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Vitamin D supplementation in pregnant or breastfeeding women or young children for preventing asthma (Review)

Patchen BK, Best CM, Boiteau J, Solvik BS, Vonderschmidt A, Xu J, Cohen RT, Cassano PA

Patchen BK, Best CM, Boiteau J, Solvik BS, Vonderschmidt A, Xu J, Cohen RT, Cassano PA.
Vitamin D supplementation in pregnant or breastfeeding women or young children for preventing asthma.
Cochrane Database of Systematic Reviews 2025, Issue 8. Art. No.: CD013396.
DOI: 10.1002/14651858.CD013396.pub2.

This Cochrane Review was published in the Cochrane Database of Systematic Reviews 2025, Issue 8. Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the Cochrane Review.

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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 3
SUMMARY OF FINDINGS 5
BACKGROUND 13
OBJECTIVES 15
METHODS 15
RESULTS 21
Figure 1. 22
Figure 2. 26
Figure 3. 27
DISCUSSION 33
AUTHORS' CONCLUSIONS 36
ACKNOWLEDGEMENTS 36
REFERENCES 38
CHARACTERISTICS OF STUDIES 49
DATA AND ANALYSES 85
Analysis 1.1. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 1: Asthma 87
Analysis 1.2. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 2: Wheeze 87
Analysis 1.3. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 3: Atopic dermatitis 87
Analysis 1.4. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 4: Adverse events 88
Analysis 1.5. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 5: Any airway infection 89
Analysis 1.6. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 6: Lower respiratory tract infection 89
Analysis 1.7. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 7: Upper respiratory tract infection 90
Analysis 1.8. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 8: Allergic sensitisation – total IgE (continuous) 90
Analysis 1.9. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 9: Allergic sensitisation – skin prick against common allergens 90
Analysis 1.10. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 10: Airway inflammation – eosinophil counts (continuous) 91
Analysis 1.11. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 11: Airway inflammation – exhaled nitric oxide (continuous) 91
Analysis 2.1. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 1: Asthma 92
Analysis 2.2. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 2: Wheeze 92
Analysis 2.3. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 3: Atopic dermatitis 93
Analysis 2.4. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 4: Adverse events 93
Analysis 2.5. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 5: Any airway infection 94
Analysis 2.6. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 6: Lower respiratory tract infection 94
Analysis 2.7. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 7: Upper respiratory tract infection 94
Analysis 2.8. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 8: Allergic sensitisation – specific IgE against common allergens (dichotomous) 95
Analysis 2.9. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 9: Allergic sensitisation – skin prick against common allergens 95

Analysis 2.10. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 10: Airway inflammation – elevated eosinophil counts (dichotomous) 95
Analysis 3.1. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 1: Asthma 97
Analysis 3.2. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 2: Asthma (6-year follow-up data) 97
Analysis 3.3. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 3: Wheeze 97
Analysis 3.4. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 4: Atopic dermatitis 98
Analysis 3.5. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 5: Adverse events 99
Analysis 3.6. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 6: Any airway infection 100
Analysis 3.7. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 7: Lower respiratory tract infection 100
Analysis 3.8. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 8: Allergic sensitisation – total IgE (continuous) 100
Analysis 3.9. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 9: Allergic sensitisation – specific IgE against common allergens (dichotomous) 101
Analysis 3.10. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 10: Allergic sensitisation – skin prick against common allergens 101
Analysis 4.1. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 1: Asthma 102
Analysis 4.2. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 2: Wheeze 102
Analysis 4.3. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 3: Atopic dermatitis 103
Analysis 4.4. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 4: Adverse events 103
Analysis 4.5. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 5: Any airway infection 104
Analysis 4.6. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 6: Lower respiratory tract infection 104
Analysis 4.7. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 7: Upper respiratory tract infection 105
Analysis 4.8. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 8: Allergic sensitisation – specific IgE against common allergens (dichotomous) 105
Analysis 5.1. Comparison 5: Exploratory analysis – studies combined regardless of comparator or participants receiving the intervention, Outcome 1: Asthma – as defined by trial authors 106
Analysis 5.2. Comparison 5: Exploratory analysis – studies combined regardless of comparator or participants receiving the intervention, Outcome 2: Wheeze – as defined by trial authors 107
ADDITIONAL TABLES 108
APPENDICES 113
HISTORY 118
CONTRIBUTIONS OF AUTHORS 118
DECLARATIONS OF INTEREST 118
SOURCES OF SUPPORT 119
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 119
INDEX TERMS 119

[Intervention Review]

Vitamin D supplementation in pregnant or breastfeeding women or young children for preventing asthma

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Editorial group: Cochrane Central Editorial Service.
Publication status and date: New, published in Issue 8, 2025.

Citation: Patchen BK, Best CM, Boiteau J, Solvik BS, Vonderschmidt A, Xu J, Cohen RT, Cassano PA. Vitamin D supplementation in pregnant or breastfeeding women or young children for preventing asthma. *Cochrane Database of Systematic Reviews* 2025, Issue 8. Art. No.: CD013396. DOI: 10.1002/14651858.CD013396.pub2.

ABSTRACT

Background

Randomised controlled studies evaluating vitamin D supplementation in pregnancy or early childhood for preventing childhood asthma have yielded inconclusive results. Previous systematic reviews of vitamin D for asthma prevention focused on studies comparing vitamin D to placebo or studies intervening in pregnancy, limiting the body of evidence.

Objectives

Primary: to evaluate the efficacy of any vitamin D supplementation and high-dose vitamin D supplementation in early life, including the prenatal period, for preventing asthma in children.

Secondary: to assess the efficacy of vitamin D supplementation:

• for preventing asthma in children at risk of vitamin D deficiency at the start of the trial or whose mothers were at risk;
• by intervention timing and the cumulative dose administered;
• in preventing factors associated with early childhood asthma, including atopic dermatitis, respiratory tract infections, sensitisation to allergens, and airway inflammation.

Search methods

We searched CENTRAL, MEDLINE, Embase, ClinicalTrials.gov, the International Clinical Trials Registry Platform, and the Cochrane Airways and Skin Trial Registers. We checked the reference lists of relevant systematic reviews and meta-analyses. We contacted authors to obtain additional study information as needed. Date of last search: October 2023.

Selection criteria

We included randomised controlled studies comparing higher versus lower/standard dose vitamin D (≤ 400 international units (IU)/day) or any vitamin D versus placebo/no treatment in generally healthy pregnant or lactating women or children up to five years of age that evaluated childhood asthma, wheeze, atopic dermatitis, airway infections, allergic sensitisation, and airway inflammation. We excluded trials recruiting populations with pre-existing conditions.

Data collection and analysis

We followed standard Cochrane methodological procedures, including using Cochrane's Screen4Me workflow. We considered participants rather than events as the unit of analysis, performed fixed-effect meta-analysis, and reported risk ratios (RRs) or mean differences (MDs) with 95% confidence intervals (CIs) for four comparisons: (1) any vitamin D versus placebo/no supplementation in pregnant or breastfeeding women; (2) any vitamin D versus placebo/no supplementation in infants or children; (3) high versus low/standard dose vitamin D in pregnant or breastfeeding women; (4) high versus low/standard dose vitamin D in infants or children. Our outcomes were: asthma, wheeze, atopic dermatitis, airway infections, allergic sensitisation, airway inflammation, and adverse events. We narratively described results that could not be meta-analysed. We used the Cochrane risk of bias tool (RoB) to assess bias in the studies. We used GRADE to assess the certainty of the evidence.

Main results

We included 18 studies involving a total of 10,611 participants, of which 16 contributed data to meta-analyses. Studies were conducted around the world, with most taking place in higher-income countries. The dose and frequency of vitamin D ranged from 200 IU/day to 100,000 IU bolus quarterly, and the duration of supplementation ranged from 28 days to two years.

Comparison 1. Any vitamin D versus placebo/no supplementation in pregnant or breastfeeding women (4 studies)

Compared to placebo or no supplementation, any vitamin D given to pregnant or breastfeeding women may reduce the risk of early childhood asthma (RR 0.17, 95% CI 0.05 to 0.61; 1 study, 236 participants; low-certainty evidence) and likely has little to no effect on childhood airway infections (RR 1.00, 95% CI 0.97 to 1.04; 3 studies, 1564 participants; moderate-certainty evidence). The evidence is very uncertain for wheeze, atopic dermatitis, allergic sensitisation, airway inflammation, or adverse events.

Comparison 2. Any vitamin D versus placebo/no supplementation in infants or children (5 studies)

Compared to placebo or no supplementation, any vitamin D given to infants or children may have little to no effect on childhood wheeze (RR 0.89, 95% CI 0.68 to 1.16; 2 studies, 431 participants; low-certainty evidence), atopic dermatitis (RR 1.01, 95% CI 0.80 to 1.28; 2 studies, 448 participants; low-certainty evidence), airway infections (RR 0.92, 95% CI 0.83 to 1.01; 2 studies, 500 participants; low-certainty evidence), allergic sensitisation (RR 2.25, 95% CI 0.60 to 8.50; 1 study, 228 participants; low-certainty evidence), or airway inflammation measured by eosinophil counts (RR 1.06, 95% CI 0.65 to 1.74; 1 study, 226 participants; low-certainty evidence). The evidence is very uncertain for asthma and adverse events.

Comparison 3. High versus low/standard dose vitamin D in pregnant or breastfeeding women (4 studies)

Compared to low/standard dose, high-dose vitamin D given to pregnant or breastfeeding women likely reduces the risk of childhood wheeze (RR 0.79, 95% CI 0.64 to 0.98; 3 studies, 1439 participants; moderate-certainty evidence), but likely results in little to no difference in childhood asthma, although the direction and magnitude of effect is similar to that for wheeze (RR 0.81, 95% CI 0.63 to 1.04; 2 studies, 1355 participants; moderate-certainty evidence). Compared to low/standard dose, high-dose vitamin D in pregnancy likely has little to no effect on childhood atopic dermatitis (RR 0.91, 95% CI 0.75 to 1.11; 3 studies, 1439 participants; moderate-certainty evidence), airway infections (RR 0.95, 95% CI 0.82 to 1.11; 3 studies, 1441 participants; moderate-certainty evidence), or allergic sensitisation (RR 1.01, 95% CI 0.87 to 1.18; 2 studies, 1110 participants; moderate-certainty evidence). The evidence is very uncertain for adverse events. No studies evaluated airway inflammation.

Comparison 4. High versus low/standard dose vitamin D in infants or children (7 studies)

Compared to low/standard dose, high-dose vitamin D given to infants or children may slightly reduce airway infections (RR 0.94, 95% CI 0.90 to 0.98; 6 studies, 2385 participants; low-certainty evidence) but may have little to no effect on atopic dermatitis (RR 0.76, 95% CI 0.55 to 1.05; 1 study, 769 participants; low-certainty evidence). The evidence is very uncertain for asthma, wheeze, allergic sensitisation, and adverse events. No studies evaluated airway inflammation.

Authors' conclusions

Evidence supporting a protective effect of vitamin D supplementation in early life, including the prenatal period, on childhood asthma is limited. Moderate-certainty evidence suggests that high-dose vitamin D in pregnancy likely helps prevent childhood wheeze. Evidence for the effects of vitamin D in early childhood on asthma or wheeze is less certain. Additional high-quality studies, especially in infants and children, are needed to establish with any certainty the effects of vitamin D supplementation on childhood asthma and associated factors.

PLAIN LANGUAGE SUMMARY

Does vitamin D treatment in pregnant or breastfeeding women or young children prevent childhood asthma?

Key messages

• The children of women given high doses of vitamin D during pregnancy are less likely to develop wheeze (a whistling sound heard on exhalation, due to lower airway swelling, inflammation, or constriction) than children whose mothers did not take vitamin D in pregnancy.

• Vitamin D treatment in early childhood may have little effect on preventing asthma or wheeze, though we are uncertain of these results.

• We are very uncertain about the evidence for any unwanted effects of vitamin D treatment in pregnant or breastfeeding women or young children.

Background

Asthma is a common childhood condition that affects the lungs. Children with asthma experience recurrent attacks of breathlessness, wheezing, and coughing due to inflammation, mucous production, and narrowing of the airways. Atopic dermatitis (a chronic inflammatory skin disease), sensitisation to allergens, and recurrent respiratory tract infections may contribute to the development of asthma. Vitamin D is an essential nutrient that affects the immune system. Previous studies have connected low vitamin D status to an increased risk of allergic disease.

What did we want to find out?

We wanted to find out if vitamin D treatment in early life helps prevent: (a) childhood asthma, wheeze, or both; and (b) risk factors for childhood asthma, including atopic dermatitis, airway infections, sensitisation to allergens, and airway inflammation.

We also wanted to find out if vitamin D treatment was associated with any unwanted effects.

What did we do?

We searched for studies exploring any of the following comparisons:

• any vitamin D versus placebo (an inactive 'dummy' medicine) or no treatment in pregnant or breastfeeding women;
• any vitamin D versus placebo/no treatment in young children;
• higher-dose vitamin D with lower/standard dose (400 international units/day or less) vitamin D in pregnant or breastfeeding women,
• higher-dose vitamin D with lower/standard dose (400 international units/day or less) vitamin D in young children.

Our outcomes of interest were childhood asthma, wheeze, atopic dermatitis, airway infections, allergic sensitisation, and airway inflammation.

We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and the number of people in the study.

What did we find?

We found 18 studies involving a total of 10,611 pregnant women, infants, mother/infant pairs, and children up to age five. Four studies compared any vitamin D with placebo/no treatment in pregnant women, five studies compared any vitamin D with placebo/no treatment in young children, four studies compared higher versus lower doses of vitamin D in pregnant women, and seven studies compared higher versus lower doses of vitamin D in young children. Studies were conducted around the world; most were done in higher-income countries. The largest study included 3046 participants; the smallest included 50. The duration of vitamin D treatment ranged from 28 days to two years, with most studies treating for six months or less.

Main results

Any vitamin D treatment in pregnancy may help prevent childhood asthma (1 study, 236 participants), and higher-dose vitamin D treatment in pregnancy likely helps prevent childhood wheeze (3 studies, 1439 participants).

Vitamin D treatment in early childhood, regardless of dose and comparison, may have little effect on asthma or wheeze, though we are uncertain of these results. High-dose vitamin D treatment in early childhood may help prevent airway infections (6 studies, 2385 participants).

Vitamin D treatment in pregnancy or early childhood, regardless of dose and comparison, may have little to no effect on atopic dermatitis, sensitisation to allergens, and markers of airway inflammation.

We are uncertain whether vitamin D treatment in pregnancy or early childhood has any unwanted effects because the studies reported limited information about unwanted effects.

What are the limitations of the evidence?

For interventions in pregnancy, we are moderately confident in the effects of high-dose vitamin D on wheeze and asthma. We are less confident in the effects of any vitamin D on asthma because the evidence is based on results from one small study. However, these findings are limited to prenatal vitamin D treatment in the second and third trimesters; the effects of vitamin D treatment starting around the time a woman becomes pregnant or in the first trimester are unclear.

For interventions in young children, we have low confidence in our findings for the effects of vitamin D, regardless of dose, on any outcome evaluated.

We have little confidence in the findings for unwanted effects because the evidence is based on a few cases and there were not enough studies evaluating most unwanted effects.

How current is this evidence?

The evidence is current to October 2023.

Summary of findings 1. Summary of findings table - Vitamin D compared to placebo/no supplementation in pregnant or breastfeeding women

Vitamin D compared to placebo/no supplementation in pregnant or breastfeeding women

Patient or population: pregnant or breastfeeding women
Setting: participants in the community
Intervention: vitamin D
Comparison: placebo/no supplementation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/no supplementation	Risk with vitamin D				
Incidence of asthma follow-up: 18 months	11 per 100	**2 per 100** (1 to 7)	**RR 0.17** (0.05 to 0.61)	236 (1 RCT)	⊕⊕⊖⊖ Low[a,b]	Vitamin D in pregnant or breastfeeding women may reduce childhood asthma.
Incidence of wheeze follow-up: 3 years	14 per 100	**16 per 100** (7 to 36)	**RR 1.12** (0.50 to 2.54)	158 (1 RCT)	⊕⊖⊖⊖ Very low[b,c,d]	The evidence is very uncertain about the effect of vitamin D in pregnancy on childhood wheeze.
Incidence of atopic dermatitis follow-up: range 1 to 4 years	12 per 100	**11 per 100** (7 to 16)	**RR 0.88** (0.59 to 1.33)	600 (2 RCTs)	⊕⊖⊖⊖ Very low[b,c,d]	The evidence is very uncertain about the effect of vitamin D on childhood atopic dermatitis.
Any adverse events follow-up: range 6 months to 4 years	Adverse events were rare and inconsistently reported. Limited data for adverse events reported by at least two studies suggest that vitamin D may reduce the risk of intrauterine death (4 RCTs) and infant death (2 RCTs), but may have little to no effect on other maternal or infant adverse events (2-4 RCTs).			(4 RCTs)	⊕⊖⊖⊖ Very low[e]	The evidence is very uncertain about the effect of vitamin D on maternal or infant adverse events.
Incidence of any airway infection follow-up: range 6 months to 3 years	92 per 100	**92 per 100** (90 to 96)	**RR 1.00** (0.97 to 1.04)	1564 (3 RCTs)	⊕⊕⊕⊖ Moderate[f]	Vitamin D likely has little to no effect on airway infections. Similar conclusions were reached when lower and upper respiratory tract infections were considered separately,

						although the evidence for these outcomes was less certain.
Serum IgE levels (a measure of allergic sensitisation) follow-up: 3 years	The mean serum IgE levels was **3.74** KU/L	The mean serum IgE with vitamin D was **0.3 KU/L lower** (0.92 lower to 0.32 higher)	-	86 (1 RCT)	⊕⊖⊖⊖ Very low[b,c,d]	The evidence is very uncertain about the effect of vitamin D on childhood allergic sensitisation assessed by total serum IgE. Similar conclusions were drawn for allergic sensitisation assessed by skin prick reactions to common allergens.
Exhaled nitric oxide (a measure of airway inflammation) follow-up: 3 years	The mean exhaled nitric oxide was **23.5** parts per billion (ppb)	The mean exhaled nitric oxide with vitamin D was **4.2 parts per billion (ppb) lower** (10.44 lower to 2.04 higher)	-	62 (1 RCT)	⊕⊖⊖⊖ Very low[b,c]	The evidence is very uncertain about the effect of vitamin D on airway inflammation assessed by exhaled nitric oxide. Similar conclusions were drawn for airway inflammation assessed by eosinophil counts.

