancy), comparator interventions, outcomes accessed (eczema and/or food allergy), effect estimates and safety outcomes where applicable. Discrepancies between reviewers will be resolved through discussion, with involvement of a third reviewer if necessary. For previously included studies, any updated information resulting from additional publications, corrections or retractions will also be extracted and incorporated.

Where necessary, corresponding authors will be contacted to request missing or additional data or clarification.

Risk of bias assessment

For each included trial, two independent reviewers will use the Cochrane Risk of Bias 2 (RoB 2.0) tool to assess the risk of bias for each reported food allergy and/or eczema outcome for the effect of assignment to intervention at baseline (intention-to-treat (ITT) effect)(69). Disagreements will be resolved through discussion and by consulting a third reviewer if necessary.

Risk of bias assessments for previously included studies will be updated as required by the identification of any additional or discrepant relevant data as a result of additional publications, corrections or retractions.

Data synthesis

All analyses will be performed using Stata version 18 or later(70).

Characteristics of the included studies

We will present clinical and methodological characteristics of the study populations (including location and latitude of the study population, stage of pregnancy or age of infant at intervention, maternal or infant race/ethnicity, family history, and allergy status), in addition to details of the intervention in appropriate tables.

Meta-analysis models

We will synthesise the findings with meta-analyses when there are two or more RCTs with low risk of bias and similar study designs with comparable interventions and outcomes. Prevalence and cumulative incidence results will be reported separately according to the type (maternal or infant) and time (during pregnancy or breastfeeding, at birth or during infancy) of vitamin D supplementation. Because eczema and food allergy may resolve during childhood, outcomes will be pooled in the following categories based on the median/mean age of participants at outcome assessment: infancy (0-2 years of age), early childhood (3-6 years of age), later childhood (7-9 years of age) and adolescence (10-14 years of age). Estimates of odds ratios (ORs) and their corresponding 95% Confidence Intervals (CIs) will be converted to risk ratios (RRs) using the following formula: $RR = OR/[(1 - P_0) + (P_0 \times OR)]$, where P_0 is the risk of eczema or food allergy in the control group. In studies reporting mean differences instead of risk estimates, authors will be contacted to recalculate the risk estimates as RRs.

We will fit random-effects meta-analysis models and estimate τ^2 using the restricted maximum likelihood estimator (REML). Heterogeneity will be assessed using the I^2 and τ^2 statistics (I^2 > 30%, moderate heterogeneity; I^2 > 75%, considerable heterogeneity). If I^2 is larger than 75%, we will not present pooled results and will explore possible reasons for high heterogeneity, including population latitude or baseline level of vitamin D, dose of vitamin D used in the intervention and/or control group, or family/personal history of allergic disease. Forest plots will be presented to visualise the distribution of effects across included trials separately for each outcome.

Results will be reported separately for the time of vitamin D supplementation (during pregnancy, breastfeeding or infancy) and outcome assessment (infancy, early childhood, later childhood and adolescence). If more than 10 RCTs meet the eligibility criteria for a given outcome, small study effects will be assessed visually using funnel plots.

Sensitivity analyses

We will conduct a sensitivity analysis where we include all RCTs (i.e., do not restrict to only those with low risk of bias). If maternal interventions span both pregnancy and breastfeeding, these results will be included in the analyses for both intervention time periods, with sensitivity analyses removing these results.

Certainty of evidence

We will use the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) methodology to rate the certainty in the body of evidence in our key findings(71).

Changes to the methods

For **Update 1.1**, the following changes have been made from the baseline overview:

Eligibility criteria

Publication language: The baseline review excluded non-English language studies. Publications in all languages will be eligible for the LSR in order to reduce the risk of bias as advised by the Cochrane Handbook(72). For reports where an official translation to English language is not available from the publisher, Google Translate will be used in the first instance, with additional translation assistance sought where possible.

Study type: The baseline review synthesised evidence from both (a) RCTs that investigated the effect of vitamin D supplementation during pregnancy or infancy on the risk of eczema and food allergy in childhood, and (b) prospective cohort studies and case-cohort studies that measured the maternal antenatal, cord blood or infant 25-hydroxyvitamin D (25(OH)D) levels and/or maternal or infant dietary intake prior to the assessment of eczema/food allergy. To ensure feasibility and focus on the type of evidence that is most directly applicable to guidelines, the LSR will examine only RCT evidence (a).

Non-randomised and quasi-randomised trials were also eligible for inclusion in part (a) of the baseline review. Given that all six trials identified in the baseline systematic review were randomised and scored well in the randomisation domain of RoB 2.0, only RCTs will be eligible for the LSR.

Population: The population has been expanded from the baseline systematic review to include maternal interventions during breastfeeding as well as pregnancy. Maternal supplementation with high doses of vitamin D during breastfeeding can potentially increase vitamin D content of breastmilk and thus vitamin D intake in breastfed infants(73).

Outcomes: The definitions for eczema and food allergy outcomes have been clarified from the baseline systematic review. None of the RCTs included in the baseline systematic review used the most subjective criteria ‘parental report of using eczema medication’ or ‘parental report of food allergy including medication or history’, so these criteria were removed to focus only on more objective definitions.

Given the importance of considering safety outcomes in guideline development, the LSR will examine safety outcomes in addition to eczema and food allergy.

Search strategy

The search strategy from the baseline review has been modified in line with the revised eligibility criteria described above. Additional modifications were made to correct errors in the original search and to translate the search to the database platforms available at the primary institute of the LSR team.

Specific modifications are reported along with the full search strategy in **Appendix 2**.

Data synthesis

The baseline systematic review reported meta-analysis of outcomes from all eligible RCTs regardless of risk of bias, with a restricted analysis using only studies with low risk of bias. For this living systematic review, the primary analysis will be meta-analysis of RCTs with low risk of bias. We will also conduct a conduct a sensitivity analysis including all RCTs, consistent with the baseline systematic review methods.

The baseline systematic review focused on results reported closest to 1 year of age and at the longest follow-up. The living systematic review will instead pool outcomes in the following categories, based on the median/mean age of participants at outcome assessment: infancy (0-2 years of age), early childhood (3-6 years of age), later childhood (7-9 years of age) and adolescence (10-14 years of age). The baseline review presented odds ratios, whereas this living review will present risk ratios, which is the commonly used metric in randomised trials.