*__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

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_448200995230365953.

[a] We downgraded one level for indirectness as the intervention continued in infants after delivery in one study.
[b] We downgraded one level for imprecision as there was a small number of events and the optimal information size was not reached.
[c] We downgraded one level for serious limitations in study design as there was a high risk of bias in at least one domain that was sufficient to lower confidence in the estimate of effect.
[d] We downgraded an additional level for imprecision as the 95% confidence interval included both appreciable benefit and appreciable harm (RR < 0.8 AND > 1.2).
[e] We considered the certainty of the evidence across the different adverse events to be low to very low due mainly to imprecision as there was a small number of events and the 95% confidence interval often included both appreciable harm and appreciable benefit. For some adverse events, there were also concerns about risk of bias and indirectness, as some studies had high risk of bias for at least one domain or the intervention was continued in infants after delivery, further decreasing our certainty in the evidence.
[f] We downgraded one level for inconsistency as there was substantial heterogeneity in intervention effects (P value for Chi2 test < 0.10).

Summary of findings 2. Summary of findings table - Vitamin D compared to placebo/no supplementation in infants or young children

Vitamin D compared to placebo/no supplementation in infants or young children

Patient or population: infants or young children
Setting: participants in the community
Intervention: vitamin D
Comparison: placebo/no supplementation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/no supplementation	Risk with vitamin D				
Incidence of asthma follow-up: range 18 months to 2.5 years	15 per 100	**10 per 100** (7 to 15)	**RR 0.69** (0.47 to 1.03)	588 (3 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]	The evidence is very uncertain about the effect of vitamin D on childhood asthma.
Incidence of wheeze follow-up: range 6 to 12 months	35 per 100	**31 per 100** (24 to 40)	**RR 0.89** (0.68 to 1.16)	431 (2 RCTs)	⊕⊕⊖⊖ Low[b,c]	Vitamin D may have little to no effect on childhood wheeze.
Incidence of atopic dermatitis follow-up: range 6 to 12 months	38 per 100	**39 per 100** (31 to 49)	**RR 1.01** (0.80 to 1.28)	448 (2 RCTs)	⊕⊕⊖⊖ Low[b,c]	Vitamin D may have little to no effect on childhood atopic dermatitis.
Any adverse events follow-up: range 6 months to 2 years	Adverse events were rare and inconsistently reported. Limited data for adverse events evaluated by at least two studies suggest that vitamin D may increase the risk of hypercalcaemia (2 RCTs) but may have little to no effect on elevated serum 25-hydroxyvitamin D (25OHD) (2 RCTs) and infant/child death (2 RCTs).			(4 RCTs)	⊕⊖⊖⊖ Very low[d]	The evidence is very uncertain about the effects of vitamin D on adverse events.
Incidence of any airway infection follow-up: range 12 to 18 months	75 per 100	**69 per 100** (62 to 75)	**RR 0.92** (0.83 to 1.01)	500 (2 RCTs)	⊕⊕⊖⊖ Low[b,c]	Vitamin D may have little to no effect on airway infections. Similar conclusions were reached when considering lower and upper respiratory tract infections separately.

Allergic sensitisation assessed with: serum IgE follow-up: 12 months	3 per 100	**6 per 100** (2 to 23)	**RR 2.25** (0.60 to 8.50)	228 (1 RCT)	⊕⊕⊖⊖ Low[c,e]	Vitamin D may have little to no effect on allergic sensitisation assessed by elevated serum IgE against common allergens. Similar conclusions were drawn for allergic sensitisation assessed by skin prick reactions to common allergens.
Airway inflammation - not measured	-	-	-	-	-	No studies comparing any vitamin D to placebo/no treatment in young children evaluated exhaled nitric oxide. One study found that vitamin D may have little to no effect on elevated eosinophil counts, an alternative measure of airway inflammation.

*__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; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_448243912063113146.

[a] We downgraded one level for inconsistency as there was evidence of substantial heterogeneity in intervention effects (P value for Chi2 test < 0.10).
[b] We downgraded one level for indirectness as the intervention started in participant mothers during pregnancy.
[c] We downgraded one level for imprecision as there was a small number of events and/or the optimal information size was not reached.
[d] We considered the certainty of the evidence across the different adverse events to be low to very low, due mainly to imprecision as there was a small number of events and the 95% confidence interval often included both appreciable harm and appreciable benefit (RR < 0.8 AND > 1.2).
[e] We downgraded an additional level for imprecision as the 95% confidence interval included both appreciable benefit and appreciable harm (RR < 0.8 AND > 1.2).

Summary of findings 3. Summary of findings table - High-dose vitamin D compared to low-dose vitamin D in pregnant or breastfeeding women

High-dose vitamin D compared to low-dose vitamin D in pregnant or breastfeeding women

Patient or population: pregnant or breastfeeding women
Setting: participants in the community
Intervention: high-dose vitamin D
Comparison: low-dose vitamin D

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low-dose vitamin D	Risk with high-dose vitamin D				
Incidence of asthma follow-up: 3 years	17 per 100	**14 per 100** (11 to 17)	**RR 0.81** (0.63 to 1.04)	1355 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	High-dose vitamin D likely has little to no effect on childhood asthma compared to low-dose vitamin D. This conclusion is based on the certainty of the evidence and the confidence interval containing the null. However, we note that the absolute estimate of effect is similar in direction and magnitude to that for wheeze, which included an additional study and more participants.
Incidence of wheeze follow-up: range 1 to 3 years	22 per 100	**17 per 100** (14 to 21)	**RR 0.79** (0.64 to 0.98)	1439 (3 RCTs)	⊕⊕⊕⊖ Moderate[a]	High-dose vitamin D likely reduces childhood wheeze compared to low-dose vitamin D.
Incidence of atopic dermatitis follow-up: range 1 to 3 years	23 per 100	**21 per 100** (17 to 26)	**RR 0.91** (0.75 to 1.11)	1439 (3 RCTs)	⊕⊕⊕⊖ Moderate[a]	High-dose vitamin D likely has little to no effect on childhood atopic dermatitis compared to low-dose vitamin D.
Any adverse events follow-up: range 1 to 3 years	Adverse events were rare and inconsistently reported. Limited data for adverse events evaluated by at least two studies suggest that high-dose vitamin D may have little to no effect on any maternal or infant adverse events compared to low-dose vitamin D.			(3 RCTs)	⊕⊕⊖⊖ Low[b]	High-dose vitamin D may have little to no effects on maternal or child adverse events compared to low-dose vitamin D.
Incidence of any airway infection follow-up: range 9 months to 3 years	32 per 100	**31 per 100** (27 to 36)	**RR 0.95** (0.82 to 1.11)	1441 (3 RCTs)	⊕⊕⊕⊖ Moderate[a]	High-dose vitamin D likely has little to no effect on childhood airway infections compared to low-dose vitamin D. Similar conclusions were drawn for analyses considering lower respiratory tract infections specifically (3 RCTs).
Allergic sensitisation assessed with: serum IgE follow-up: 3 years	31 per 100	**31 per 100** (27 to 37)	**RR 1.01** (0.87 to 1.18)	1110 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	High-dose vitamin D likely has little to no effect on allergic sensitisation assessed by elevated serum IgE against common allergens compared to low-dose vitamin D. Similar conclusions were drawn for allergic sensitisation assessed by total serum IgE (1 RCT) and skin

						prick reactions to common allergens (1 RCT), although the evidence for these outcomes was less certain.
Airway inflammation - not measured	-	-	-	-	-	No studies comparing higher versus lower/standard doses of vitamin D in pregnant or breastfeeding women evaluated exhaled nitric oxide or other measures of airway inflammation.

*__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; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_448244887528726111.

[a] We downgraded one level for imprecision as there was a small number of events and/or the optimal information size was not reached.
[b] We considered the certainty of the evidence across the different adverse events to be low, due mainly to imprecision as there was a small number of events and the 95% confidence interval often included both appreciable harm and appreciable benefit (RR < 0.8 AND > 1.2).

Summary of findings 4. Summary of findings table - High-dose vitamin D compared to low-dose vitamin D in infants or young children

High-dose vitamin D compared to low-dose vitamin D in infants or young children

Patient or population: infants or young children
Setting: participants in the community
Intervention: high-dose vitamin D
Comparison: low-dose vitamin D

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low-dose vitamin D	Risk with high-dose vitamin D				

Incidence of asthma follow-up: range 1 to 2 years	126 per 1000	**93 per 1000** (48 to 182)	**RR 0.74** (0.38 to 1.44)	201 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]	The evidence is very uncertain about the effect of high-dose vitamin D on childhood asthma compared to low-dose vitamin D.
Incidence of wheeze follow-up: 12 months	184 per 1000	**125 per 1000** (94 to 166)	**RR 0.68** (0.51 to 0.90)	1095 (2 RCTs)	⊕⊖⊖⊖ Very low[a,c,d]	The evidence is very uncertain about the effect of high-dose vitamin D on childhood wheeze compared to low-dose vitamin D.
Incidence of atopic dermatitis follow-up: 12 months	189 per 1000	**144 per 1000** (104 to 198)	**RR 0.76** (0.55 to 1.05)	769 (1 RCT)	⊕⊕⊖⊖ Low[a,c]	High-dose vitamin D may may have little to no effect on childhood atopic dermatitis compared to low-dose vitamin D.
Any adverse events follow-up: range 14 weeks to 3 years	Adverse events were rare and inconsistently reported. Limited data for adverse events evaluated by at least two studies suggest that high-dose vitamin D may have little to no effect on infant elevated serum 25-hydroxyvitamin D (25OHD) or hypercalcaemia compared to low-dose vitamin D.			(3 RCTs)	⊕⊖⊖⊖ Very low[e]	The evidence is very uncertain about the effect of high-dose vitamin D on adverse events compared to low-dose vitamin D.
Incidence of any airway infection follow-up: range 14 weeks to 3 years	723 per 1000	**679 per 1000** (651 to 708)	**RR 0.94** (0.90 to 0.98)	2385 (6 RCTs)	⊕⊕⊖⊖ Low[a,d]	High-dose vitamin D may slightly reduce childhood airway infections compared to low-dose vitamin D. The evidence is very uncertain about the effects of high-dose vitamin D specifically on lower respiratory tract infections.
Allergic sensitisation assessed with: serum IgE follow-up: 12 months	165 per 1000	**165 per 1000** (119 to 229)	**RR 1.00** (0.72 to 1.39)	723 (1 RCT)	⊕⊖⊖⊖ Very low[a,c]	The evidence is very uncertain about the effect of high-dose vitamin D on allergic sensitisation assessed by elevated serum IgE levels against common allergens compared to low-dose vitamin D.
Airway inflammation - not measured	-	-	-	-	-	No studies comparing higher versus lower/standard doses of vitamin D in young children evaluated exhaled nitric oxide or other measures of airway inflammation.

*__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; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_448244944287883001.

[a] We downgraded one level for serious limitations in study design as there was a risk of bias in at least one domain that was sufficient to lower confidence in the estimate of effect.
[b] We downgraded one level for indirectness as the intervention started in participant mothers during pregnancy in one study.
[c] We downgraded one level for imprecision as there was a small number of events and/or the optimal information size was not reached.
[d] We downgraded one level for inconsistency as there was substantial heterogeneity in intervention effects (P value for Chi2 test < 0.10).
[e] We considered the certainty of the evidence across the different adverse events to be low, due mainly to imprecision as there was a small number of events and the 95% confidence intervals included both appreciable harm and appreciable benefit (RR < 0.8 AND > 1.2). There were also concerns about risk of bias as all studies had high or unclear risk of bias for at least one domain, further decreasing our certainty in the evidence.

BACKGROUND

Description of the condition

Asthma is a chronic lung disease characterised by recurrent attacks of breathlessness, coughing, and wheezing due to inflammation, mucus production, and narrowing of the airways. Asthma is one of the most common chronic conditions in childhood, with a global lifetime prevalence in children aged six to seven years estimated at 9.0%, and country-specific estimates ranging from 0.4% to 23.9% (Asher 2021). Asthma is a leading cause of emergency department visits and hospitalisations in children (Masoli 2004), as well as school absences and associated missed days of work for caregivers (Kraemer 1994; Weiss 2000). It often requires long-term medical management, costing billions annually (Nunes 2017; Perry 2019). Global death rates attributed to childhood asthma are estimated at 0.5 per 100,000 population, with higher rates in children under five years of age (Zhang 2022). Asthma in early childhood can also contribute to long-term lung function loss and increase the risk of chronic obstructive pulmonary disease (COPD) in adulthood – a leading cause of mortality worldwide (Sears 2003; Tai 2014).

The diagnosis of asthma is typically based on the presence of recurrent respiratory symptoms including wheeze, shortness of breath, cough, and chest tightness, in response to known and unknown triggers, including viral infections, aeroallergen or irritant exposure, exercise, and cold air. In adults and children older than five years of age, an asthma diagnosis can be supported by lung function testing with spirometry that demonstrates reversible airflow limitation (Gaillard 2021; GINA 2022). Confirming asthma diagnoses in infants and young children can be difficult, as episodes of wheezing and prolonged cough are common and not necessarily specific to asthma, and widespread objective lung function testing is not feasible. In children younger than five years, asthma diagnosis may be suspected based on respiratory symptom patterns, medical history (including past or family history of asthma or other allergic diseases (atopic dermatitis, allergic rhinitis, food allergies)), physical examination findings, and clinical improvement in symptoms with a two- to three-month trial of controller treatment (inhaled corticosteroids and/or leukotriene modifiers) that reverses when treatment is stopped (GINA 2022). However, because these factors are not specific to asthma, it is recommended that young children with suspected asthma are followed closely for the progression and persistence of symptoms and response to asthma medication (NICE 2017).

The development of childhood asthma and its persistence into adulthood is hypothesised to be driven by early life gene-environment interactions. Factors that increase the risk of developing asthma include a family history of asthma in a first degree relative, maternal smoking during pregnancy, early life environmental tobacco smoke exposure (also referred to as secondhand or passive smoking), early life atopy and/or allergic sensitisation (which often precedes childhood asthma in what is known as the "atopic march"), and the occurrence of respiratory tract infections (RTIs), especially lower RTIs (Castro-Rodríguez 2000; GINA 2022; Paller 2019; Pavord 2018). Factors that protect against the development of asthma are more elusive. Experts largely agree that there is a window of opportunity during the prenatal period and in early life to prevent the development of asthma (GINA 2022). However, evidence from intervention studies is limited, and current recommendations for the primary prevention of childhood asthma are restricted to avoiding exposure to tobacco and other pollutants during pregnancy and the first year of life, encouraging vaginal delivery, and avoiding broad-spectrum antibiotics during the first year of life (GINA 2022). Breastfeeding is also recommended, although for general health reasons. Evidence for an effect of breastfeeding on asthma risk is inconsistent: the results from some studies show a beneficial effect, while the results of other studies are less convincing (Azad 2017; Bigman 2020; Harvey 2020). Given the worldwide prevalence of childhood asthma, identifying additional strategies for the primary prevention of childhood asthma is critical. Vitamin D nutritional status during pregnancy and early life represents an easily modifiable factor that may influence the development of childhood asthma, and multiple studies have evaluated the effects of vitamin D interventions in early life on asthma development and associated factors. Summarising the evidence from these studies is important to understand the plausibility of vitamin D supplementation as a strategy to prevent childhood asthma.

Description of the intervention

This section describes the biochemical properties of vitamin D, its functional effects, and the public health relevance of vitamin D interventions.

Vitamin D is a secosteroid that occurs in two forms: cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Within the body, vitamin D must be activated to the hormonal form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), via a two-step hydroxylation process. The first hydroxylation produces 25-hydroxyvitamin D (25(OH)D). Serum 25(OH)D is used to assess vitamin D status, and it reflects the supply of vitamin D from dietary intake and cutaneous production (Ross 2011). A further hydroxylation produces $1,25(OH)_2D$. Vitamin D_3 is produced in the skin upon exposure to ultraviolet B light within the 290 to 315 nm range (Holick 2008; Ross 2011). Vitamin D_3 and vitamin D_2 may be consumed in the diet; both vitamin D_3 and vitamin D_2 occur naturally in a limited number of foods and are included in some fortified foods and dietary supplements (Holick 2008; Ross 2011). The physiologic effects of vitamin D are mediated mainly through $1,25(OH)_2D$ via interaction with the vitamin D receptor (VDR) and subsequent regulation of gene expression (Bikle 2000).

Vitamin D is critical for maintenance of calcium and phosphorus homeostasis and bone health. Public health and clinical guidelines on vitamin D are based on the relation of serum 25(OH)D concentration to bone health. In the USA, the recommended dietary allowance (RDA) for vitamin D to prevent risk of vitamin D deficiency is 600 international units (IU)/day for most life stage groups, including pregnant/lactating women and children aged one year or older (Ross 2011). Other high-income countries have similar public health recommendations. Pregnant women in many high-income countries are instructed to consume a daily multivitamin-mineral supplement. In the USA, these prenatal supplements typically contain 400 IU of vitamin D (ACOG 2011). Thus, most pregnant women in high-income countries consume some supplemental vitamin D as part of routine prenatal care. A similar situation applies in infancy. Breast milk normally has little vitamin D content, and the American Academy of Pediatrics recommends that all breastfed infants receive 400 IU per day of supplemental vitamin, usually in the form of liquid drops (Wagner 2008). Supplemental vitamin D is administered orally in most cases; however, vitamin D formulations for intramuscular injection are available in some countries (Dawson-Hughes 2018).

In the late 20th century, researchers discovered that many cells with no known role in bone mineral homeostasis, including cells in the reproductive system, airway, skin, and immune system, express CYP27B1 (the primary enzyme responsible for conversion of 25(OH)D to $1,25(OH)_2D$). This suggests an extraskeletal function of vitamin D in these tissues and in the immune system. However, optimal serum 25(OH)D levels for preventing outcomes other than adverse bone outcomes have not been established, and prevention of outcomes not related to bone health may require doses higher than those provided during usual care. Studies have therefore tested whether providing supplemental vitamin D at levels above the recommended intake prevents extraskeletal outcomes such as immune outcomes (Aglipay 2017; Litonjua 2016). In general, these experimental doses have not exceeded age-specific tolerable upper intake levels, which range from 1000 IU/day for infants up to six months of age, to 4000 IU/day for children nine years of age and older and adults (including pregnant and lactating women). Doses higher than the age-specific tolerable upper intake levels have typically been administered on a weekly or less frequent basis.

The serum 25(OH)D response to vitamin D supplementation depends on the dose and duration of supplementation. It also depends on vitamin D status at baseline, as the response is non-linear and is greater in individuals with low baseline status (Ross 2011). The serum 25(OH)D concentration has been shown to plateau after six weeks of supplementation with a given dose (Ross 2011). For the same cumulative dose, weekly is as effective as daily administration, and some but not all studies have found that monthly bolus dosing is also effective (Ross 2011).

How the intervention might work

This section describes previous evidence of the various biological pathways through which vitamin D affects the immune and airway systems and may contribute to the primary prevention of childhood asthma (Bikle 2012; Litonjua 2012).

Vitamin D may influence the development of childhood asthma and factors associated with asthma through its many immunomodulatory effects, including regulation of T cell populations and support of the innate immune response. Most cells of the immune system express the VDR (Hewison 2012). Macrophages and dendritic cells also express the activating enzyme CYP27B1 to produce $1,25(OH)_2D$ (Fritsche 2003; Kreutz 1993). Overall, $1,25(OH)_2D$ restrains inflammation (Dimeloe 2012); for example, by inducing the secretion of anti-inflammatory T regulatory cell (Treg) cytokines (Hewison 2012; Mullin 2007), and by suppressing pro-inflammatory cytokines (Cantorna 2014). Tregs suppress inappropriate immune activation and are thought to be a critical factor in protecting against allergic sensitisation; evidence shows that $1,25(OH)_2D$ promotes induction of Tregs either directly or through dendritic cells (Barrat 2002; Chambers 2011; Unger 2009). $1,25(OH)_2D$ also regulates the balance between T helper type 1 and type 2 cells and suppresses the T helper type 17 inflammatory response (Daniel 2008; Pichler 2002). Because T cell regulation begins during foetal life (Mold 2008), and because the immune system matures rapidly in infancy, exposure to vitamin D in early life may impact the development of the immune system and the risk of paediatric asthma. Beyond its influence on T cells, $1,25(OH)_2D$ supports the immune response in the airways and at epithelial barriers of the skin, including through expression of antimicrobial peptides (Wei 2015).

Vitamin D may also affect asthma risk through non-immunologic pathways. For example, the airway epithelial cells and the skin keratinocytes express CYP27B1 and VDR, indicating that both the airway and the skin can produce and respond to vitamin D directly (Bikle 2012; Hansdottir 2008). The fact that both foetal lung fibroblasts and pulmonary alveolar type II cells contain the VDR may support a possible role for vitamin D in foetal lung development (Liu 2014), lung maturation, and surfactant production (Rehan 2002; Weiss 2011). Animal, laboratory, and gene expression studies have suggested that vitamin D impacts lung structure and function during the early lung development period (Chen 2016; Foong 2015; Kho 2013; Lykkedegn 2015). Additionally, vitamin D is important for the proper functioning of the reproductive system, which in turn regulates and supports early immune system development and lung maturation (Arshad 2022; Mansur 2022; Wagner 2018).

Why it is important to do this review

Current therapies for asthma can control inflammation and symptoms but cannot entirely prevent irreversible damage to the airway (Berair 2014). The 2017 Commission on Asthma, published in *The Lancet*, called on the medical community to move beyond management of asthma attacks towards a greater focus on primary prevention (Camargo 2018).

One-third of pregnant women in the USA are at risk of inadequate vitamin D status (Ginde 2010), and most breastfed infants require supplementation to avoid risk of vitamin D deficiency (Wagner 2008). Current clinical guidelines do not include recommendations for routine screening of vitamin D status in obstetric and paediatric patients (ACOG 2011; Wagner 2008). If vitamin D supplementation can reduce the risk of developing asthma, atopic dermatitis, or both in childhood, the potential population health benefit of improving vitamin D status during pregnancy and in early childhood could be substantial. Furthermore, the annual cost of daily vitamin D supplementation is inexpensive relative to the annual cost of managing asthma (Nunes 2017).

Observational studies have connected low vitamin D status (i.e. low serum 25(OH)D concentration) in early childhood to increased risk and severity of atopic disease later on (Anderson 2015; Camargo 2011; Erkkola 2009; Jones 2012). In the USA, African Americans are at increased risk of low serum 25(OH)D, paediatric asthma, and atopic dermatitis (Freishtat 2010). However, some observational studies have reported an opposite (i.e. positive) association between vitamin D exposure and risk of allergy and atopy (Back 2009; Hypponen 2004). Several randomised controlled studies have directly tested whether vitamin D supplementation in early life can reduce asthma incidence and related outcomes in children. While individual studies have not consistently shown a protective effect of vitamin D supplementation against childhood asthma, a meta-analysis combining data from two flagship studies intervening in pregnant women – Chawes 2016 and Litonjua 2016 – provided evidence of a 25% reduction in the risk of asthma/recurrent wheeze at zero to three years of age (Wolsk 2017). Conducting a systematic review and meta-analysis to identify and combine all available data on vitamin D interventions to prevent childhood asthma is important to understand the effectiveness of vitamin D exposure in pregnancy and early life for preventing childhood asthma.

Thus far, one Cochrane review has reported on the role of vitamin D in the management of asthma in adults and children (Martineau 2016; updated Williamson 2023). However, no Cochrane review has examined vitamin D for the prevention of asthma. One systematic review published in 2017 investigated the effects of vitamin D supplementation in pregnancy on prevention of allergic outcomes in children, but it did not include any randomised controlled trials (RCTs) in which vitamin D supplementation was given to children (Vahdaninia 2017). Another systematic review covered vitamin D supplementation in both pregnancy and early childhood, but it did not include RCTs that compared high-dose to low-dose vitamin D supplementation (Yepes-Nuñez 2018). Drawing on the Yepes-Nuñez 2018 review, the World Allergy Organization's guidelines for allergic disease prevention recommended against vitamin D for the prevention of allergic diseases in children – a conditional conclusion characterised by evidence of very low certainty (Yepes-Nuñez 2016). Given that most prenatal multivitamin-mineral supplements contain vitamin D (typically 400 IU), and that prenatal supplementation is part of usual care in many countries, the systematic review by Yepes-Nuñez and colleagues is incomplete because at least two larger trials have studied multiple doses of vitamin D supplementation in pregnant women (Chawes 2016; Litonjua 2016). Further, to our knowledge, no systematic review has specifically considered the effects of vitamin D in the context of key asthma risk factors, such as family history of allergic disease and cigarette smoke exposure, which could modify the vitamin D effect. This Cochrane review – which considers trials intervening in pregnant or breastfeeding women or young children with any vitamin D versus placebo/no vitamin D and higher doses of vitamin D versus lower doses of vitamin D – is needed to estimate the efficacy of vitamin D supplementation for preventing childhood asthma.

Summarising and grading the evidence on the benefits and harms of vitamin D supplementation for preventing childhood asthma using Cochrane methods is important for healthcare policy-makers and for clinical practice. This systematic review contributes to the evidence base that clinicians use to make informed decisions on the management of vitamin D status in pregnant women, lactating women, infants, and young children for the prevention of asthma. Results of this review may be especially relevant for people at risk of vitamin D deficiency and those at elevated risk of allergic disease.

OBJECTIVES

Primary: to evaluate the efficacy of any vitamin D supplementation and high-dose vitamin D supplementation in early life, including the prenatal period, for preventing asthma in children.

Secondary: to assess the efficacy of vitamin D supplementation:

- for preventing asthma in children at risk of vitamin D deficiency at the start of the trial or whose mothers were at risk;
- by intervention timing and the cumulative dose administered;
- in preventing factors associated with early childhood asthma, including atopic dermatitis, respiratory tract infections, sensitisation to allergens, and airway inflammation.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled studies. We included open-label studies, so long as interventions were randomly allocated, and addressed potential bias introduced by lack of blinding through sensitivity analyses, defined as "a repeat of the primary analysis or meta-analysis, substituting alternative decisions or ranges of values for decisions that were arbitrary or unclear" (Higgins 2011), to examine whether the findings still hold when only certain type(s) of studies are included (e.g. only studies with appropriate blinding). We included data reported in full-text papers, data published in abstract form only, and unpublished data obtained from email correspondence with the authors of the published studies where appropriate.

Types of participants

We included studies that intervened with vitamin D supplementation in the first five years of life, including the foetal period. For studies that intervened in pregnancy, we planned to include all studies regardless of the stage of pregnancy when the intervention occurred. We restricted participants to the first five years of life to target primary prevention of childhood asthma – the main outcome of this review. This decision was guided by evidence that the development of asthma and atopic dermatitis begins in early childhood, with most cases presenting by the age of five (Sawicki 2018; Thomsen 2015), and that interventions occurring after this aetiological period may therefore be ineffective for primary prevention. We included any studies that measured or planned to measure our outcomes of interest (e.g. asthma, wheeze) through the teenage years (< 19 years old), as long as vitamin D supplementation was implemented during the first five years, including the foetal period. We included studies which provided vitamin D to the following types of participants: healthy pregnant or lactating females, healthy preterm or full-term infants, and/or healthy children up to five years of age.

Because our objective was to evaluate vitamin D for the primary prevention of asthma, we excluded studies that recruited infants or children with asthma or recurrent wheeze. However, we included studies that recruited participants with a family history of atopic disease, as these studies may represent high-risk populations. We also included studies in preterm infants, as long as the infants were generally healthy and not receiving respiratory support, as these studies may also represent high-risk populations (Caffarelli 2023). We excluded studies designed for other diseased populations (e.g. studies in pregnant women with gestational diabetes or in children with atopic dermatitis or diabetes). Other diseases for exclusion included, but were not limited to: comorbidities such as any suppurative airway disease including cystic fibrosis; and any systemic disease including anaemia, bone disease, renal disease, immunodeficiency/autoimmune disease, and cancer.

For our primary analysis, we meta-analysed interventions targeting mothers and interventions targeting infants or children separately. Given immune system development begins in utero and continues through infancy and childhood, we also performed exploratory meta-analyses combining all interventions regardless of the type of participant who received the intervention.

If only a subset of a study's participants fit our criteria (e.g. the study provided vitamin D intervention to children aged two to six years old), we contacted the study investigators for assistance in disaggregating the data if the published report did not provide the needed information. We moved these studies to the category of "awaiting classification" if disaggregation of the data was not possible.

Types of interventions

We included studies that compared any dose of vitamin D supplementation (oral or injectable form of vitamin D_2 or D_3) versus placebo or no supplementation, as well as studies that compared higher-dose vitamin D supplementation with lower-dose/standard of care vitamin D supplementation. The decision to include both comparisons was motivated by two main factors. First, the optimal dose and duration of vitamin D to prevent asthma is unknown, and second, low-dose vitamin D (400 to 600 IU per day) is included in the standard of care for pregnant persons and infants in many countries. These doses are recommended to prevent vitamin D deficiency, but not all individuals require supplemental vitamin D to maintain sufficient serum vitamin D levels. In addition, current definitions of deficiency/sufficiency levels are based mainly on skeletal outcomes, and some researchers hypothesise that doses above the recommended daily intake may help prevent extraskeletal outcomes.

We included any co-intervention as long as it was equivalent in intervention and comparator groups (e.g. a common co-intervention is calcium or a prenatal vitamin). We excluded RCTs that administered vitamin D metabolites such as 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, which are available in pharmaceutical forms. In addition, we excluded any studies of vitamin D-fortified foods. Because the critical period for intervention and the target level of serum 25-hydroxyvitamin D for preventing asthma are unknown, we included studies of any duration.

For our primary analysis, we performed separate meta-analyses to summarise the intervention effect of any vitamin D supplementation versus placebo/no supplementation and the intervention effect of higher-dose vitamin D versus lower-dose vitamin D/standard of care. In light of the considerations outlined above, for our primary outcomes, asthma and wheeze, we also present the results of exploratory meta-analyses combining all studies regardless of comparator.

Types of outcome measures

We reviewed the evidence for prevention of the occurrence of childhood asthma and associated factors, ascertained in children (< 19 years of age). For each study, we prioritised outcome data reported at the last time point specified in the original trial registry.

Primary outcomes

- Asthma – as defined by trial authors
- Wheeze – as defined by trial authors

We included all studies evaluating author-defined asthma, and performed sensitivity analyses to segregate physician-assessed asthma from parent-reported asthma. Because confirmation of asthma diagnosis may not be possible in infants and young children, we also considered wheeze as a primary outcome. We included all studies evaluating author-defined wheeze, and performed sensitivity analyses for studies evaluating persistent/recurrent wheeze, which is more clinically predictive of childhood asthma than 'ever wheeze' (defined, variously, by two included studies as any wheezing episodes in the previous 12 months or since birth). For both asthma and wheeze, we prioritised outcome data reported at the last time point specified in the original trial registry.

Secondary outcomes

- Atopic dermatitis – as defined by trial authors
- Any adverse event – to measure the safety of vitamin D supplementation. We included all author-defined adverse events, including obstetric complications, perinatal outcomes, and any unwanted effects in infants or young children, that were observed in trial participants during the intervention, the follow-up period, or both, regardless of age at the time of the adverse event.
- Airway infection (e.g. any upper or lower respiratory tract infection)
- Sensitisation to allergens (including serum immunoglobulin E (IgE) level and skin prick test results)
- Airway inflammation (any tests for peripheral blood eosinophil/neutrophil counts, sputum eosinophil/neutrophil counts, or exhaled nitric oxide (eNO or FeNO))

We included sensitisation to allergens because this can precede atopic dermatitis and asthma.

If studies defined an outcome differently, we conducted a meta-analysis that combined studies with compatible definitions and narratively described the results from studies with incompatible outcomes. For outcomes that are either physician-assessed or parent-assessed, we performed sensitivity analysis including only studies with the physician-assessed outcomes. For airway infection, we performed a meta-analysis for any airway infection (i.e. any author-defined airway infection, including upper or lower airway infection), as well as separate meta-analyses for upper and lower airway infections, and conducted sensitivity analysis including only studies with physician-assessed respiratory tract infections and/or respiratory tract infections assessed with diagnostic tests (i.e. laboratory tests, chest radiograph). For adverse events, we performed separate meta-analyses for all specific events evaluated by at least two studies. For allergic sensitisation and airway inflammation, we performed separate meta-analyses when results for IgE, skin prick tests, peripheral white blood cell counts, and exhaled nitric oxide were expressed as continuous or dichotomous outcomes.

For all secondary outcomes, we prioritised data reported at the last time point specified in the original trial registry.

We did not use types of outcome measures as a criterion for inclusion at the study screening stage. If the study title or abstract made it clear that the study investigated an eligible intervention, we screened the full text and any associated protocols and trial registries to ascertain whether the study measured or planned to measure asthma, wheeze, atopic dermatitis, respiratory tract infection, sensitisation to allergens, or airway inflammation.

Search methods for identification of studies

Electronic searches

The Cochrane Airways Information Specialist identified studies from the following sources.

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, via the Cochrane Register of Studies Online (crso.cochrane.org)
- Cochrane Airways Trials Register and the Cochrane Skin Trials Register
- MEDLINE Ovid SP 1946 to date
- Embase Ovid SP 1974 to date
- US National Institutes of Health Ongoing Trials Register – ClinicalTrials.gov (www.clinicaltrials.gov)
- World Health Organization International Clinical Trials Registry platform (apps.who.int/trialsearch)

The search strategy for each source is presented in Appendix 1. All databases were searched from their inception to 23 October 2023, and there was no restriction on language of publication.

Searching other resources

We checked the reference lists of relevant reviews and meta-analyses for additional references. We also searched relevant clinical trial registry websites for additional study information.

On 16 May 2024, we searched PubMed for errata or retractions related to the included studies published as full-text reports, following the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Technical Supplement to Chapter 4: Searching for and selecting studies, Section 3.9; Higgins 2022). We did not include retracted studies in this review, and we noted any errata in the description of the included studies.