The baseline review used both fixed and random-effects models for meta-analysis, whereas this living review will fit only random-effects meta-analysis models and estimate τ^2 using restricted maximum likelihood estimator (REML). Random-effects meta-analysis allows for heterogeneity between the eligible trials, rather than assume that the observed differences from the trial results are due solely to chance(74).

If this living review identifies more than 10 RCTs which meet the eligibility criteria for a given outcome, we have pre-specified that small study effects will be assessed visually using funnel plots. This has been added because funnel plots are only recommended with more than 10 RCTs.

Ethics and dissemination

Ethical approval is not required as this living review will only include data from previously published studies.

The results of each update of this living review will be made publicly available as a summary document through the OSF Project at doi:10.17605/OSF.IO/CWX7D. This living review is intended to support the rapid translation of evidence into guidelines for allergy prevention and may be used to inform future studies and reviews.

References

1. Zeng R, Li Y, Shen S, Qiu X, Chang CL, Koplin JJ, et al. Is antenatal or early-life vitamin D associated with eczema or food allergy in childhood? A systematic review. *Clin Exp Allergy.* 2023;53(5):511-25.
2. Pawankar R, Canonica GW, Holgate ST, and Lockey RF. Allergic diseases and asthma: a major global health concern. *Curr Opin Allergy Clin Immunol.* 2012;12(1):39-41.
3. Schmitt J, Apfelbacher CJ, and Flohr C. Eczema. *BMJ Clin Evid 2011;2011.* 2011.
4. Waserman S, and Watson W. Food allergy. *Allergy Asthma Clin Immunol.* 2011;7 Suppl 1(Suppl 1):S7.
5. Renz H, Allen KJ, Sicherer SH, Sampson HA, Lack G, Beyer K, et al. Food allergy. *Nat Rev Dis Primers.* 2018;4:17098.
6. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, and Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol.* 2009;124(6):1251-8.e23.
7. Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn J, Fiocchi A, et al. A global survey of changing patterns of food allergy burden in children. *World Allergy Organ J.* 2013;6(1):21.
8. Peters RL, Soriano VX, Allen KJ, Tang MLK, Perrett KP, Lowe AJ, et al. The Prevalence of IgE-Mediated Food Allergy and Other Allergic Diseases in the First 10 Years: The Population-Based, Longitudinal HealthNuts Study. *J Allergy Clin Immunol Pract.* 2024;12(7):1819-30 e3.
9. Hill DJ, Heine RG, Hosking CS, Brown J, Thiele L, Allen KJ, et al. IgE food sensitization in infants with eczema attending a dermatology department. *J Pediatr.* 2007;151(4):359-63.
10. Hill DJ, Hosking CS, de Benedictis FM, Oranje AP, Diepgen TL, Bauchau V, et al. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. *Clin Exp Allergy.* 2008;38(1):161-8.
11. Peters RL, Guarnieri I, Tang MLK, Lowe AJ, Dharmage SC, Perrett KP, et al. The natural history of peanut and egg allergy in children up to age 6 years in the HealthNuts population-based longitudinal study. *J Allergy Clin Immunol.* 2022;150(3):657-65 e13.
12. Martin PE, Eckert JK, Koplin JJ, and et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clinical & Experimental Allergy 2015;45(1):255-264.* 2015.
13. Yang EJ, Beck KM, Sekhon S, Bhutani T, and Koo J. The impact of pediatric atopic dermatitis on families: A review. *Pediatr Dermatol.* 2019;36(1):66-71.
14. Ohya Y, Williams H, Steptoe A, Saito H, Iikura Y, Anderson R, et al. Psychosocial factors and adherence to treatment advice in childhood atopic dermatitis. *J Invest Dermatol.* 2001;117(4):852-7.
15. Warren C, Gupta R, Seetasith A, Schuldt R, Wang R, Iqbal A, et al. The clinical burden of food allergies: Insights from the Food Allergy Research & Education (FARE) Patient Registry. *World Allergy Organ J.* 2024;17(3):100889.
16. Casale TB, Warren C, Gupta S, Schuldt R, Wang R, Iqbal A, et al. The mental health burden of food allergies: Insights from patients and their caregivers from the Food Allergy Research & Education (FARE) Patient Registry. *World Allergy Organ J.* 2024;17(4):100891.
17. Bilaver L, Thivalapill N, Jiang JL, Choi J, Fithian E, Ibrahim K, et al. The Economic Burden of Childhood Food Allergies on Households in the FORWARD Study. *Journal of Allergy and Clinical Immunology.* 2023;151(2):Ab186-Ab.
18. Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, and Meltzer D. The economic impact of childhood food allergy in the United States. *JAMA Pediatr.* 2013;167(11):1026-31.

19. Olsson M, Bajpai R, Wee LWY, Yew YW, Koh MJA, Thng S, et al. The cost of childhood atopic dermatitis in a multi-ethnic Asian population: a cost-of-illness study. *Br J Dermatol.* 2020;182(5):1245-52.

20. Olsson M, Bajpai R, Yew YW, and et al. Associations between health-related quality of life and health care costs among children with atopic dermatitis and their caregivers: A cross-sectional study. *Pediatr Dermatol 2020;37(2):284-293.* 2020.

21. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK, and Qureshi AA. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. *J Invest Dermatol.* 2017;137(1):26-30.

22. Smith Begolka W, Chovatiya R, Thibau IJ, and Silverberg JI. Financial Burden of Atopic Dermatitis Out-of-Pocket Health Care Expenses in the United States. *Dermatitis.* 2021;32(1S):S62-S70.

23. Hua X, Dalziel K, Brettig T, Dharmage SC, Lowe A, Perrett KP, et al. Out-of-hospital health care costs of childhood food allergy in Australia: A population-based longitudinal study. *Pediatr Allergy Immunol.* 2022;33(11):e13883.

24. Molloy J, Ponsonby AL, Allen KJ, Tang ML, Collier FM, Ward AC, et al. Is Low Vitamin D Status A Risk Factor For Food Allergy? Current Evidence And Future Directions. *Mini Rev Med Chem.* 2015;15(11):944-52.