Data collection and analysis

Six review authors (BP, JX, CB, JB, AV, BS) contributed to data collection and analyses, including abstract screening, full-text review, data extraction, and risk of bias assessment. All steps were performed in duplicate and independently by two review authors, and disagreements were addressed through a third review author (PC) who served as a tie-breaker. Four review authors (BP, JX, CB, PC) contributed to the assessment of the certainty of the evidence, and any disagreements were resolved through discussion among review authors.

Selection of studies

We used Cochrane's Screen4Me workflow to help assess the search results and determine what papers to include for title and abstract screening. Screen4Me comprises three components: known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and labelled as an RCT or as 'Not an RCT'; the RCT classifier – a machine learning model that distinguishes RCTs from non-RCTs, and if appropriate, Cochrane Crowd – Cochrane's citizen science platform where the Crowd help to identify and describe health evidence (Marshall 2018; Noel-Storr 2020; Noel-Storr 2021; Thomas 2021). More information about Screen4Me and the evaluations that have been done can be found at the Screen4Me webpage. In this review, we used the Crowd Known Assessments and RCT Classifier components of the Screen4Me workflow.

After Screen4Me exclusion, two review authors independently screened the titles and abstracts of the remaining records and voted to "include" (eligible or potentially eligible/unclear) or "exclude" each record using Covidence (https://www.covidence.org/). If the two authors did not agree on whether to include or exclude a record, a third author served as a tiebreaker. Full-text reports of all records for which the consensus was to "include" (i.e. studies meeting our inclusion criteria for types of studies, types of interventions, and types of participants) were then retrieved for full-text review. Two review authors independently reviewed the full-text reports for inclusion in the review and recorded the reasons for exclusion of ineligible studies. We identified and collated multiple records reporting on the same study, so that each study, rather than each record, is the unit of interest in the review. We excluded duplicate studies. We were not blinded to the names of study authors, institutions, and journals, nor to the results of included studies. Any disagreement on the inclusion/exclusion of studies was resolved through discussion or through a third review author who conducted an independent review (blinded to the votes of other review authors) and served as the tie-breaker; all decisions were fully discussed and documented. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and a 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

Two review authors independently extracted data using a customised, piloted data extraction form developed from the Cochrane Airways Group's data collection form template. Data extraction elements included author information, methods, participants included/excluded, intervention details, outcomes assessed, and results (see Appendix 2 for a detailed list of the data sought and extracted).

Two review authors then entered the information into the data extraction form within Covidence. We finalised the extracted data by comparing the data extracted by each review author, discussing any disagreements, and consulting a third review author when necessary to adjudicate any disagreements. We consulted study entries in trial registries and other publications of included studies (such as published protocols) for study details as necessary. We contacted study authors to request information or additional data if any elements were missing or unclear. For example, some studies have measured outcomes of interest in this review but reported the outcomes in a way that precluded meta-analysis with other studies. In these cases, we reached out to the authors for more information (e.g. number of children with outcomes per intervention arm). If we were unable to obtain clear information necessary for the review, we indicated that these data were missing or unclear, and listed the study as "awaiting classification". We manually entered the final data into Review Manager (RevMan 2024). One pair of review authors were assigned to each primary/secondary outcome and verified that the data in RevMan for meta-analysis was transferred correctly by comparing the data presented in RevMan against the final version of extracted data in Covidence. We also spot-checked study characteristics in RevMan against the original study report for accuracy.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were resolved by discussion or by consultation with the review group. We were not blinded to the names of study authors, institutions, and journals, nor to the results of included studies.

We judged each potential source of bias as high, low, or unclear, and provided justification for our judgement in the risk of bias table. We summarised risk of bias judgements across the included studies for each of the domains listed below. Risk of bias was considered separately for different outcomes when necessary. Where information on risk of bias was related to unpublished data or correspondence with a study author, we noted this in the risk of bias table. When considering supplementation effects, risk of bias was accounted for through sensitivity analyses.

We assessed the risk of bias according to the following domains (below are the domains of risk of bias for individual-level controlled studies with two intervention arms; additional domains of risk of bias related to cluster-randomised studies and studies with more than two intervention arms are presented in Appendix 3) (Higgins 2011).

- Random sequence generation – (1) high risk of bias: if the study used some systematic, non-random approach to generate the sequence, such as using odd or even dates of birth, dates of admission, clinical record numbers, judgement of the clinician, preference of participants, results of a lab test, or availability of the intervention; (2) low risk of bias: if the study used a random sequence generation process such as a random numbers table, a computer random number generator, coin tossing, shuffling of cards or envelopes, dice throwing, or drawing of lots; or (3) unclear risk of bias: if there was insufficient information to make a judgement of low or high risk.
- Allocation concealment – (1) high risk of bias: if the study used an open random allocation schedule (e.g. a list of random numbers), envelopes without appropriate safeguards (e.g. unsealed, non-opaque, not sequentially numbered), alternation/rotation, date of birth, case record number, or any other unconcealed procedure; (2) low risk of bias: if the study used central allocation (e.g. telephone, web-based, pharmacy-controlled randomisation), sequentially numbered drug containers of identical appearance, or sequentially numbered, opaque, sealed envelopes, so that investigators and participants could not foresee assignments; or (3) unclear risk of bias: if there was insufficient information to make a judgement of low or high risk.
- Blinding of participants and personnel – (1) high risk of bias: if there was incomplete or no blinding of participants and personnel; (2) low risk of bias: if the outcome was not likely to be influenced by lack of blinding, or if blinding was ensured; or (3) unclear risk of bias: if there was insufficient information to make a judgement of low or high risk, or if the study did not address this issue.
- Blinding of outcome assessment – (1) high risk of bias: if there was incomplete or no blinding of outcome assessors; (2) low risk of bias: if the outcome was not likely to be influenced by lack of blinding, or if blinding was ensured; or (3) unclear risk of bias: if there was insufficient information to make a judgement of low or high risk, or if the study did not address this issue.
- Incomplete outcome data – (1) high risk of bias: the reason for missing data was related to true outcomes, or imputation of missing data was inappropriate, or missing data were sufficient to have induced clinically relevant bias, or the "as-treated" analysis was done with substantial departure of the intervention received from that assigned at randomisation; (2) low risk of bias: if there were no missing data, or missing data had been imputed appropriately, or the reason for missing data was not related to the outcome, or missing data were balanced in numbers across groups with similar reasons, or missing data represented a small proportion or had little difference in effect size compared with that observed so as not to have had a clinically relevant impact on the observed effect estimate; or (3) unclear risk of bias: if there was insufficient information about exclusion and attrition to make a judgment of low or high risk of missing data, or the study did not address this issue.
- Selective outcome reporting – (1) high risk of bias: if the study did not report all prespecified primary outcomes, or primary outcomes were reported using measurement(s), analysis method(s), or subsets of the data that were not prespecified, or a reported primary outcome was not prespecified (unless clear justification was provided), or a primary outcome was reported incompletely so that it could not be entered into a meta-analysis, or the study failed to include results for a key outcome that one would expect to be reported by such a study. If the RCT had a clinical trial registration number, we compared outcomes described in the trial protocol or in registry databases with those reported in the final paper. We also compared outcomes described in the methods sections of papers with those actually reported in the results sections for bias assessment; (2) low risk of bias: if the study's prespecified (primary and secondary) outcomes were reported in the prespecified way (e.g. in the trial registry, study protocol or paper methods); or (3) unclear risk of bias: if there was insufficient information to make a judgement of low or high risk.
- Other bias – (1) high risk of bias: potential bias related to specific study design, or the study has been claimed to have been fraudulent, or the study has some other problem; (2) low risk of bias: if the study seems to have no other bias; or (3) unclear risk of bias: if there was insufficient information to evaluate whether there is an unidentified important risk of bias, or whether an identified problem will lead to bias.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol (Best 2019), and justified any deviations from it in Differences between protocol and review.

Measures of treatment effect

For dichotomous outcomes (e.g. incidence of asthma), we presented the risk ratio (RR) with 95% confidence interval (CI), as the RR provides a direct comparison of risks that are directly calculated from the data for most trials. For continuous outcomes (e.g. serum IgE), we presented either the mean difference (MD) and 95% CI using the same scale between studies, or the standardised mean difference (SMD) and corresponding 95% CI. When results were based on transformed data (i.e. geometric means), meta-analysis was conducted on the transformation scale (i.e. natural log scale rather than geometric means), as described in the *Cochrane*

Handbook for Systematic Reviews of Interventions (Chapter 6, section-6-5-2-4, Higgins 2022).

Any data from rating scales were entered with a consistent direction of effect (e.g. lower scores always indicate improvement).

We undertook meta-analyses only where it was meaningful; that is, when interventions, participants, outcomes, and the underlying clinical question were similar enough for pooling to make sense.

We planned to describe skewed data narratively (e.g. as medians and interquartile ranges for each group).

If both changes from baseline and endpoint scores were available for continuous data, we planned to use changes from baseline. When a study reported outcomes at multiple time points, we used the last time point specified in the original trial registry.

We used intention-to-treat (ITT) or "full analysis set" analyses where they were reported (i.e. those where data have been imputed for participants who were randomly assigned but did not complete the study) instead of complete or per-protocol (PP) analyses.

Unit of analysis issues

For dichotomous outcomes, we used participants, rather than events, as the unit of analysis (e.g. number of children having persistent wheezing rather than number of wheezing events per child). If only rate ratios or incidence rates were reported in a study, and we were unable to obtain the number of participants, we described the study results narratively.

We planned to include both individual- and cluster-randomised studies. If cluster-randomised studies had estimates at the individual level while taking clustering into account, by using methods such as multilevel models, generalised estimating equations, or variance component analysis, we planned to meta-analyse the effect estimates and standard errors for the cluster-randomised studies with other individual-randomised studies using the inverse-variance method in Review Manager. If cluster-randomised studies performed analysis on individuals without taking clustering into account, we planned to try to extract information about the outcome data, including total sample size, an estimated intraclass correlation coefficient (ICC) from the trial itself or other similar studies, the number of clusters in each intervention group, and the average size of each cluster, use the extracted information to estimate the effective sample size and/or inflated variance for these cluster-randomised studies, and incorporate the adjusted estimates into the inverse-variance meta-analysis in Review Manager (Chapter 16; Higgins 2011). If cluster-randomised studies performed analysis on individuals without taking clustering into account, and we could not extract information to estimate the effective sample size or inflated variance, we planned to request data from study investigators. For any analysis combining data from individual- and cluster-randomised studies, we planned to consider differences in effects being assessed in different types of studies (e.g. herd effect in cluster-randomised studies) with sensitivity analyses to investigate whether the findings are consistent when only individual-level studies are included. We also assessed individual-randomised trials for potential clustering that could have occurred (e.g. the same physician delivered the intervention to a certain number of participants) and planned to consider the issues of cluster-randomised studies in these studies as well.

To overcome the unit of analysis error in multi-arm studies, we combined groups to create a single pairwise comparison if possible; that is, we combined all groups with the same intervention of interest into a single intervention group, and combined all various control groups into a single control group. For dichotomous outcomes, the sample size and the number of people with events were summed across multiple intervention groups to a single intervention group and a single control group, and for continuous outcomes, means and standard deviations of the multiple intervention groups were combined into a single intervention group and a single control group using a formula described in detail in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 7, Section 7.7.3.8; Higgins 2011).

We performed meta-analysis only on studies reporting raw data (i.e. number of children with incident asthma or mean serum IgE) from ITT analysis. For studies that reported only adjusted effect estimates, we recorded these estimates and described the results narratively.

Dealing with missing data

We contacted study investigators to request any missing data necessary for ITT meta-analysis, including for studies presented only in abstract form or conference proceedings where we could not find a full report. After obtaining any additional data, we reassessed and characterised the missingness for each study. We took into consideration any potential bias introduced due to missingness through sensitivity analysis limited to studies with low risk of bias due to missing data, as well as the GRADE rating for affected outcomes.

Assessment of heterogeneity

We used the I^2 statistic to quantify inconsistency across studies in each analysis and followed the guide below to interpret the I^2 statistic (Chapter 9; Higgins 2011):

- 0% to 40%: may not be important heterogeneity;
- 30% to 60%: may represent moderate heterogeneity*;
- 50% to 90%: may represent substantial heterogeneity*;
- 75% to 100%: considerable heterogeneity*.

*The importance of the I^2 statistic could depend on several factors, including (1) magnitude and direction of effects, and (2) strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, confidence interval of I^2; uncertainty in I^2 could be substantial when the number of studies included is small).

If we identified substantial heterogeneity, we first checked whether the imported data were correct and whether estimates used the same scale and unit. If data were imported correctly, we reported the heterogeneity and explored possible causes with our prespecified subgroup analysis and meta-regression. If we observed substantial heterogeneity for a given outcome that could not be explained through prespecified subgroup analysis or meta-regression, we downgraded the evidence for inconsistency.

Assessment of reporting biases

Our search strategy was designed to identify all registered clinical studies of vitamin D supplementation for asthma/wheeze and related outcomes, including ongoing studies and results reported in conference proceedings. For any outcome where we were able

to meta-analyse more than 10 studies, we created and examined a funnel plot to explore possible small study and publication biases.

Data synthesis

We performed analyses for four comparisons: (1) any vitamin D versus placebo/no supplementation in pregnant or breastfeeding women; (2) any vitamin D versus placebo/no supplementation in infants or children; (3) high-dose versus low/standard (≤ 400 IU/day) dose vitamin D in pregnant or breastfeeding women; and (4) high-dose versus low/standard (≤ 400 IU/day) dose vitamin D in infants or children. For each comparison, we performed meta-analysis for all of our primary and secondary outcomes evaluated and similarly defined by at least two studies. For our primary outcomes, asthma and wheeze, we also present the results of an exploratory meta-analysis combining all studies meeting our inclusion criteria, regardless of the type of participant receiving the intervention and the intervention dose and comparator. We used Review Manager for conducting all meta-analyses. We used the inverse-variance method for continuous outcomes and the Mantel-Haenszel method for dichotomous outcomes.

We conducted sensitivity analyses restricted to studies with a low risk of bias. If the results from these analyses differed from the main analysis, we planned to rely more on the findings from studies at low risk of bias.

We used fixed-effect models for all analyses and examined heterogeneity by evaluating the I^2 statistic (as described above) and through subgroup analysis.

Subgroup analysis and investigation of heterogeneity

For each comparison, we carried out the following subgroup analyses where the number of studies allowed. All subgroup analyses were conducted at the study level.

- Mean participant serum 25-hydroxyvitamin D concentration at baseline (< 12 ng/mL versus ≥ 12 ng/mL and < 20 ng/mL versus ≥ 20 ng/mL and < 30 ng/mL versus ≥ 30 ng/mL), given that the intervention effect may depend on baseline levels. We considered multiple potential thresholds because the optimal levels to prevent extraskeletal effects are not known.
- Participants with a family history of atopic/allergic disease, to assess whether the effect of vitamin D intervention differs in individuals at greater risk of developing atopy.
- Smoking status of mothers (never versus former versus current), to control for potential confounding of the effectiveness of vitamin D by smoking history.

We assessed our primary outcomes – incidence of asthma and wheeze – in subgroup analyses.

We defined all subgroups to be mutually exclusive (i.e. studies could only contribute to one subgroup in each subgroup analysis). We evaluated differences between subgroups with the formal test for subgroup interactions in RevMan.

Sensitivity analysis

We planned to carry out the following sensitivity analyses by restricting the meta-analysis to subgroups of included studies, as follows.

- Trials randomised at the level of the individual.
- Trials with evidence of adherence (where adherence was defined as evidence of greater serum 25(OH)D at completion of the intervention in the intervention versus comparator group, or as evidence of an increase in 25(OH)D between baseline and end of intervention in the treated group).
- Trials with low risk of bias in domains 1, 2, 3, and 4 (random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment).
- Trials with low risk of bias due to missing data.
- Trials funded by universities, public sector, or not-for-profit organisations (i.e. exclusion of industry-funded studies).
- Trials with physician-assessed outcome(s).
- Trials where wheeze was measured by transthoracic objective recording.
- Trials where respiratory tract infections were confirmed by diagnostic test(s).
- Trials where blood or sputum biomarkers were measured by the gold standard method.

We planned to perform these sensitivity analyses, where the number of studies permitted, for our primary outcomes of asthma and wheeze unless otherwise specified.

Summary of findings and assessment of the certainty of the evidence

We created separate summary of findings tables including the main results of our primary and secondary outcomes for each of our four comparisons: (1) any vitamin D versus placebo/no supplementation in pregnant or breastfeeding women; (2) any vitamin D versus placebo/no supplementation in infants or children; (3) high versus low/standard (≤ 400 IU/day) dose vitamin D in pregnant or breastfeeding women; and (4) high versus low/standard (≤ 400 IU/day) dose vitamin D in infants or children. Specifically, in each summary of findings table, we report results for asthma incidence, wheeze incidence, atopic dermatitis incidence, any adverse events (described narratively as all adverse events are considered notable), airway infection incidence (composite outcome including upper airway infections, lower airway infections and non-specified airway infections), sensitisation to allergens measured as serum IgE, and airway inflammation measured as exhaled nitric oxide, along with the time points where each outcome was assessed. We did not prioritise specific time points as the optimal time point for asthma prevention is not known. For sensitisation to allergens, we prioritised serum IgE over skin prick results as the former is a biomarker test less vulnerable to subjective interpretation. For airway inflammation, we prioritised exhaled nitric oxide over blood eosinophil or neutrophil counts as the former is an airway-specific (rather than systemic) marker of inflammation. For serum IgE and exhaled nitric oxide, we prioritised continuous measures over dichotomous measures, as continuous analyses are generally better powered to detect effects, and we report results for dichotomous measures only for comparisons where continuous measures were not available.

We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence as it relates to studies that contributed data for the specified outcomes. Two authors independently assessed all results for each comparison using the methods and recommendations described in Section

8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT). We resolved any disagreements by discussion or by consultation with the review group. We justified our decisions to downgrade the certainty of the evidence in footnotes, and made comments to aid the reader's understanding of the review where necessary.

RESULTS

Description of studies

Please see Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

Our electronic searches yielded 22,194 records, and we identified an additional 23 records through other sources (e.g. screening references of included studies). After removing duplicates, 16,542 records remained. We used Cochrane's Screen4Me workflow to help identify potential reports of randomised trials. Through the Screen4Me assessment process, 454 records were rejected by Crowd Known Assessments and 4983 records were rejected by RCT Classifier. Using Covidence, we screened the titles and abstracts of the 11,105 records remaining after the Screen4Me stage, and excluded 10,286 by title/abstract screening. We identified 819 records as potentially eligible and obtained their full texts. Of these, we identified 18 studies (65 records) that met our inclusion criteria, 10 ongoing studies (14 records), and nine studies (15 records) we labelled as 'awaiting classification'. Please see Figure 1 for a flow diagram of the results of our electronic searches.

Figure 1. PRISMA study flow diagram

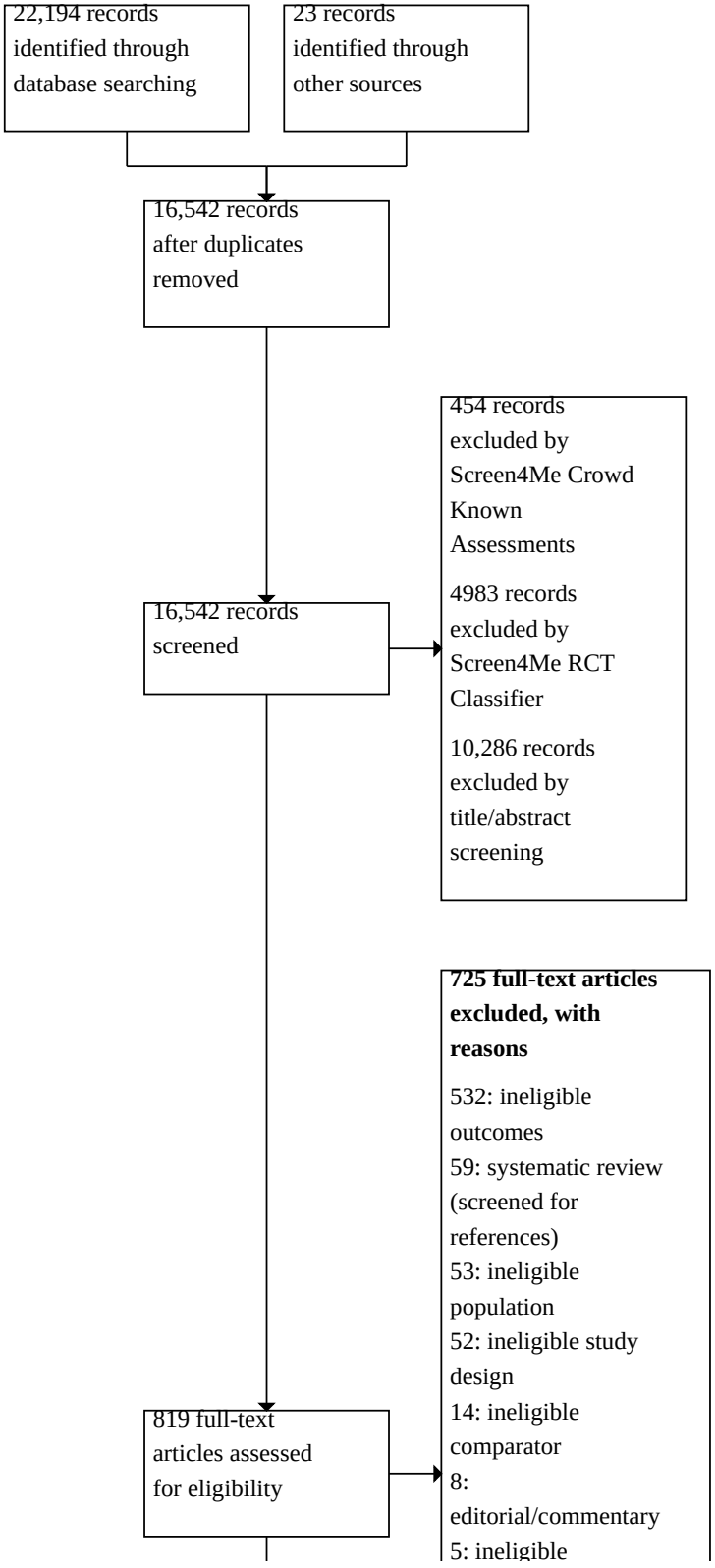
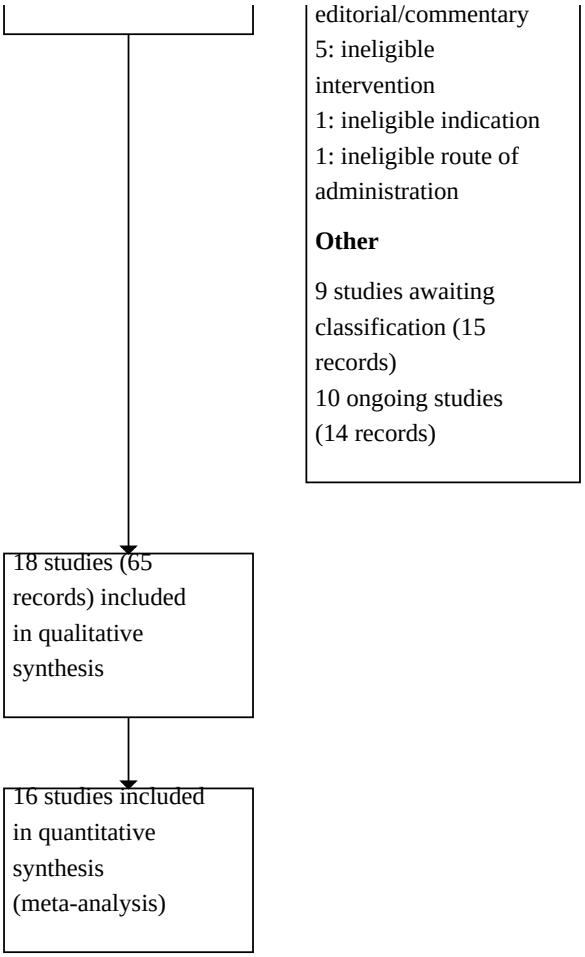


Figure 1. (Continued)



Included studies

We included 18 parallel-arm randomised controlled studies involving 10,611 participants. All studies were randomised at the level of the individual; there were no eligible cluster-based randomised studies. Many of the included studies have multiple records (including trial registries, follow-up studies, and secondary analyses) that we collected under a single study ID. Therefore, in total, we included 18 studies reported in 65 records, including two studies with records reporting follow-up data collected at time points beyond those specified in original trial protocols. One study had an erratum for an undisclosed conflict of interest (Hibbs 2018). Another included study (Morris 2021), which was nested in the Maternal Vitamin D for Infant Growth (MDIG) study, had an erratum in the primary MDIG report for an error in the statistical code used to derive the baseline parity variable and errors in the recording of sex of 14 infants. We obtained data from the included studies primarily from published journal articles. For two studies (Golan-Tripto 2020; Rosendahl 2018), we obtained additional data through electronic communications with trial authors. For Galdo 2018, we extracted data from a conference abstract, as we found no published, full-length journal articles related to this study. For all studies, we obtained additional information on study characteristics, including information needed to complete the risk of bias assessment, from study protocols, trial registries, and previous publications (i.e. journal articles on different outcomes) when available. To our knowledge, none of the included studies have been retracted. We included 16 studies in the quantitative syntheses.

Settings and populations

Three studies were conducted in the USA (Hibbs 2018; Litonjua 2016; Salas 2018), three in India (Kalra 2012; Sahoo 2017; Yadav 2022), two in the UK (El-Heis 2022; Goldring 2013), and one each in Canada (Aglipay 2017), Denmark (Chawes 2016), Finland (Rosendahl 2018), Israel (Golan-Tripto 2020), Spain (Galdo 2018), Australia (Rueter 2020), New Zealand (Grant 2015), Bangladesh (Morris 2021), Afghanistan (Manaseki-Holland 2012), and China (Zhou 2018). Latitudes of the study locations ranged from 32 to 36 degrees South, and 23 to 60 degrees North.

The participants who received the intervention were pregnant/lactating women in seven studies (Chawes 2016; El-Heis 2022; Goldring 2013; Kalra 2012; Litonjua 2016; Morris 2021; Sahoo 2017), full-term infants in six studies (Galdo 2018; Manaseki-Holland 2012; Rosendahl 2018; Rueter 2020; Yadav 2022; Zhou 2018), preterm infants in three studies (Golan-Tripto 2020; Hibbs 2018; Salas 2018), pregnant women/infant pairs in one study (Grant 2015),

and children one to five years of age in one study (Aglipay 2017). Using the Institute of Medicine Dietary Reference Intake (IOM DRI) Committee definitions of risk of vitamin D deficiency (i.e. serum 25-hydroxyvitamin D concentrations of less than 12 ng/mL) and risk of vitamin D inadequacy (i.e. serum 25-hydroxyvitamin D concentrations of between 12 ng/mL and 20 ng/mL), at baseline, most participants (based on study means, medians, or proportions of participants) were at risk of vitamin D deficiency in five studies (Galdo 2018; Golan-Tripto 2020; Goldring 2013; Morris 2021; Sahoo 2017), and vitamin D inadequacy in five studies (El-Heis 2022; Kalra 2012; Salas 2018; Yadav 2022; Zhou 2018). A family history of allergic disease, including asthma, atopic dermatitis, allergic rhinitis, and/or food allergy, was reported in seven studies, including two studies that recruited for family history of allergic disease (Litonjua 2016; Rueter 2020). Smoking or exposure to smoking in the household, which was reported for nine studies, ranged from 0% in one trial that recruited non-smokers (Sahoo 2017), to 36% to 40% of trial participants (Golan-Tripto 2020; Hibbs 2018).

Interventions and comparator groups

The included studies' interventions varied in dose, frequency, and timing of the intervention. We grouped studies by intervention and comparator into four comparison groups: (1) any dose of vitamin D versus placebo or no supplementation in pregnant or breastfeeding women; (2) any dose of vitamin D versus placebo or no supplementation in infants or young children; (3) higher-dose vitamin D versus lower/standard (≤ 400 IU/day or equivalent) dose vitamin D in pregnant or breastfeeding women; and (4) higher-dose vitamin D versus lower/standard (≤ 400 IU/day or equivalent) dose vitamin D in infants or young children. We included Grant 2015 in comparisons 1 and 2, as this study intervened in mother/infant pairs. We included Salas 2018 in comparisons 2 and 4, as this study allocated infants to three intervention groups: placebo (comparator arm), lower-dose vitamin D (200 IU/day), and higher-dose vitamin D (800 IU/day). Key characteristics of the studies included in each comparison are presented in Table 1.

Comparison 1: any vitamin D versus placebo or no supplementation in pregnant or breastfeeding women

Four studies compared vitamin D to placebo or no supplementation in pregnant or breastfeeding women, with a total of 2874 participants. Two studies, including one with multiple intervention arms, intervened daily (El-Heis 2022; Grant 2015), one study with multiple intervention arms intervened weekly (Morris 2021), and one study with multiple intervention arms intervened both daily and with a single bolus (Goldring 2013). Daily intervention doses ranged from 800 IU/day to 2000 IU/day, weekly intervention doses ranged from 4200 IU/week to 28,000 IU/week, and the bolus intervention was a one-time dose of 200,000 IU. Two of the studies started the intervention around the second trimester of pregnancy (El-Heis 2022; Morris 2021), and two studies started the intervention around the third trimester of pregnancy (Goldring 2013; Grant 2015). Two studies stopped the intervention at the time of delivery (El-Heis 2022; Goldring 2013), one study continued the intervention after delivery for 26 weeks (Morris 2021), and one study intervened in mother/infant pairs and switched from intervening in mothers to intervening in infants at the time of delivery (Grant 2015).

Comparison 2: any vitamin D versus placebo or no supplementation in infants or young children

Five studies compared vitamin D to placebo or no supplementation in infants or young children, with a total of 3890 participants. Four studies, including two with multiple intervention arms, intervened daily (Grant 2015; Hibbs 2018; Rueter 2020; Salas 2018), and one study intervened with quarterly boluses (Manaseki-Holland 2012). Daily doses ranged from 200 IU/day to 800 IU/day and the quarterly bolus dose was 100,000 IU. One study intervened in mother/infant pairs and switched from intervening in mothers to intervening in infants at birth (Grant 2015). Two studies started the intervention at birth (Hibbs 2018; Salas 2018), one study started around two weeks of age (Rueter 2020), and one study started around six months of age (Manaseki-Holland 2012). The duration of the intervention ranged from 28 days (Salas 2018) to 18 months (Manaseki-Holland 2012).

Comparison 3: higher-dose vitamin D versus lower/standard (≤ 400 IU/day) dose vitamin D in pregnant or breastfeeding women

Four studies compared higher doses of vitamin D to lower/standard (≤ 400 IU/day or equivalent) doses of vitamin D in pregnant or breastfeeding women, with a total of 2098 participants. Two studies intervened daily (Chawes 2016; Litonjua 2016), and two studies intervened with single or repeated bolus doses (Kalra 2012; Sahoo 2017). Daily doses ranged from 2800 IU/day to 4400 IU/day, and bolus doses ranged from 60,000 IU every eight weeks to 120,000 IU at the second and third trimesters. In three studies, the comparison group received 400 IU/day vitamin D (Chawes 2016; Litonjua 2016; Sahoo 2017), and in one study, the comparison group received a single bolus of 60,000 IU at the second trimester (Kalra 2012). All studies started the intervention between weeks 10 and 24 of pregnancy. Three studies stopped the intervention at delivery (Kalra 2012; Litonjua 2016; Sahoo 2017), and one study continued the intervention for one week postpartum (Chawes 2016).

Comparison 4: higher-dose vitamin D versus lower/standard (≤ 400 IU/day) dose vitamin D in infants or young children

Seven studies compared higher doses of vitamin D to lower/standard (≤ 400 IU/day or equivalent) doses of vitamin D in infants or young children, with a total of 2504 participants. All seven studies intervened daily, with doses ranging from 800 IU/day to 2000 IU/day. In six studies, the comparison group received 400 IU/day (Aglipay 2017; Galdo 2018; Golan-Tripto 2020; Rosendahl 2018; Yadav 2022; Zhou 2018), and in one study, the comparison group received 200 IU/day (Salas 2018). Four studies started the intervention at birth (Galdo 2018; Golan-Tripto 2020; Salas 2018; Yadav 2022), one study started at two weeks of age (Rosendahl 2018), one study started around eight months of age (Zhou 2018), and one study started between the ages of one and five years (Aglipay 2017). The duration of the intervention ranged from 14 weeks (Yadav 2022) to 3.2 years (Aglipay 2017).

Primary Outcomes

Asthma

Asthma (as defined by trial authors) was reported in six studies (Chawes 2016; Grant 2015; Hibbs 2018; Litonjua 2016; Rosendahl 2018; Salas 2018). Diagnosis of asthma was determined by physician or medical staff assessment in one study (Chawes 2016), by medical records in one study (Grant 2015), by parental report of symptoms in two studies (Hibbs 2018; Rosendahl 2018), by

parental report of asthma medication use in one study (Salas 2018), and as a composite outcome of parental report of doctor diagnosis or parental report of symptoms in one study (Litonjua 2016). Asthma was evaluated in children aged 12 to 18 months in three studies (Grant 2015; Hibbs 2018; Rosendahl 2018), two years in one study (Salas 2018), and three years in two studies (Chawes 2016; Litonjua 2016). Two studies also reported follow-up data for asthma evaluated at six years, which was three years beyond the latest time point specified in the original study protocol (Chawes 2016; Litonjua 2016).

Wheeze

Wheeze (as defined by trial authors) was reported in eight studies (Chawes 2016; Goldring 2013; Hibbs 2018; Litonjua 2016; Rosendahl 2018; Rueter 2020; Sahoo 2017; Zhou 2018). Definitions of wheeze considered across the studies varied (Table 1). One study assessed 'persistent wheeze', defined as five or more wheezing episodes within six months (Chawes 2016); three studies assessed 'recurrent wheeze', defined as two or more wheezing episodes and/or reports of asthma controller medication use (Aglipay 2017; Goldring 2013; Hibbs 2018; Litonjua 2016); two studies assessed 'ever wheeze', defined as any wheezing episodes in the previous 12 months (Rosendahl 2018) or since birth (Sahoo 2017); and two studies did not report diagnostic criteria (Rueter 2020; Zhou 2018). Wheeze diagnosis was determined by physician or medical staff assessment in three studies (Chawes 2016; Rueter 2020; Zhou 2018), by parental report of symptoms in four studies (Aglipay 2017; Hibbs 2018; Rosendahl 2018; Sahoo 2017), and as a composite outcome of parental report of doctor diagnosis or parental report of symptoms in one study (Litonjua 2016). Goldring 2013 evaluated wheeze by parental report as the primary outcome, and by primary care report as a secondary outcome. Wheeze was evaluated in children aged 12 to 18 months in four studies (Hibbs 2018; Rosendahl 2018; Sahoo 2017; Zhou 2018), three years in four studies (Chawes 2016; Goldring 2013; Litonjua 2016; Rueter 2020), and one to five years in one study (Aglipay 2017). Aglipay 2017 reported data on wheeze only in abstract form and could not be included in meta-analysis.