25. Vuillermin PJ, Ponsonby AL, Kemp AS, and Allen KJ. Potential links between the emerging risk factors for food allergy and vitamin D status. *Clin Exp Allergy.* 2013;43(6):599-607.

26. Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. *Am J Clin Nutr.* 2012;95(6):1357-64.

27. Saraf R, Morton SM, Camargo CA, Jr., and Grant CC. Global summary of maternal and newborn vitamin D status - a systematic review. *Matern Child Nutr.* 2016;12(4):647-68.

28. Schmid A, and Walther B. Natural vitamin D content in animal products. *Adv Nutr.* 2013;4(4):453-62.

29. Itkonen ST, Erkkola M, and Lamberg-Allardt CJE. Vitamin D Fortification of Fluid Milk Products and Their Contribution to Vitamin D Intake and Vitamin D Status in Observational Studies—A Review. *Nutrients.* 2018;10(8):1054.

30. Itkonen ST, Andersen R, Bjork AK, Brugard Konde A, Eneroth H, Erkkola M, et al. Vitamin D status and current policies to achieve adequate vitamin D intake in the Nordic countries. *Scand J Public Health.* 2021;49(6):616-27.

31. Ramasamy I. Vitamin D Metabolism and Guidelines for Vitamin D Supplementation. *Clin Biochem Rev.* 2020;41(3):103-26.

32. Balvers MG, Brouwer-Brolsma EM, Endenburg S, de Groot LC, Kok FJ, and Gunnewiek JK. Recommended intakes of vitamin D to optimise health, associated circulating 25-hydroxyvitamin D concentrations, and dosing regimens to treat deficiency: workshop report and overview of current literature. *J Nutr Sci.* 2015;4:e23.

33. Debinska A, Sikorska-Szaflik H, Urbanik M, and Boznanski A. The role of vitamin D in atopic dermatitis. *Dermatitis.* 2015;26(4):155-61.

34. Rochat 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. *Clin Exp Allergy.* 2010;40(5):786-94.

35. Fisher SA, Rahimzadeh M, Brierley C, Gration B, Doree C, Kimber CE, et al. The role of vitamin D in increasing circulating T regulatory cell numbers and modulating T regulatory cell phenotypes in patients with inflammatory disease or in healthy volunteers: A systematic review. *PLoS One.* 2019;14(9):e0222313.

36. van der Aar AM, Sibiryak DS, Bakdash G, van Capel TM, van der Kleij HP, Opstelten DJ, et al. Vitamin D3 targets epidermal and dermal dendritic cells for induction of distinct regulatory T cells. *J Allergy Clin Immunol.* 2011;127(6):1532-40.e7.

37. Mabrouk RR, Amer Ha A, Soliman DA, Mohamed NA, El-Ghoneimy DH, and Atef SM. Role of Vitamin D in the Induction of Regulatory T Cells Producing Interleukin 10 in Children with Cow Milk Allergy. *Egyptian Journal of Hospital Medicine 2016;65:454-467.* 2016.

38. Petriashvili M. Impact of Maternal Vitamin D Status on the Formation of Atopic Dermatitis in Young Children. *Glob Pediatr Health.* 2021;8:2333794X211022916.

39. Palmer DJ, Sullivan TR, Skeaff CM, Smithers LG, Makrides M, and 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 Organ J.* 2015;8(1):28.

40. Osborne NJ, Ukoumunne OC, Wake M, and Allen KJ. Prevalence of eczema and food allergy is associated with latitude in Australia. *J Allergy Clin Immunol.* 2012;129(3):865-7.

41. Weiland SK, Hüsing A, Strachan DP, Rzehak P, and Pearce N. Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. *Occup Environ Med.* 2004;61(7):609-15.

42. Osborne NJ, Ukoumunne OC, Wake M, and Allen KJ. Prevalence of eczema and food allergy is associated with latitude in Australia. *Journal of Allergy and Clinical Immunology.* 2012;129(3):865-7.

43. 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. *Annals of Allergy, Asthma & Immunology.* 2013;110(2):80-5.e1.

44. Rana S, Rogers LJ, and Halliday GM. Systemic low-dose UVB inhibits CD8 T cells and skin inflammation by alternative and novel mechanisms. *Am J Pathol.* 2011;178(6):2783-91.

45. Wang X, Jiao X, Tian Y, Zhang J, Zhang Y, Li J, et al. Associations between maternal vitamin D status during three trimesters and cord blood 25(OH)D concentrations in newborns: a prospective Shanghai birth cohort study. *Eur J Nutr.* 2021;60(6):3473-83.

46. Jacquemyn Y, Ajaji M, and Karepouan N. Vitamin D levels in maternal serum and umbilical cord blood in a multi-ethnic population in Antwerp, Belgium. *Facts Views Vis Obgyn.* 2013;5(1):3-5.

47. Engelsen O. The relationship between ultraviolet radiation exposure and vitamin D status. *Nutrients.* 2010;2(5):482-95.

48. Rueter K, Jones AP, Siafarikas A, Lim EM, Bear N, Noakes PS, et al. Direct infant UV light exposure is associated with eczema and immune development. *J Allergy Clin Immunol.* 2019;143(3):1012-20 e2.

49. Chawes BL, Bønnelykke K, Stokholm J, Vissing NH, Bjarnadóttir E, Schoos AM, 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.

50. 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.

51. Litonjua AA, Carey VJ, Laranjo N, Stubbs BJ, Mirzakhani H, O'Connor GT, et al. Six-Year Follow-up of a Trial of Antenatal Vitamin D for Asthma Reduction. *N Engl J Med.* 2020;382(6):525-33.

52. El-Heis S, D'Angelo S, Curtis EM, Healy E, Moon RJ, Crozier SR, et al. Maternal antenatal vitamin D supplementation and offspring risk of atopic eczema in the first 4 years of life: evidence from a randomized controlled trial. *British Journal of Dermatology.* 2022;187(5):659-66.

53. 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.