Secondary outcomes

Our secondary outcomes included atopic dermatitis, adverse events (any maternal, infant, or child adverse or severe adverse events), airway infections, sensitisation to allergens, and airway inflammation.

Atopic dermatitis

Atopic dermatitis (or eczema) was evaluated in eight studies (Chawes 2016; El-Heis 2022; Goldring 2013; Hibbs 2018; Litonjua 2016; Rosendahl 2018; Rueter 2020; Sahoo 2017). Atopic dermatitis was diagnosed by doctors, nurses, or trained research personnel in four studies (Chawes 2016; El-Heis 2022; Rueter 2020; Sahoo 2017), parental report in three studies (Hibbs 2018; Litonjua 2016; Rosendahl 2018), and medical records in one study (Goldring 2013).

Any adverse events

Sixteen of 18 included studies reported specific maternal, infant, and child adverse or severe adverse events. The remaining two studies did not report any data but stated that the profile of adverse events was similar in the intervention and comparator groups (Galdo 2018; Kalra 2012). Adverse events evaluated in mothers included author-defined elevated serum 25-hydroxyvitamin D concentrations (Litonjua 2016; Sahoo 2017), hypercalcaemia (El-Heis 2022; Goldring 2013; Grant 2015; Litonjua 2016; Morris 2021; Sahoo 2017), hypercalciuria (Morris 2021), nausea/vomiting (El-Heis 2022), diarrhoea (El-Heis 2022), abdominal pain (El-Heis 2022), and headache (El-Heis 2022). Adverse events evaluated in infants or children included author-defined elevated serum 25-hydroxyvitamin D concentration (Golan-Tripto 2020; Grant 2015; Litonjua 2016; Manaseki-Holland 2012; Morris 2021; Rosendahl 2018; Sahoo 2017; Yadav 2022), hypercalcaemia (Aglipay 2017; Grant 2015; Hibbs 2018; Morris 2021; Rosendahl 2018; Sahoo 2017; Yadav 2022), hypercalciuria (Morris 2021), elevated alkaline phosphatase (Hibbs 2018), and vomiting/diarrhoea (Zhou 2018). Severe adverse events evaluated in mothers included maternal death (Chawes 2016; Litonjua 2016; Morris 2021), intrauterine death (Chawes 2016; El-Heis 2022; Goldring 2013; Grant 2015; Litonjua 2016; Morris 2021), preterm delivery before 32 weeks (Chawes 2016; El-Heis 2022; Litonjua 2016; Morris 2021), eclampsia/pre-eclampsia (Chawes 2016; Litonjua 2016), hypertension (El-Heis 2022, Morris 2021), gestational diabetes (Chawes 2016), HELLP syndrome (H: haemolysis; EL: elevated liver enzymes; LP: low platelet count) (Litonjua 2016), urolithiasis/nephrolithiasis (Morris 2021), clinical encounters (Morris 2021), hospitalisation (Chawes 2016; Litonjua 2016; Morris 2021), antibiotics use (Chawes 2016), infection (Chawes 2016; El-Heis 2022), severe postpartum haemorrhage (El-Heis 2022), emergency caesarean section (Chawes 2016), and instrumental delivery (El-Heis 2022). Severe adverse events evaluated in infants or children included neonatal demise (Litonjua 2016), infant death (Chawes 2016; Goldring 2013; Hibbs 2018; Manaseki-Holland 2012; Morris 2021; Salas 2018), congenital malformations (Chawes 2016; El-Heis 2022; Litonjua 2016; Morris 2021), neonatal hospitalisation (Chawes 2016; Morris 2021; Yadav 2022), neonatal intensive care unit (NICU) admission (Litonjua 2016), low birth weight (< 2500 grams at > 37 gestational weeks) (Morris 2021), foetal growth retardation (El-Heis 2022), and a composite outcome for clinical encounters (Morris 2021).

Airway infections

Fourteen studies evaluated airway infections, including any non-specific, lower or upper respiratory tract infections (Aglipay 2017; Chawes 2016; Galdo 2018; Golan-Tripto 2020; Goldring 2013; Grant 2015; Hibbs 2018; Kalra 2012; Litonjua 2016; Manaseki-Holland 2012; Morris 2021; Rosendahl 2018; Yadav 2022; Zhou 2018). Four studies reported specifically on lower airway infections (Kalra 2012; Litonjua 2016; Manaseki-Holland 2012; Zhou 2018), one reported specifically on upper airway infection (Aglipay 2017), and six studies reported on both lower and upper airway infections (Chawes 2016; Galdo 2018; Goldring 2013; Hibbs 2018; Morris 2021; Rosendahl 2018). Airway infections were assessed by physicians and/or diagnostic tests, including laboratory tests and chest radiographs, in five studies (Aglipay 2017; Chawes 2016; Manaseki-Holland 2012; Morris 2021; Zhou 2018).

Sensitisation to allergens

Six studies evaluated allergic sensitisation, including skin prick test and IgE levels (Chawes 2016; Goldring 2013; Grant 2015; Litonjua 2016; Rosendahl 2018; Rueter 2020).

Airway inflammation

Three studies evaluated measures providing evidence of airway inflammation, including exhaled nitric oxide and blood eosinophil counts (Chawes 2016; Goldring 2013; Hibbs 2018).

Ongoing studies and studies awaiting classification

We identified 10 studies that, to the best of our knowledge, were ongoing, had no publicly available results, or both (see Characteristics of ongoing studies). We listed nine studies as awaiting classification generally because we were either unable to use the results as reported, or unable to obtain the necessary results from the study authors, or both (see Characteristics of studies awaiting classification for details).

Excluded studies

We excluded 725 full-text reports. The main reasons for exclusion of full texts were: outcomes not measured (i.e. to the best of our knowledge, trials did not measure or plan to measure asthma, wheeze, atopic dermatitis, respiratory tract infections, allergic sensitisation, or airway inflammation), ineligible participants (i.e. not intervening in generally healthy pregnant or lactating women or young children or not evaluating outcomes in young children), and ineligible study design (i.e. systematic reviews, editorials/commentaries, observational studies, non-randomised studies). Other less common reasons for exclusion included ineligible intervention, ineligible comparator, ineligible route of administration, ineligible indication, and no full-text found. Please see the PRISMA flow diagram for a full list of the reasons for exclusion (Figure 1). We present an indicative sample of 30 excluded studies in the Characteristics of excluded studies table.

Risk of bias in included studies

Details of the risk of bias assessments for included studies are available in the Characteristics of included studies table, while Figure 2 and Figure 3 depict summaries of these assessments.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

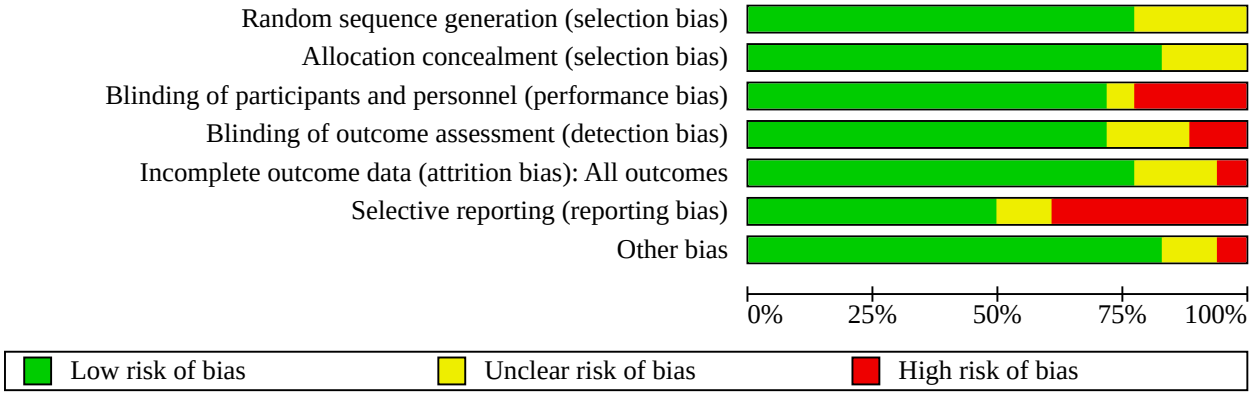
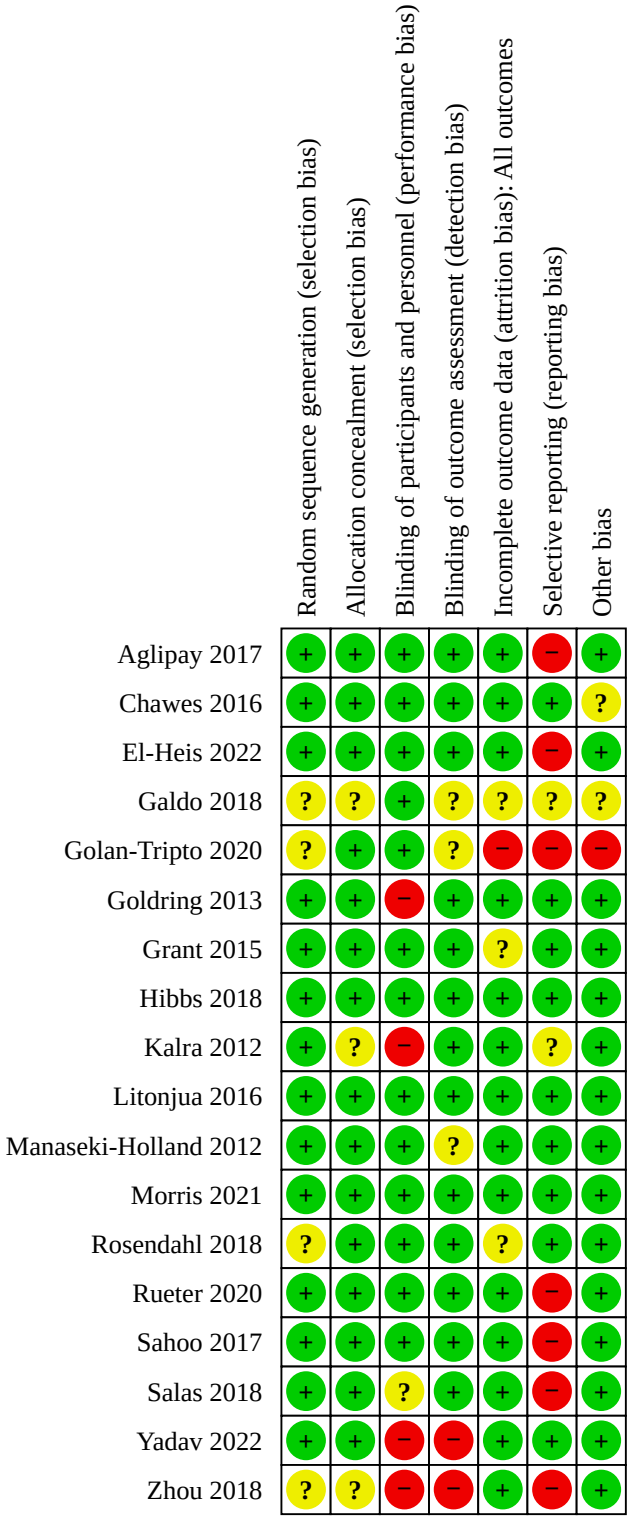


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

We rated 13 of the 18 included studies to be at low risk of bias for both random sequence generation and allocation concealment. We rated five studies as having an unclear risk of bias for random sequence generation, allocation concealment, or both: two studies did not present adequate details on randomisation sequence generation (Golan-Tripto 2020; Rosendahl 2018); one study did not present adequate details on allocation concealment (Kalra 2012); one study did not present adequate details on both randomisation sequence generation and allocation concealment (Zhou 2018); and one study, reported only in abstract form, presented no details on either random sequence generation or allocation concealment (Galdo 2018).

Blinding

We rated 10 studies as having a low risk of bias for both performance (blinding of the participants and investigators) and detection bias (blinding of the outcome assessors). We rated two studies as having a high risk of performance bias as participants were not blinded to treatment allocation (Goldring 2013, Kalra 2012). We rated two studies as having a high risk of both performance bias and detection bias as neither participants nor outcome assessors were blinded (Yadav 2022; Zhou 2018). We considered these biases more likely to impact outcomes assessed by parental report (respiratory tract infections: Goldring 2013; Kalra 2012), and/or medical staff (respiratory tract infections, Yadav 2022; wheeze, Zhou 2018), and less likely to impact outcomes assessed by laboratory/diagnostic tests (exhaled nitric oxide (eNO) measurements, skin prick test results: Goldring 2013), and diagnoses obtained from medical records (wheeze, atopic dermatitis: Goldring 2013). We rated one study as having an unclear risk of performance bias (Salas 2018), and three studies as having an unclear risk of detection bias (Galdo 2018; Golan-Tripto 2020; Manaseki-Holland 2012), because there was inadequate information to make judgements about blinding.

Incomplete outcome data

We rated one study with very poor participant retention as being at high risk of attrition bias (Golan-Tripto 2020). We rated three studies as being at unclear risk of bias: Rosendahl 2018 had substantial attrition in both arms and did not provide sufficient information to determine if attrition was related to the outcome; Grant 2015 had unexplained differing retention rates across different outcomes; and Galdo 2018 (reported only in abstract form) presented no details on attrition or retention. We rated the remaining 14 studies as having a low risk of attrition bias.

Selective reporting

We rated nine studies as having a low risk of reporting bias, seven studies as high risk, and two studies as unclear risk. The reasons for high risk of reporting bias included reporting on outcomes not specified in the trial registry or study protocols (El-Heis 2022; Rueter 2020; Sahoo 2017; Salas 2018; Zhou 2018), omitting prespecified outcomes (Aglipay 2017), reporting results by vitamin D status achieved rather than randomisation group (Golan-Tripto 2020), and reporting results at times not specified in the trial protocol (Rueter 2020). This could reduce the reliability of the results for: asthma (could be missing data – Aglipay 2017; includes data not prespecified – Salas 2018); wheeze (includes data not prespecified – Rueter 2020; Sahoo 2017; Zhou 2018); atopic dermatitis (includes data not prespecified – El-Heis 2022; Sahoo 2017); and allergic sensitisation (includes data collected at time points that were not prespecified – Rueter 2020). The reasons for judging the two studies to be at unclear risk of reporting bias were that they did not cite, and we could not find, any protocols or trial registries to verify reporting of study outcomes (Galdo 2018; Kalra 2012).

Other potential sources of bias

We considered one study to be at high risk of bias from other sources, two studies to be at unclear risk of bias from other sources, and 15 studies to be at low risk. The study judged to be at high risk in this domain had higher participant adherence and a larger change in serum vitamin D in the control group compared to the intervention group (Golan-Tripto 2020). Of the two studies judged to be at unclear risk, Chawes 2016 was a concomitant factorial designed, double-blind RCT of 2.4 g per day of long-chain n-3 polyunsaturated fatty acids (PUFAs) during pregnancy, and Galdo 2018 was presented only in abstract form.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Vitamin D compared to placebo/no supplementation in pregnant or breastfeeding women; **Summary of findings 2** Summary of findings table - Vitamin D compared to placebo/no supplementation in infants or young children; **Summary of findings 3** Summary of findings table - High-dose vitamin D compared to low-dose vitamin D in pregnant or breastfeeding women; **Summary of findings 4** Summary of findings table - High-dose vitamin D compared to low-dose vitamin D in infants or young children

We evaluated the effects of the interventions separately for each comparison. Within each comparison, we performed meta-analyses for similarly defined outcomes evaluated by at least two studies using a fixed-effect model. We narratively described results from studies that could not be meta-analysed (i.e. studies with unit of analysis issues or incompatible outcome definitions). The results are summarised in: Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4. For our primary outcomes, asthma and wheeze, we also performed exploratory analyses combining studies across comparisons.

Comparison 1: any vitamin D versus placebo/no supplementation in pregnant or breastfeeding women

Primary outcomes

Asthma

Evidence from one study in 236 participants found that, compared with placebo, supplementation with vitamin D in pregnant women may reduce childhood asthma (risk ratio (RR) 0.17, 95% confidence interval (CI) 0.05 to 0.61; low-certainty evidence; Analysis 1.1) (Grant 2015). In absolute terms, the result means that 11 children out of 100 developed asthma in the control group, compared with two children (95% CI 1 to 7) out of 100 in the vitamin D group.

Subgroup analyses. The mean serum 25-hydroxyvitamin D (25(OH)D) at baseline in this study was equal to or greater than 20 ng/mL but less than 30 ng/mL (risk of insufficiency). This study did not recruit for a family history of allergic disease or for maternal smoking. Given there was only one study evaluating asthma for this comparison, we could not perform formal subgroup analyses.

Wheeze

Limited evidence from one study evaluating wheeze in a total of 158 participants found that supplementation with vitamin D versus no supplementation in pregnant women may have little to no effect on childhood wheeze, but the evidence is very uncertain (RR 1.12, 95% CI 0.50 to 2.54; very low-certainty evidence; Analysis 1.2) (Goldring 2013).

Subgroup analyses. Most participants in this study were at risk of vitamin D deficiency (serum 25(OH)D < 12 ng/mL) at study baseline. This study did not recruit for a family history of allergic disease. Given there was only one study evaluating wheeze for this comparison, we could not perform formal subgroup analyses.

Secondary outcomes

Atopic dermatitis

Two studies evaluated atopic dermatitis in a total of 600 participants and found that supplementation with vitamin D versus no supplementation in pregnant women may have little to no effect on childhood atopic dermatitis, but the evidence is very uncertain (RR 0.88, 95% CI 0.59 to 1.33; I^2 = 0%; very low-certainty evidence; Analysis 1.3) (El-Heis 2022; Goldring 2013).

Adverse events

All four studies comparing vitamin D to placebo/no supplementation in pregnant or breastfeeding women reported on at least one maternal and/or infant adverse event (El-Heis 2022; Goldring 2013; Grant 2015; Morris 2021). We performed meta-analysis for adverse events evaluated by at least two studies (Analysis 1.4). Data from these studies suggest that compared to placebo or no supplementation in pregnant or breastfeeding women, vitamin D may reduce the risk of intrauterine death (RR 0.45, 95% CI 0.23 to 0.90; I^2 = 0%; 4 studies, 2670 participants) and infant death (RR 0.41, 95% CI 0.18 to 0.93; I^2 = 61%; 2 studies, 1478 participants), and may have little to no effect on infant elevated 25(OH)D (RR 3.73, 95% CI 0.50 to 27.63; I^2 = 0%; 2 studies, 467 participants), infant hypercalcaemia (RR 3.45, 95% CI 0.20 to 61.03; 2 studies (1 with 0 events in both groups), 1179 participants), maternal hypercalcaemia (RR 1.71, 95% CI 0.21 to 13.83; 4 studies (3 with 0 events in both groups), 2714 participants), congenital malformations (RR 0.60, 95% CI 0.36 to 1.01; I^2 = 79%; 2 studies, 2263 participants), preterm delivery (RR 1.63, 95% CI 0.77 to 3.47; I^2 = 0%; 2 studies, 2263 participants), and maternal hypertension (RR 1.25, 95% CI 0.76 to 2.05; I^2 = 33%; 2 studies, 2432 participants), but the evidence is very uncertain. Additional adverse events reported by just one study are shown in Table 2. We considered the certainty of the evidence for adverse events to be low to very low across the different adverse events reported, due mainly to imprecision since the number of events were small, and to inconsistency in how adverse events were assessed.

Airway infection

Any airway infection

Three studies evaluated airway infections in a total of 1564 participants, and found that compared to no supplementation, supplementation with vitamin D in pregnant or breastfeeding women likely has little to no effect on childhood airway infections (RR 1.00, 95% CI 0.97 to 1.04; I^2 = 80%; moderate-certainty evidence; Analysis 1.5) (Goldring 2013; Grant 2015; Morris 2021).

Lower respiratory tract infection

Two studies reported specifically on lower respiratory tract infections in a total of 1325 participants, and similarly found that supplementation with vitamin D in pregnant or breastfeeding women may have little to no effect on childhood lower respiratory tract infections (RR 1.08, 95% CI 0.82 to 1.42; I^2 = 0%; low-certainty evidence; Analysis 1.6) (Goldring 2013; Morris 2021).

Upper respiratory tract infection

Two studies reported specifically on upper respiratory tract infections in a total of 1328 participants, and found that supplementation with vitamin D in pregnant or breastfeeding women may have little to no effect on childhood upper respiratory tract infections (RR 1.29, 95% CI 0.82 to 2.04; I^2 = 0%; low-certainty evidence; Analysis 1.7) (Goldring 2013; Morris 2021).

Allergic sensitisation

Serum IgE

Limited evidence from one study evaluating total serum IgE levels in 86 participants suggests that, compared to placebo, vitamin D supplementation in pregnant women may have little to no effect on offspring total serum IgE levels, but the evidence is very uncertain (mean difference (MD) -0.30 kilo units per litre (KU/L), 95% CI -0.92 to 0.32; very low-certainty evidence; Analysis 1.8) (Goldring 2013).

Skin prick

Limited evidence from one study evaluating skin prick reactions in 95 participants suggests that vitamin D supplementation in pregnant women may have little to no effect on the risk of offspring sensitisation to common allergens, but the evidence is very uncertain (RR 0.62, 95% CI 0.27 to 1.44; very low-certainty evidence; Analysis 1.9) (Goldring 2013).

Airway inflammation

Blood eosinophil counts

Limited evidence from one study evaluating blood eosinophil counts in 80 participants suggests that, compared to placebo, vitamin D supplementation in pregnant women may have little to no effect on offspring eosinophil counts, but the evidence is very uncertain (MD -0.28, 95% CI -1.21 to 0.65; very low-certainty evidence; Analysis 1.10) (Goldring 2013).

Exhaled nitric oxide

Limited evidence from one study evaluating exhaled nitric oxide in 62 participants suggests that vitamin D in pregnant women may have little to no effect on offspring exhaled nitric oxide levels, but the evidence is very uncertain (MD -4.20, 95% CI -10.44 to 2.04; very low-certainty evidence; Analysis 1.11) (Goldring 2013).

Comparison 2: any vitamin D versus placebo/no supplementation in infants or young children

Primary outcomes

Asthma

Three studies evaluated asthma in a total of 588 participants, and found that, compared to placebo or no supplementation, vitamin D supplementation in infants or children may have little to no effect on childhood asthma, but the evidence is very uncertain (RR 0.69, 95% CI 0.47 to 1.03; I^2 = 68%; very low-certainty evidence; Analysis

2.1) (Grant 2015; Hibbs 2018; Salas 2018). Of note, in Grant 2015, the intervention started in pregnant mothers and switched to infants after delivery. Excluding this study from the analysis did not alter the findings (RR 0.89, 95% CI 0.58 to 1.38).

Subgroup analyses. The mean serum 25(OH)D at baseline was less than 20 ng/mL (risk of deficiency) in one study (Salas 2018), and from 20 ng/mL up to 30 ng/mL (risk of insufficiency) in two studies (Grant 2015; Hibbs 2018). However, given the small number of studies, we did not perform formal subgroup analysis, following the guidelines outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 10, Section 10.11, Higgins 2022). None of the studies recruited for a family history of allergic disease or for maternal smoking.

Wheeze

Two studies evaluated wheeze in a total of 431 participants, and found that vitamin D supplementation in infants or children may have little to no effect on childhood wheeze (RR 0.89, 95% CI 0.68 to 1.16; low-certainty evidence; Analysis 2.2) (Hibbs 2018; Rueter 2020).

Subgroup analyses. The mean serum 25(OH)D at baseline was from 20 ng/mL up to 30 ng/mL (risk of insufficiency) in one study (Hibbs 2018), and 30 ng/mL or higher (likely sufficient) in the other study (Rueter 2020). However, given the small number of studies, we did not perform formal subgroup analysis, following the guidelines outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 10, Section 10.11, Higgins 2022). Neither study recruited for a family history of allergic disease or for maternal smoking.

Secondary outcomes

Atopic dermatitis

Two studies evaluated atopic dermatitis in a total of 448 participants, and found that vitamin D supplementation in infants or children may have little to no effect on childhood atopic dermatitis (RR 1.01, 95% CI 0.80 to 1.28; I^2 = 71%; low-certainty evidence; Analysis 2.3) (Hibbs 2018; Rueter 2020).

Adverse events

Four studies reported data for at least one adverse event (Grant 2015; Hibbs 2018; Manaseki-Holland 2012; Salas 2018). We performed meta-analysis for adverse events evaluated by at least two studies (Analysis 2.4). Limited evidence from these studies suggests that, compared to placebo or no supplementation, vitamin D in infants or young children may increase the risk of hypercalcaemia (RR 34.74, 95% CI 2.11 to 571.92; 2 studies (1 with no events in either arm), 497 participants), but may have little to no effect on the risk of elevated serum 25(OH)D (RR 5.61, 95% CI 0.68 to 45.93; I^2 = 0%; 2 studies, 3263 participants) or infant/child death (RR 1.55, 95% CI 0.80 to 3.02; 2 studies, 3146 participants), but the evidence is very uncertain for both of these outcomes. Findings for additional adverse events reported by just one study are shown in Table 2.

Airway infection

Any airway infection

Two studies reported on airway infections in a total of 500 participants, and found that vitamin D supplementation in infants may have little to no effect on airway infections (RR 0.92, 95% CI 0.83 to 1.01; low-certainty evidence; Analysis 2.5) (Grant 2015; Hibbs 2018). One additional study reported incident rates of pneumonia which could not be meta-analysed (Manaseki-Holland 2012). Data from this study, which intervened in 3046 infants with 100,000 IU vitamin D versus placebo (no vitamin D) every three months, also suggest that vitamin D supplementation may have little to no effect on airway infections (incidence rate ratio 1.06, 95% CI 0.89 to 1.27).

Lower respiratory tract infection

Limited evidence from one study evaluating lower respiratory tract infections in 300 participants suggests that vitamin D in infants may have little to no effect on the risk of lower respiratory tract infections (RR 0.86, 95% CI 0.57 to 1.29; low-certainty evidence; Analysis 2.6) (Hibbs 2018). Of note, this study reported lower respiratory tract infections as adverse events.

Upper respiratory tract infection

Limited evidence from one study reporting on upper respiratory tract infections in 300 participants suggests that vitamin D in infants may have little to no effect on the risk of upper respiratory tract infections (RR 0.94, 95% CI 0.60 to 1.48; low-certainty evidence; Analysis 2.7) (Hibbs 2018). Of note, this study reported upper respiratory tract infections as adverse events.

Allergic sensitisation

Serum IgE

Limited evidence from one study evaluating allergic sensitisation (defined as serum IgE levels ≥ 0.35 kilo units of allergen-specific antibodies per litre (KUA/L) for at least one allergen) in 228 participants suggests that vitamin D in infants may have little to no effect on the risk of allergic sensitisation to common allergens (RR 2.25, 95% CI 0.60 to 8.50; low-certainty evidence; Analysis 2.8) (Hibbs 2018).

Skin prick

Limited evidence from one study evaluating skin prick reactions in 136 participants suggests that vitamin D in infants may have little to no effect on the risk of allergic sensitisation to common allergens (RR 1.18, 95% CI 0.63 to 2.20; low-certainty evidence; Analysis 2.9) (Rueter 2020).

Airway inflammation

Blood eosinophil counts

Limited evidence from one study evaluating blood eosinophil counts in 226 participants suggests that vitamin D in infants may have little to no effect on the risk of elevated (> 4%) blood eosinophil levels (RR 1.06, 95% CI 0.65 to 1.74; low-certainty evidence; Analysis 2.10) (Hibbs 2018).

Comparison 3: higher versus lower/standard vitamin D in pregnant or breastfeeding women

Primary outcomes

Asthma

Two studies evaluated asthma in 1355 participants, and found that, compared to lower/standard doses of vitamin D, higher doses in pregnancy likely have little to no effect on childhood asthma (RR 0.81, 95% CI 0.63 to 1.04; I^2 = 29%; moderate-certainty evidence; Analysis 3.1) (Chawes 2016; Litonjua 2016). However, we note that

the estimated effect for asthma was similar in magnitude and direction to the estimated effect for wheeze (Analysis 3.3, described below), which included an additional study and more participants and found a likely effect of vitamin D. Chawes 2016 and Litonjua 2016 also reported data on childhood asthma at a six-year follow-up (three years after the trial endpoint). Meta-analysis of the six-year follow-up data suggests that higher-dose vitamin D during pregnancy likely has little to no effect on asthma later in childhood (RR 1.21, 95% CI 0.92 to 1.59).

Subgroup analyses. In Litonjua 2016, the mean serum 25(OH)D at baseline was from 20 ng/mL up to 30 ng/mL (risk of insufficiency) and participants were recruited for a family history of allergic disease, while in Chawes 2016, the mean serum 25(OH)D at baseline was 30 ng/mL or higher (likely sufficient) and participants were not recruited based on a family history of allergic disease. Given the small number of studies, we did not perform formal subgroup analysis, following the guidelines outlined in the *Cochrane Handbook* (Higgins 2022). Neither study recruited based on maternal smoking status.

Wheeze

Three studies evaluated wheeze in 1439 participants and found that, compared to lower/standard doses of vitamin D, higher doses of vitamin D in pregnancy likely reduce offspring wheeze (RR 0.79, 95% CI 0.64 to 0.98; I^2 = 0%; moderate-certainty evidence; Analysis 3.3) (Chawes 2016; Litonjua 2016; Sahoo 2017). In absolute terms, the result means that 22 children out of 100 developed wheeze in the low/standard-dose vitamin D group, compared with 17 children (95% CI 14 to 21) out of 100 in the higher-dose vitamin D group.

Subgroup analyses. The mean serum 25(OH)D at baseline was less than 12 ng/mL (risk of severe deficiency) in Sahoo 2017, from 20 ng/mL up to 30 ng/mL (risk of insufficiency) in Litonjua 2016, and was 30 ng/mL or higher (likely sufficient) in one study Chawes 2016. Litonjua 2016 recruited for a history of allergic disease and Sahoo 2017 recruited never-smokers. Given the small number of studies, we did not perform formal subgroup analysis, following the guidelines outlined in the *Cochrane Handbook* (Higgins 2022).

Secondary outcomes

Atopic dermatitis

Three studies evaluated atopic dermatitis in a total of 1439 participants, and found that higher doses of vitamin D in pregnancy likely have little to no effect on offspring atopic dermatitis compared to lower/standard doses (RR 0.91, 95% CI 0.75 to 1.11; I^2 = 0%; moderate-certainty evidence; Analysis 3.4) (Chawes 2016; Litonjua 2016; Sahoo 2017).

Adverse events

Three studies reported data for at least one maternal or infant adverse event (Chawes 2016; Litonjua 2016; Sahoo 2017). We performed meta-analyses for adverse events reported by at least two studies (Analysis 3.5). Limited data from these studies suggest that higher doses of vitamin D in pregnancy may have little to no effect on infant elevated 25(OH)D (RR 2.97, 95% CI 0.12 to 72.78; 2 studies (1 with no events in either group), 928 participants), intrauterine death (RR 0.99, 95% CI 0.48 to 2.06; I^2 = 9%; 2 studies, 1499 participants), congenital malformations (RR 0.84, 95% CI 0.53 to 1.34; 2 studies, 1460 participants), preterm delivery (RR 0.64, 95% CI 0.26 to 1.61; 2 studies, 1460 participants), pre-eclampsia (RR 1.03, 95% CI 0.71 to 1.49; I^2 = 0%; 2 studies, 1499 participants), or maternal hospitalisation (RR 1.02, 95% CI 0.74 to 1.39; I^2 = 0%; 2 studies, 1499 participants), but the evidence is very uncertain. Compared to lower/standard doses, the effect of higher doses of vitamin D in pregnancy on maternal hypercalcaemia or maternal death is unclear (2 studies with no events in either group for each outcome). Additional adverse events reported by only one study are shown in Table 2.

Airway infection

Any airway infection

Three studies reporting on airway infections in 1441 participants found that higher doses of vitamin D in pregnancy likely have little to no effect on the risk of offspring airway infections compared to lower/standard doses (RR 0.95, 95% CI 0.82 to 1.11; I^2 = 0%; moderate-certainty evidence; Analysis 3.6) (Chawes 2016; Kalra 2012; Litonjua 2016).

Lower respiratory tract infection

Three studies reported specifically on lower respiratory tract infections in 1441 participants, and similarly found that higher doses of vitamin D in pregnancy likely have little to no effect on the risk of offspring lower respiratory tract infections (RR 0.95, 95% CI 0.82 to 1.11; I^2 = 0%; moderate-certainty evidence; Analysis 3.7) (Chawes 2016; Kalra 2012; Litonjua 2016).

Upper respiratory tract infection

No studies included in this comparison reported specifically on upper respiratory tract infections.

Allergic sensitisation

Serum IgE

Two studies evaluating allergic sensitisation (defined as serum IgE levels ≥ 0.35 KUA/L for at least one allergen) in 1110 participants found that higher doses of vitamin D in pregnancy likely have little to no effect on the risk of offspring allergic sensitisation compared to lower/standard doses (RR 1.01, 95% CI 0.87 to 1.18; I^2 = 67%; moderate-certainty evidence; Analysis 3.9) (Chawes 2016; Litonjua 2016). Litonjua 2016 also reported on total serum IgE levels in 538 participants, and similarly found that higher doses of vitamin D in pregnancy may have little to no effect on total serum IgE levels (MD -0.24 KU/L, 95% CI -0.51 to 0.03; low-certainty evidence; Analysis 3.8).

Skin prick

Limited evidence from one study evaluating skin prick results in 577 participants suggests that higher doses of vitamin D in pregnancy may have little to no effect on the risk of skin prick positivity to at least one allergen (RR 1.22, 95% CI 0.68 to 2.17; low-certainty evidence; Analysis 3.10) (Chawes 2016).

Airway inflammation

No studies included in this comparison reported on markers of airway inflammation.

Comparison 4: higher versus lower/standard vitamin D in infants or young children

Primary outcomes

Asthma

Two studies evaluated asthma in 201 participants, and found that higher doses of vitamin D in infants may have little to no effect on childhood asthma, but the evidence is very uncertain (RR 0.74, 95% CI 0.38 to 1.44; I^2 = 38%; very low-certainty evidence; Analysis 4.1) (Grant 2015; Salas 2018). Of note, in Grant 2015, the intervention started in pregnant mothers and switched to infants after delivery.

Subgroup analyses. The mean serum 25(OH)D at baseline was less than 20 ng/mL (risk of deficiency) in Salas 2018 and was from 20 ng/mL up to 30 ng/mL (risk of insufficiency) in Grant 2015. Given the small number of studies, we did not perform formal subgroup analysis, following the guidelines outlined in the *Cochrane Handbook* (Higgins 2022). Neither study recruited for a family history of allergic disease or maternal smoking status.