54. Rueter K, Jones AP, Siafarikas A, Lim EM, Bear N, Noakes PS, et al. Direct infant UV light exposure is associated with eczema and immune development. *J Allergy Clin Immunol.* 2019;143(3):1012-20.e2.

55. Rueter K, Jones AP, Siafarikas A, Lim EM, Prescott SL, and Palmer DJ. In "High-Risk" Infants with Sufficient Vitamin D Status at Birth, Infant Vitamin D Supplementation Had No Effect on Allergy Outcomes: A Randomized Controlled Trial. *Nutrients.* 2020;12(6).

56. Rosendahl J, Pelkonen AS, Helve O, Hauta-alus H, Holmlund-Suila E, Valkama S, et al. High-Dose Vitamin D Supplementation Does Not Prevent Allergic Sensitization of Infants. *Journal of Pediatrics.* 2019;209:139.

57. Rueter K, Jones AP, Siafarikas A, Lim EM, Bear N, Noakes PS, et al. Direct infant UV light exposure is associated with eczema and immune development. *Journal of Allergy and Clinical Immunology.* 2019;143(3):1012.

58. Allen KJ, Panjari M, Koplin JJ, Ponsonby AL, Vuillermin P, Gurrin LC, et al. VITALITY trial: protocol for a randomised controlled trial to establish the role of postnatal vitamin D supplementation in infant immune health. *BMJ Open.* 2015;5(12):e009377.

59. Tham EH, Leung ASY, Yamamoto-Hanada K, Dahdah L, Trikamjee T, Warad VV, et al. A systematic review of quality and consistency of clinical practice guidelines on the primary prevention of food allergy and atopic dermatitis. *World Allergy Organization Journal.* 2023;16(4):100770.

60. Elliott JH, Synnot A, Turner T, Simmonds M, Akl EA, McDonald S, et al. Living systematic review: 1. Introduction-the why, what, when, and how. *J Clin Epidemiol.* 2017;91:23-30.

61. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ.* 2021;372(372):n160.

62. Akl EA, Khabsa J, Iannizzi C, Piechotta V, Kahale LA, Barker JM, et al. Extension of the PRISMA 2020 statement for living systematic reviews (PRISMA-LSR): checklist and explanation. *BMJ.* 2024;387:e079183.

63. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J.* 1995;8(3):483-91.

64. Hanifin JM. Diagnostic features of atopic dermatitis. *Acta Derm Venereol.* 1980;92:44-7.

65. Williams HC. Diagnostic Criteria for Atopic Dermatitis: Where Do We Go From Here? *Archives of Dermatology.* 1999;135(5):583-6.

66. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, and Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol.* 2016;75:40-6.

67. Clarivate Analytics. In: Team TE ed. Philadelphia: Clarivate Analytics; 2013.

68. Veritas Health Innovation. Melbourne, Australia. : Veritas Health Innovation; 2025.

69. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.

70. StataCorp. College Station, TX: StataCorp LLC; 2023.

71. 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.

72. Lefebvre C GJ, Briscoe S, Featherstone R, Littlewood A, Metzendorf M-I, Noel-Storr A, Paynter R, Rader T, Thomas J, Wieland LS. In: Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. ed. *Cochrane Handbook for Systematic Reviews of Interventions version 651*. Cochrane; 2025.

73. Dawodu A, Salameh KM, Al-Janahi NS, Bener A, and Elkum N. The Effect of High-Dose Postpartum Maternal Vitamin D Supplementation Alone Compared with Maternal Plus Infant Vitamin D Supplementation in Breastfeeding Infants in a High-Risk Population. A Randomized Controlled Trial. *Nutrients.* 2019;11(7).

74. Deeks JJ, Higgins JP, Altman DG, and Group obotCSM. *Cochrane Handbook for Systematic Reviews of Interventions*. 2019:241-84.

75. Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf MI, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. 2019:67-107.

Appendix 1: Declaration of interests

Interests judged by the review team not to require management in relation to this review are declared here for transparency:

Leadership of trials for food allergy or eczema prevention: AJL, JJK, DJP, KPP are lead investigators on trials of other (non-vitamin D) eczema or food allergy prevention strategies.

Support from commercial interests not related to vitamin D supplementation: AJL has received an investigational product (EpiCeram) free of charge from Primus Pharmaceuticals for use in a study that aims to prevent eczema and food allergy using a skin barrier intervention. SCD and AJL have received an investigator-initiated grant from GlaxoSmithKline for unrelated research, and SCD also holds a similar grant from AstraZeneca. SCD, AJL and JJK have received grant funding from Sanofi Regeneron for unrelated research. JJK and RLP received research awards from the Stallergenes Greer Foundation, paid to their institutions. RLP received grant funding from the National Peanut Board (USA) for unrelated research. KPP has received research grants from Aravax, DBV Technologies, Novartis and Siolta and consultant fees from Aravax and Novartis, paid to their institution, outside the submitted work. KH's organisation Allergy & Anaphylaxis Australia receives unrestricted educational grants from pharmaceutical companies, listed here: https://allergyfacts.org.au/about-us/our-supporters/. SV's organisation National Allergy Council has in the past received unrestricted education grants from the organisations listed here: https://nationalallergycouncil.org.au/about-us/funding.

Research salary support through grants or fellowships: CJH is supported by a Postdoctoral Fellowship funded through the CFAR Centre of Research Excellence (NHMRC GNT2015724). RZ is supported by the Australian Commonwealth Government and the University of Melbourne PhD scholarship. DJP is supported by a Stan Perron Charitable Foundation Fellowship. KPP is supported by a Melbourne Children's Clinician-Scientist Fellowship and a NHMRC fellowship (GNT2008911). JJK is supported by a HERA grant through The University of Queensland. AJL is supported by a Dame Kate Campbell Fellowship from the University of Melbourne.

The remaining authors have stated that they have no interests to declare in relation to this work.

Declaration of interests will be updated on an annual basis, and the impact of any interests declared will be reviewed and managed accordingly.

Appendix 2: Search strategy

PubMed

Version/platform/url: https://pubmed.ncbi.nlm.nih.gov/advanced/

#	Query
#1	"Vitamin D"[Mesh] OR "Calcitriol"[Mesh] OR "Receptors, Calcitriol"[Mesh] OR "Cholecalciferol"[Mesh] OR "vitamin d"[tiab] OR "calcitriol"[tiab] OR "cholecalciferol"[tiab] OR "colecalciferol"[tiab] OR "1,25-dihydroxycholecalciferol"[tiab] OR "1,25-dihydroxyvitamin d3"[tiab] OR "1,25-dihydroxyvitamin d"[tiab] OR "25-hydroxyvitamin d"[tiab] OR "25-hydroxy vitamin d"[tiab] OR "25-hydroxycholecalciferol"[tiab] OR "1,25-dihydroxycholecalciferol"[tiab] OR "1 alpha, 25-dihydroxycholecalciferol"[tiab] OR "ergocalciferol"[tiab] OR "25(OH)D"[tiab] OR "1,25(OH)2D3"[tiab]
#2	"Pregnancy"[Mesh] OR "Pregnant People"[Mesh] OR "Infant"[Mesh] OR "Breast Feeding"[Mesh] OR "Lactation"[Mesh] OR "Prenatal Care"[Mesh] OR "Perinatal Care"[Mesh] OR "pregnant"[tiab] OR "pregnanc*"[tiab] OR "prenatal"[tiab] OR "antenatal"[tiab] OR "intrauterine"[tiab] OR "perinatal"[tiab] OR "pre-natal"[tiab] OR "ante-natal"[tiab] OR "intra-uterine"[tiab] OR "peri-natal"[tiab] OR "postpartum"[tiab] OR "post-partum"[tiab] OR "infan*"[tiab] OR "neonat*"[tiab] OR "neo-nat*"[tiab] OR "newborn*"[tiab] OR "new-born*"[tiab] OR "baby"[tiab] OR "babies"[tiab] OR "postpartum"[tiab] OR "gestation"[tiab] OR "breastfeed*"[tiab] OR "breast feed*"[tiab] OR "breastfed"[tiab] OR "breast fed"[tiab] OR "lacta*"[tiab]
#3	"Allergy and Immunology"[Mesh] OR "immunology"[Subheading] OR Hypersensitivity[Mesh] OR "Dermatitis, Atopic"[Mesh] OR "Allergens"[Mesh] OR "Eczema"[Mesh] OR "immunology"[tiab] OR "hypersensitiv*"[tiab] OR "allerg*"[tiab] OR "atopic dermatiti*"[tiab] OR "atopic neurodermatiti*"[tiab] OR "disseminated neurodermatiti*"[tiab] OR "eczema"[tiab] OR "atopic sensitization"[tiab] OR "atopic sensitisation"[tiab]
#4	"Controlled Clinical Trials as Topic"[Mesh] OR "Controlled Clinical Trial" [Publication Type] OR "drug therapy" [Subheading] OR "randomized"[tiab] OR "randomised"[tiab] OR "randomly"[tiab] OR "trial"[tiab] OR "placebo"[tiab] OR "groups"[tiab]
#5	"Animals"[Mesh] NOT "Humans"[Mesh]
#6	(#1 AND #2 AND #3 AND #4) NOT #5

Changes from baseline

- 1st concept
  - Added ergocalciferol / "25(OH)D"[tiab] / "cholecalciferol"[tiab] OR "colecalciferol"[tiab]
  - Removed vitamin d insufficiency/deficiency keywords & Mesh
  - Replaced 1,25 AND (OH) AND 2D3 with "1,25(OH)2D3"[tiab]
- 2nd concept
  - Added breastfeeding & lactation (variations & Mesh)
  - Added terms from PRESS (excl. "Vitamin D Deficiency"[Mesh])
  - Removed exposure terms / uterus, foetus / foetal blood / cord blood
- 3rd concept
  - Removed respirator sounds / wheeze / asthma terms / replicated terms
  - Changed "hypersensitivity"[tiab] to "hypersensitiv*"[tiab]
  - Added "Allergens"[Mesh] OR "Eczema"[Mesh]
- 4th concept
  - Only RCTs – replaced with adapted Cochrane filter(75)

Planned changes for future updates

- Add line #7

#7	#6 AND (**YYYY/MM/DD**:**yyyy/mm/dd**[dp])

Where **DD-MM-YYYY** represents the date of the last search, and **dd-mm-yyyy** represents the date of the current search.

PRESS review

The updated PubMed search was developed by Greta Vos and reviewed by David Honeyman using the PRESS checklist.(66)

The suggestion to add "Vitamin D Deficiency"[Mesh] to the subject headings was not incorporated into the final search because this LSR seeks to examine vitamin D supplementation regardless of vitamin D status at the time of intervention. All other feedback was incorporated.

***PRESS Guideline* — Search Submission & Peer Review Assessment**

SEARCH SUBMISSION: THIS SECTION TO BE FILLED IN BY THE SEARCHER

Searcher: Greta Vos	Email: [redacted]
Date submitted: 06/05/2025	Date requested by: *[Maximum = 5 working days]*

Systematic Review Title:

Vitamin D for the prevention of food allergy and eczema: a living systematic review

This search strategy is …

X	My PRIMARY (core) database strategy — First time submitting a strategy for search question and database
	My PRIMARY (core) strategy — Follow-up review NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions
	SECONDARY search strategy— First time submitting a strategy for search question and database
	SECONDARY search strategy — NOT the first time submitting a strategy for search question and database. If this is a response to peer review, itemize the changes made to the review suggestions

Database

(i.e., MEDLINE,CINAHL…): *[mandatory]*

PubMed

Interface

(i.e., Ovid, EBSCO…): *[mandatory]*

PubMed

Research Question

(Describe the purpose of the search) *[mandatory]*

1. Does maternal vitamin D supplementation during pregnancy influence the offspring's risk of developing eczema and/or food allergy?
2. Does maternal vitamin D supplementation during lactation influence the offspring's risk of developing eczema and/or food allergy?
3. Does vitamin D supplementation during infancy influence the risk of the infant developing eczema and/or food allergy?

PICO Format

(Outline the PICOs for your question — i.e., Patient, Intervention, Comparison, Outcome, and Study Design — as applicable)

P	Pregnant and/or breastfeeding women, at the time of intervention: - Any maternal age - Any stage of pregnancy AND/OR breastfeeding - Any (including unknown) risk/diagnosis/family history of allergic disease Infants, at the time of intervention: - Any (including unknown) risk or family history of allergic disease - Any diagnosis of allergic disease other than the target condition Infancy as defined by the study, or 0-12 months of age if not specified.
I	Maternal and/or infant supplementation with vitamin D
C	No vitamin D supplementation (including placebo) Varying dosage of vitamin D supplementation, when the only difference between groups is level of vitamin D in the supplement.
O	Eczema or food allergy in offspring (maternal intervention) or individual (infant intervention) Outcomes assessed at any age and defined as: Eczema - (i) (parental report of) doctor-diagnosed eczema, or assessed by (ii) International Study of Asthma and Allergies in Children (ISAAC) criteria[a], (iii) Hanifin & Rajka criteria[b] or (iv) the UK Working Party's diagnostic criteria[c] Food allergy - (i) positive oral food challenge, and/or (ii) clinical history and evidence of sensitisation to the trigger allergen (positive skin prick test or sIgE), and/or (iii) (parental report of) doctor-diagnosed food allergy. Safety outcomes as reported by the study.

Inclusion Criteria

(List criteria such as age groups, study designs, etc., to be included) *[optional]*

Study type: RCTs
Peer reviewed publications
All languages
Human studies only
No date limit

Exclusion Criteria

(List criteria such as study designs, date limits, etc., to be excluded) *[optional]*

Publications that do not report original data
Conference abstracts
Preprints
Other study designs: quasi-randomised controlled trials & non-randomised controlled trials

Was a search filter applied?

Yes X ☐ No ☐

If YES, which one(s) (e.g., Cochrane RCT filter, PubMed Clinical Queries filter)? Provide the source if this is a published filter. *[mandatory if YES to previous question — textbox]*

Cochrane RCT filter (adapted): https://training.cochrane.org/chapter04-tech-supplonlinepdfv65270924 (p.74-75)

Other notes or comments you feel would be useful for the peer reviewer? ***[optional]***

Original systematic review:

Zeng, R., Li, Y., Shen, S., Qiu, X., Chang, C. L., Koplin, J. J., Perrett, K. P., Dharmage, S. C., Lodge, C. J., & Lowe, A. J. (2023). Is antenatal or early-life vitamin D associated with eczema or food allergy in childhood? A systematic review. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology, 53(5), 511–525. https://doi.org/10.1111/cea.14281

Please copy and paste your search strategy here, exactly as run, including the number of hits per line. ***[mandatory]***

#	Query	Results
#1	"Vitamin D"[Mesh] OR "Calcitriol"[Mesh] OR "Receptors, Calcitriol"[Mesh] OR "Cholecalciferol"[Mesh] OR "vitamin d"[tiab] OR "calcitriol"[tiab] OR "cholecalciferol"[tiab] OR "colecalciferol"[tiab] OR "1,25-dihydroxycholecalciferol"[tiab] OR "1,25-dihydroxyvitamin d3"[tiab] OR "cholecalciferol"[tiab] OR "1,25-dihydroxyvitamin d"[tiab] OR "25-hydroxyvitamin d"[tiab] OR "25-hydroxy vitamin d"[tiab] OR "25-hydroxycholecalciferol"[tiab] OR "1,25-dihydroxycholecalciferol"[tiab] OR "1 alpha, 25-dihydroxycholecalciferol"[tiab] OR "ergocalciferol"[tiab] OR "25(OH)D"[tiab] OR "1,25(OH)2D3"[tiab]	112,603
#2	"Pregnancy"[Mesh] OR "Pregnant People"[Mesh] OR "Infant"[Mesh] OR "Breast Feeding"[Mesh] OR "Lactation"[Mesh] OR "pregnant"[tiab] OR "pregnanc*"[tiab] OR "prenatal"[tiab] OR "antenatal"[tiab] OR "intrauterine"[tiab] OR "perinatal"[tiab] OR "infan*"[tiab] OR "postpartum"[tiab] OR "gestation"[tiab] OR "breastfeed*"[tiab] OR "breast feed*"[tiab] OR "breastfed"[tiab] OR "breast fed"[tiab] OR "lacta*"[tiab]	2,738,056
#3	"Allergy and Immunology"[Mesh] OR "immunology"[Subheading] OR Hypersensitivity[Mesh] OR "Dermatitis, Atopic"[Mesh] OR "Allergens"[Mesh] OR "Eczema"[Mesh] OR "immunology"[tiab] OR "hypersensitiv*"[tiab] OR "allerg*"[tiab] OR "atopic dermatiti*"[tiab] OR "atopic neurodermatiti*"[tiab] OR "disseminated neurodermatiti*"[tiab] OR "eczema"[tiab] OR "atopic sensitization"[tiab] OR "atopic sensitisation"[tiab]	2,126,647
#4	"Controlled Clinical Trials as Topic"[Mesh] OR "Controlled Clinical Trial" [Publication Type] OR "drug therapy" [Subheading] OR "randomized"[tiab] OR "randomised"[tiab] OR "randomly"[tiab] OR "trial"[tiab] OR "placebo"[tiab] OR "groups"[tiab]	6,420,772
#5	"Animals"[Mesh] NOT "Humans"[Mesh]	5,331,035
#6	(#1 AND #2 AND #3 AND #4) NOT #5	361

PEER REVIEW ASSESSMENT: THIS SECTION TO BE FILLED IN BY THE REVIEWER

Reviewer: David Honeyman	Email: [redacted]	Date completed: 6-5-25

1. TRANSLATION

A ---No revisions	☑
B --- Revision(s) suggested	☐
C --- Revision(s) required	☐

If "B" or "C," please provide an explanation or example:

2. BOOLEAN AND PROXIMITY OPERATORS

A ---No revisions	☑
B --- Revision(s) suggested	☐
C --- Revision(s) required	☐

If "B" or "C," please provide an explanation or example:

3. SUBJECT HEADINGS

A ---No revisions	☐
B --- Revision(s) suggested	☑
C --- Revision(s) required	☐

If "B" or "C," please provide an explanation or example:

Add "Vitamin D Deficiency"[Mesh]. A lot of the papers found by this search have that MeSH term

Recommend adding "Prenatal Care"[Mesh], "Perinatal Care"[Mesh]

4. TEXT WORD SEARCHING

A ---No revisions	☐
B --- Revision(s)suggested	☑
C --- Revision(s) required	☐

If "B" or "C," please provide an explanation or example:

You have "cholecalciferol"[tiab] twice

Recommend adding neonat* neo-nat* newborn* new-born* baby babies Recommend adding hyphenated versions of these: "prenatal"[tiab] OR "antenatal"[tiab] OR "intrauterine"[tiab] OR "perinatal"[tiab] OR "postpartum"[tiab]

5. SPELLING, SYNTAX, AND LINE NUMBERS

A ---No revisions	☑
B --- Revision(s)suggested	☐
C --- Revision(s) required	☐

If "B" or "C," please provide an explanation or example:

6. LIMITS AND FILTERS

A ---No revisions	☑
B --- Revision(s) suggested	☐
C --- Revision(s) required	☐

If "B" or "C," please provide an explanation or example:

OVERALL EVALUATION (Note: If one or more "revision required" is noted above, the response below must be "revisions required".)

A ---No revisions	☐
B --- Revision(s) suggested	☑
C --- Revision(s) required	☐

Additional comments:

Search is great and could be used as is, recommendations are for minor improvements only

Embase

Version/platform/url: Elsevier

#	Query
#1	'vitamin D'/exp OR 'calcitriol'/exp OR 'calcitriol receptor'/exp OR 'colecalciferol'/exp OR "vitamin d":ti,ab OR "calcitriol":ti,ab OR "cholecalciferol":ti,ab OR "colecalciferol":ti,ab OR "1,25-dihydroxycholecalciferol":ti,ab OR "1,25-dihydroxyvitamin d3":ti,ab OR "1,25-dihydroxyvitamin d":ti,ab OR "25-hydroxyvitamin d":ti,ab OR "25-hydroxy vitamin d":ti,ab OR "25-hydroxycholecalciferol":ti,ab OR "1,25-dihydroxycholecalciferol":ti,ab OR "1 alpha, 25-dihydroxycholecalciferol":ti,ab OR "ergocalciferol":ti,ab OR "25(OH)D":ti,ab OR "1,25(OH)2D3":ti,ab
#2	'pregnancy'/exp OR 'pregnant person'/exp OR 'infant'/exp OR 'breast feeding'/exp OR 'lactation'/exp OR 'prenatal care'/exp OR 'perinatal care'/exp OR "pregnant":ti,ab OR "pregnanc*":ti,ab OR "prenatal":ti,ab OR "antenatal":ti,ab OR "intrauterine":ti,ab OR "perinatal":ti,ab OR "pre-natal":ti,ab OR "ante-natal":ti,ab OR "intra-uterine":ti,ab OR "peri-natal":ti,ab OR "postpartum":ti,ab OR "post-partum":ti,ab OR "infan*":ti,ab OR "neonat*":ti,ab OR "neo-nat*":ti,ab OR "newborn*":ti,ab OR "new-born*":ti,ab OR "baby":ti,ab OR "babies":ti,ab OR "postpartum":ti,ab OR "gestation":ti,ab OR "breastfeed*":ti,ab OR "breast feed*":ti,ab OR "breastfed":ti,ab OR "breast fed":ti,ab OR "lacta*":ti,ab
#3	'allergy'/exp OR 'hypersensitivity'/exp OR 'atopic dermatitis'/exp OR 'allergen'/exp OR 'eczema'/exp OR "immunology":ti,ab OR "hypersensitiv*":ti,ab OR "allerg*":ti,ab OR "atopic dermatiti*":ti,ab OR "atopic neurodermatiti*":ti,ab OR "disseminated neurodermatiti*":ti,ab OR "eczema":ti,ab OR "atopic sensitization":ti,ab OR "atopic sensitisation":ti,ab
#4	'controlled clinical trial (topic)'/exp OR 'controlled clinical trial'/exp OR "randomized":ti,ab OR "randomised":ti,ab OR "randomly":ti,ab OR "trial":ti,ab OR "placebo":ti,ab OR "groups":ti,ab
#5	'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)
#6	(#1 AND #2 AND #3 AND #4) NOT #5

Changes from baseline

Updated PubMed search translated to Embase Elsevier.

Planned changes for future updates

- Add line #7

#7	#6 AND ([**DD-MM-YYYY**]/sd NOT [**dd-mm-yyyy**]/sd)

Where **DD-MM-YYYY** represents the date of the last search, and **dd-mm-yyyy** represents the day following the current search date.

Cochrane Central Register of Controlled Trials (CENTRAL)

Version/platform/url: The Cochrane Library (Wiley), https://www.cochranelibrary.com/advanced-search/search-manager

#	Query
#1	MeSH descriptor: [Vitamin D] explode all trees
#2	MeSH descriptor: [Calcitriol] explode all trees
#3	MeSH descriptor: [Receptors, Calcitriol] explode all trees
#4	MeSH descriptor: [Cholecalciferol] explode all trees
#5	("vitamin d" OR "calcitriol" OR "cholecalciferol" OR "colecalciferol" OR "1,25-dihydroxycholecalciferol" OR "1,25-dihydroxyvitamin d3" OR "1,25-dihydroxyvitamin d" OR "25-hydroxyvitamin d" OR "25-hydroxy vitamin d" OR "25-hydroxycholecalciferol" OR "1,25-dihydroxycholecalciferol" OR "1 alpha, 25-dihydroxycholecalciferol" OR "ergocalciferol" OR "25(OH)D" OR "1,25(OH)2D3"):ti,ab,kw
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	MeSH descriptor: [Pregnancy] explode all trees
#8	MeSH descriptor: [Pregnant People] explode all trees
#9	MeSH descriptor: [Infant] explode all trees
#10	MeSH descriptor: [Breast Feeding] explode all trees
#11	MeSH descriptor: [Lactates] explode all trees
#12	MeSH descriptor: [Prenatal Care] explode all trees
#13	MeSH descriptor: [Perinatal Care] explode all trees
#14	("pregnant" OR (pregnanc*) OR "prenatal" OR "antenatal" OR "intrauterine" OR "perinatal" OR "pre-natal" OR "ante-natal" OR "intra-uterine" OR "peri-natal" OR "postpartum" OR "post-partum" OR (infan*) OR (neonat*) OR (neo-nat*) OR (newborn*) OR (new-born*) OR "baby" OR "babies" OR "postpartum" OR "gestation" OR (breastfeed*) OR (breast NEXT feed*) OR "breastfed" OR "breast fed" OR (lacta*)):ti,ab,kw
#15	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	MeSH descriptor: [Allergy and Immunology] explode all trees
#17	MeSH descriptor: [] explode all trees and with qualifier(s): [immunology - IM]
#18	MeSH descriptor: [Hypersensitivity] explode all trees
#19	MeSH descriptor: [Dermatitis, Atopic] explode all trees
#20	MeSH descriptor: [Allergens] explode all trees
#21	MeSH descriptor: [Eczema] explode all trees
#22	("immunology" OR (hypersensitiv*) OR (allerg*) OR (atopic NEXT dermatiti*) OR (atopic NEXT neurodermatiti*) OR (disseminated NEXT neurodermatiti*) OR "eczema" OR "atopic sensitization" OR "atopic sensitisation"):ti,ab,kw
#23	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24*	#6 AND #15 AND #23

*Select “Limits” box for line 24: Content type = Trials

Changes from baseline

New database added to search.

Planned changes for future updates

Add date limit using “Limits” box for line 24:

Content type = Trials

Date published on the Cochrane Library Between **MONTH YYYY** and **month yyyy**

Where **MONTH YYYY** represents the month of the last search, and **month yyyy** represents the month of the current search.

WHO International Clinical Trials Registry Platform (ICTRP) Search Portal

Version/platform/url: Advanced search, https://trialsearch.who.int/AdvSearch.aspx

Field	Query
In the title	("vitamin d" OR "calcitriol" OR "cholecalciferol" OR "colecalciferol" OR "1,25-dihydroxycholecalciferol" OR "1,25-dihydroxyvitamin d3" OR "1,25-dihydroxyvitamin d" OR "25-hydroxyvitamin d" OR "25-hydroxy vitamin d" OR "25-hydroxycholecalciferol" OR "1,25-dihydroxycholecalciferol" OR "1 alpha, 25-dihydroxycholecalciferol" OR "ergocalciferol" OR "25(OH)D" OR "1,25(OH)2D3") **AND** ("pregnant" OR "pregnanc*" OR "prenatal" OR "antenatal" OR "intrauterine" OR "perinatal" OR "pre-natal" OR "ante-natal" OR "intra-uterine" OR "peri-natal" OR "postpartum" OR "post-partum" OR "infan*" OR "neonat*" OR "neo-nat*" OR "newborn*" OR "new-born*" OR "baby" OR "babies" OR "postpartum" OR "gestation" OR "breastfeed*" OR "breast feed*" OR "breastfed" OR "breast fed" OR "lacta*") **AND** ("immunology" OR "hypersensitiv*" OR "allerg*" OR "atopic dermatiti*" OR "atopic neurodermatiti*" OR "disseminated neurodermatiti*" OR "eczema" OR "atopic sensitization" OR "atopic sensitisation")
Recruitment status is	ALL

Changes from baseline

Trial registries added to search.

Planned changes for future updates

Add date limit using “date of registration” filter:

Date of registration is between	**DD/MM/YYYY**	and	**dd/mm/yyyy**

Where **DD/MM/YYYY** represents the date of the last search, and **dd/mm/yyyy** represents the date of the current search.

Clinicaltrials.gov

Version/platform/url: www.clinicaltrials.gov

Field	Query
Other terms	("vitamin d" OR "calcitriol" OR "cholecalciferol" OR "colecalciferol" OR "1,25-dihydroxycholecalciferol" OR "1,25-dihydroxyvitamin d3" OR "1,25-dihydroxyvitamin d" OR "25-hydroxyvitamin d" OR "25-hydroxy vitamin d" OR "25-hydroxycholecalciferol" OR "1,25-dihydroxycholecalciferol" OR "1 alpha, 25-dihydroxycholecalciferol" OR "ergocalciferol" OR "25(OH)D" OR "1,25(OH)2D3") **AND** ("pregnant" OR "pregnanc*" OR "prenatal" OR "antenatal" OR "intrauterine" OR "perinatal" OR "pre-natal" OR "ante-natal" OR "intra-uterine" OR "peri-natal" OR "postpartum" OR "post-partum" OR "infan*" OR "neonat*" OR "neo-nat*" OR "newborn*" OR "new-born*" OR "baby" OR "babies" OR "postpartum" OR "gestation" OR "breastfeed*" OR "breast feed*" OR "breastfed" OR "breast fed" OR "lacta*") **AND** ("immunology" OR "hypersensitiv*" OR "allerg*" OR "atopic dermatiti*" OR "atopic neurodermatiti*" OR "disseminated neurodermatiti*" OR "eczema" OR "atopic sensitization" OR "atopic sensitisation")
Study status	All studies

Changes from baseline

Trial registries added to search.

Planned changes for future updates

Add date limit using “first posted” filter:

First posted	From	**MM/DD/YYYY**	To	**mm/dd/yyyy**

Where **MM/DD/YYYY** represents the date of the last search, and **mm/dd/yyyy** represents the date of the current search.

Australian New Zealand Clinical Trials Registry (ANZCTR)

Version/platform/url: https://www.anzctr.org.au/TrialSearch.aspx

Field	Query
Trial search	("vitamin d" OR calcitriol OR cholecalciferol OR "colecalciferol") **AND** (pregnan* OR breast*)
Registry	All

Changes from baseline

Trial registries added to search. Search terms from WHO ICTRP were condensed for ANZCTR due to character limit.

Planned changes for future updates

Add date limit using 'registration date' filter:

Registration date	From	**DD/MM/YYYY**	To	**dd/mm/yyyy**

Where **DD/MM/YYYY** represents the date of the last search, and **dd/mm/yyyy** represents the date of the current search.