Wheeze

Two studies evaluated wheeze in a total of 1095 participants, and found that higher doses of vitamin D in infants may reduce the risk of childhood wheeze, but the evidence is very uncertain (RR 0.68, 95% CI 0.51 to 0.90; I^2 = 77%; very low-certainty evidence; Analysis 4.2) (Rosendahl 2018; Zhou 2018). One additional study reported wheeze in abstract form only and could not be meta-analysed (Aglipay 2017). This study (639 children) found that higher-dose vitamin D may have little to no effect on the occurrence of one or more wheezing episodes compared to lower/standard dose (RR 1.38, 95% CI 0.93 to 2.07).

Subgroup analyses. The mean serum 25(OH)D at baseline was less than 20 ng/mL (risk of deficiency) in Zhou 2018 and was 30 ng/mL or higher (likely sufficient) in Rosendahl 2018. Given the small number of studies, we did not perform formal subgroup analysis. Neither study recruited for a family history of allergic disease or maternal smoking status.

Secondary outcomes

Atopic dermatitis

Limited evidence from one study evaluating atopic dermatitis in 769 participants suggests that higher-dose vitamin D may have little to no effect on atopic dermatitis compared to lower/standard dose (RR 0.76, 95% CI 0.55 to 1.05; low-certainty evidence; Analysis 4.3) (Rosendahl 2018).

Adverse events

Five studies reported data on at least one adverse event (Aglipay 2017; Golan-Tripto 2020; Rosendahl 2018; Yadav 2022; Zhou 2018). We performed meta-analyses for adverse events reported by at least two studies (Analysis 4.4). Limited data from these studies suggest that higher doses of vitamin D in infancy may have little to no effect on elevated serum 25(OH)D (RR 0.33, 95% CI 0.01 to 7.81; 3 studies (2 with no events in either group), 1124 participants) or hypercalcaemia (RR 2.94, 95% CI 0.12 to 70.50; 3 studies (2 with no events in either group), 1173 participants), but the evidence is very uncertain. Data for additional adverse events reported in only one study are shown in Table 2.

Airway infection

Any airway infection

Six studies evaluated airway infections in 2385 participants, and found that higher doses of vitamin D in infants or young children may slightly reduce airway infections compared to lower/standard doses (RR 0.94, 95% CI 0.90 to 0.98; I^2 = 82%; low-certainty evidence; Analysis 4.5) (Aglipay 2017; Galdo 2018; Grant 2015; Rosendahl 2018; Yadav 2022; Zhou 2018).

Lower respiratory tract infection

Three studies reported specifically on lower respiratory tract infections in 1427 participants, and found that higher-dose vitamin D in infants may have little to no effect on the risk of lower respiratory tract infections, but the evidence is very uncertain (RR 0.89, 95% CI 0.67 to 1.18; I^2 = 63%; very low-certainty evidence; Analysis 4.6) (Galdo 2018; Rosendahl 2018; Zhou 2018).

Upper respiratory tract infection

Three studies reported specifically on upper respiratory tract infections in 1798 participants, and found that higher-dose vitamin D in infants or young children may have little to no effect on the risk of upper respiratory tract infections, but the evidence is very uncertain (RR 1.02, 95% CI 0.80 to 1.31; very low-certainty evidence; Analysis 4.7) (Aglipay 2017; Galdo 2018; Rosendahl 2018).

Allergic sensitisation

Serum IgE

Limited data from one study evaluating allergic sensitisation (defined as serum IgE levels ≥ 0.35 KUA/L for at least one allergen) in 723 participants suggests that higher-dose vitamin D in infants may have little to no effect on the risk of allergic sensitisation, but the evidence is very uncertain (RR 1.00, 95% CI 0.72 to 1.39; very low-certainty evidence; Analysis 4.8) (Rosendahl 2018).

Skin prick

No studies included in this comparison evaluated skin prick reactions.

Airway inflammation

No studies included in this comparison evaluated markers of airway inflammation.

Exploratory analysis combining studies across comparisons

Asthma

Combining data across comparisons, six studies evaluated asthma in a total of 2708 infants or children. Results from this exploratory analysis support a protective effect of any vitamin D (compared to placebo) and higher-dose vitamin D (compared to lower/standard-dose vitamin D) given to mothers during pregnancy or to young children on the risk of childhood asthma (RR 0.77, 95% CI 0.62 to 0.96; I^2 = 36%; Analysis 5.1). In absolute terms, the result means that 12 children out of 100 developed asthma in the control group, compared with nine children (95% CI 7 to 11) out of 100 in the vitamin D group.

Wheeze

Combining data across comparisons, eight studies evaluated wheeze in a total of 3123 infants or children. Results from this

exploratory analysis support a protective effect of vitamin D (compared to placebo) and higher-dose vitamin D (compared to lower/standard-dose vitamin D) given to mothers during pregnancy or to young children on the risk of wheeze (RR 0.79, 95% CI 0.68 to 0.91; I^2 = 33%; Analysis 5.2). In absolute terms, the result means that 22 children out of 100 experienced wheeze in the control group, compared with 18 children (95% CI 15 to 20) out of 100 in the vitamin D group.

DISCUSSION

This review evaluates the effect of vitamin D supplementation in pregnancy, lactation, infancy, and/or early childhood for the primary prevention of childhood asthma and related outcomes, including wheeze, atopic dermatitis, airway infections, sensitisation to allergens, and airway inflammation. It includes 18 studies involving a total of 10,611 pregnant mothers, infants, mother/infant pairs, and children up to age five. Sixteen studies involving 7266 participants contributed data to the meta-analysis for at least one outcome. We also evaluated the effects of vitamin D on any maternal and infant/child adverse events reported by the included studies.

Summary of main results

Overall, we found limited evidence supporting a protective effect of vitamin D supplementation in early life, including the prenatal period, on childhood asthma, wheeze, or associated factors, including atopic dermatitis, airway infections, allergic sensitisation, and airway inflammation. We are uncertain whether vitamin D supplementation, at the doses provided in the included studies, has any unwanted effects, as adverse events were rare and inconsistently reported across the included studies.

Comparison 1. Any vitamin D versus placebo/no supplementation in pregnant or breastfeeding women

Low-certainty evidence suggests that in pregnant women, any vitamin D compared to placebo/no supplementation may help prevent childhood asthma (1 study, 236 participants), and moderate-certainty evidence suggests that any vitamin D likely has little to no effect on airway infections (3 studies, 1564 participants). The evidence is very uncertain for wheeze, atopic dermatitis, allergic sensitisation, airway inflammation, or adverse events.

Comparison 2. Any vitamin D versus placebo/no supplementation in infants or children

Low-certainty evidence suggests that in young children, any vitamin D compared to placebo/no supplementation may have little to no effect on childhood wheeze (2 studies, 431 participants), atopic dermatitis (2 studies, 448 participants), airway infections (2 studies, 500 participants), allergic sensitisation (1 study, 228 participants), and airway inflammation (1 study, 226 participants). The evidence is very uncertain for asthma and adverse events.

Comparison 3. High versus low/standard (≤ 400 IU/day) dose vitamin D in pregnant or breastfeeding women

Moderate-certainty evidence suggests that in pregnant or breastfeeding women, high-dose vitamin D compared to low/standard-dose vitamin D likely reduces the risk of childhood wheeze (3 studies, 1439 participants), but likely results in little to no difference in childhood asthma (2 studies, 1355 participants), atopic dermatitis (3 studies, 1439 participants), airway infections (3 studies, 1441 participants), or allergic sensitisation (2 studies, 1110 participants). The evidence is very uncertain for adverse events. No studies of high-dose versus low/standard-dose vitamin D in pregnant or breastfeeding women evaluated markers of airway inflammation.

Comparison 4. High versus low/standard (≤ 400 IU/day) dose vitamin D in infants or children

Low-certainty evidence suggests that in young children, high-dose vitamin D compared to low/standard-dose vitamin D may slightly reduce airway infections (6 studies, 2385 participants), but may have little to no effect on atopic dermatitis (1 study, 769 participants). The evidence is very uncertain for asthma, wheeze, allergic sensitisation, and adverse events. No studies of high-dose versus low/standard-dose vitamin D in young children evaluated markers of airway inflammation.

Overall completeness and applicability of evidence

The overall aim of this review was to evaluate the efficacy of vitamin D supplementation during pregnancy, lactation, infancy, or early childhood for the primary prevention of childhood asthma. We considered studies that compared any dose of vitamin D supplementation to placebo/no supplementation as well as studies that compared higher doses of vitamin D to lower/standard (≤ 400 IU/day) doses of vitamin D. In general, the review found limited evidence supporting a protective effect of vitamin D for childhood asthma, wheeze, or both.

A major limitation in conducting this review was the number of studies evaluating asthma, wheeze, or both for each of our four comparisons. For asthma, only one study evaluated any vitamin D compared to placebo/no supplementation in pregnant women, three studies evaluated any vitamin D compared to placebo/no supplementation in infants or children, two studies evaluated high-dose compared to low/standard-dose vitamin D in pregnant women, and two studies evaluated high-dose compared to low/standard-dose vitamin D in infants or children. Additionally, interventions during pregnancy were limited to the second or third trimesters, limiting our ability to evaluate the effects of supplementation in early pregnancy and the first stages of foetal immune system development. The numbers were similarly small for wheeze. The small number of studies, combined with the small sample sizes of many studies, indirectness of study design (e.g. studies intervening in mother/infant pairs), heterogeneity in intervention effects, and high risk of bias in included studies, severely limited the certainty of the evidence.

The small number of studies evaluating asthma or wheeze for each comparison also limited our ability to conduct our planned subgroup analyses (Higgins 2022). The effects of vitamin D supplementation are reasonably expected to differ by baseline vitamin D status, vitamin D status achieved with the intervention, the exact timing of intervention (pre-gravid period, first, second, or third trimester of pregnancy, infancy, or early childhood), and a predisposition to the risk of developing asthma, such as parental history of asthma or other allergic diseases, or environmental tobacco smoke exposure. For example, re-analyses of data from Chawes 2016 and Litonjua 2016 stratified by baseline vitamin D status found evidence of a reduction in asthma/recurrent wheeze at three and six years, with the largest intervention effect of vitamin D supplementation among women with sufficient vitamin

D status at baseline (Wolsk 2017; reviewed in Weiss 2024). While our review protocol planned subgroup analyses to address these considerations, there were insufficient numbers of studies to complete subgroup analyses. Further, any subgroup analyses conducted at the study level – relying on the study mean serum vitamin D level at baseline and whether a study recruited for a family history of allergic disease, maternal smoke exposure, or both – would be weak. Our ability to address variability in response to vitamin D supplementation would have been strengthened with more studies or if we were able to disaggregate the data or use individual participant data from all included studies.

Other factors influencing the response of individuals to vitamin D supplementation – for example, genotype – could also influence the effect of vitamin D on childhood asthma. Secondary analyses of data from Chawes 2016 and Litonjua 2016 by maternal and child genotype at the 17q21 functional single nucleotide polymorphism rs12936231 showed differences in the effects of vitamin D supplementation on asthma and wheeze by genotype (Kelly 2019; Knihtilä 2021). However, few studies consider genotype or other factors that could influence response to vitamin D supplementation in their design. Studies conducted in at-risk populations and/or designed to include pre-planned stratifications of study results by factors influencing vitamin D status, risk of atopic disease, and response to vitamin D supplementation are needed to fully evaluate these hypotheses about the efficacy of vitamin D for preventing childhood asthma and wheeze.

For our secondary outcomes, including adverse events, we were limited by the small number of studies evaluating each outcome in each comparison. Within the different comparisons, atopic dermatitis was evaluated by one to three studies, airway infections by two to six studies, different maternal and infant/child adverse events by one to four studies, allergic sensitisation by one to two studies, and airway inflammation by one study or none. Additionally, measures that are non-specific to asthma were considered for some outcomes: for example, total IgE as a marker of allergic sensitisation and blood eosinophil counts as a marker of airway inflammation. More studies of vitamin D supplementation for asthma or wheeze prevention that measure risk factors for asthma, factors specific to the aetiology of asthma, and specific adverse events for both mothers and infants/children are needed to evaluate the effect of vitamin D on childhood atopy and to confirm the safety of vitamin D supplementation.

Another limitation in this review is the duration of follow-up of included studies. Data from two studies included in this review that intervened during pregnancy and reported follow-up data at six years (three years after the trial endpoints) suggest any effect of vitamin D on asthma observed in early childhood may not persist to later in childhood (Chawes 2016; Litonjua 2016). It is also possible that vitamin D supplementation must be sustained in order to prevent the development of asthma and related outcomes. In this review, the largest effect observed across all included studies was for Grant 2015 (RR 0.17, 95% CI 0.05 to 0.61), which intervened in pregnant women from gestational week 27 through delivery, then continued the intervention in infants from birth to six months of age. Similarly, a secondary analysis of data from Litonjua 2016, published only in abstract form, reported that the combination of high-dose vitamin D during pregnancy and sufficient vitamin D exposure during infancy was associated with a reduced risk of asthma at six years (Ramirez 2023). More studies with longer interventions and longer follow-up periods are needed to determine the optimal timing for supplementation and to evaluate whether any effects of vitamin D on asthma persist.

In addition to the studies included in the review, we identified nine potentially eligible studies, listed as 'awaiting classification', that could be included if unpublished information was obtained (for example, disaggregation of data for children younger than five years of age). We also identified 10 studies that were either ongoing at the time of our search or marked as complete but had no results available. These studies could expand the body of evidence for this review and enable further exploration of subgroup differences.

Certainty of the evidence

Of the 18 studies included in this review, we judged four to be at high risk of performance and detection bias (issues with blinding of participants, outcome assessors, or both), one at high risk of attrition bias (incomplete outcome data), and seven at high risk of reporting bias (selective reporting of outcomes). Two studies at high risk of performance or detection bias (or both) and four studies at high risk of selective reporting bias contributed to the analysis for our primary outcomes, asthma and wheeze. The high risk of performance/detection bias was unlikely to impact the results of one study where the outcome (wheeze) was ascertained from medical records, but could impact the results of the other study because the outcome (wheeze) was assessed by personnel who were not blinded to intervention allocation. The high risk of reporting bias in four studies could also impact the results of these studies, as asthma (one study) and wheeze (three studies) were not prespecified outcomes for these trials. In grading the certainty of the evidence, we considered studies' risk of bias through sensitivity analyses which omitted studies with high risk of bias, and noted the potential impact in the footnotes of the summary of findings tables.

We evaluated the certainty of the evidence for our primary and secondary outcomes within each of our four comparisons using the GRADE methodology. Our findings are shown in Summary of findings 1, Summary of findings 2, Summary of findings 3, and Summary of findings 4. The certainty of the evidence varied from very low to moderate across the different comparisons and outcomes, with the highest-certainty evidence for the effects of high-dose vitamin D compared to low/standard-dose vitamin D in pregnant or breastfeeding women. The main reasons for downgrading the certainty of the evidence were imprecision (small number of events, the optimal information size was not reached, and/or the 95% confidence interval included both appreciable benefit and appreciable harm), serious limitations in study design (risk of bias in at least one domain that was sufficient to lower confidence in the estimate of effect), inconsistency (evidence of substantial heterogeneity in intervention effects), and indirectness (the study design did not completely match the comparison, e.g. one study intervened in mother/infant pairs). We did not conduct a formal GRADE assessment for adverse events due to differences in reporting across studies and scarcity of data for most adverse events recorded.

Potential biases in the review process

We identified two main potential biases in the review process. First, review authors were not blinded to the names of study authors, institutions, and journals, nor to the results of included studies during title and abstract screening, full-text review, data extraction,

or risk of bias assessment. We mitigated this potential bias by performing all steps of the review in duplicate, with two review authors independently recording their votes to include or exclude studies, extracting data, and assessing the risk of bias, and resolving any conflicts with a third review author through discussion. Second, we made subjective decisions in our assessments of the risk of bias and the certainty of the evidence, and it is possible that other authors would have made different decisions. To mitigate this, we recorded our justifications for risk of bias assessments and the certainty of the evidence. These justifications are documented in the Characteristics of included studies and the Summary of findings 1, Summary of findings 2, Summary of findings 3, and Summary of findings 4 for transparency.

Agreements and disagreements with other studies or reviews

This review aimed to evaluate vitamin D supplementation during pregnancy, lactation, infancy, or early childhood for the primary prevention of childhood asthma. Other Cochrane reviews of vitamin D supplementation during pregnancy (Palacios 2019; Palacios 2019a), or early childhood (Huey 2020), have focused largely on the effects of vitamin D on birth and growth outcomes, such as preterm birth, linear growth, and stunting. These reviews did not include allergic diseases, including asthma and wheeze, as primary or secondary outcomes. Another Cochrane review evaluated vitamin D supplementation in children or adults for the treatment and management of asthma (Martineau 2016, updated Williamson 2023). This review, recently updated, found little to no effect of vitamin D for preventing asthma attacks or controlling asthma symptoms, but did not address asthma prevention. To our knowledge, ours is the first Cochrane review to evaluate vitamin D supplementation for the primary prevention of childhood asthma.

We are aware of several non-Cochrane reviews and meta-analyses of prenatal vitamin D supplementation for preventing childhood asthma, wheeze, and other allergic outcomes in offspring. One meta-analysis synthesised the results from two studies included in our review (Wolsk 2017; reviewed in Weiss 2024), and found that after adjusting for study-specific covariates, vitamin D supplementation reduced the risk of asthma/recurrent wheeze (adjusted odds ratio 0.74, 95% CI 0.57 to 0.96), with stronger effects among women with adequate vitamin D status (serum vitamin D ≥ 30 ng/mL) at study entry. One review included three studies (Vahdaninia 2017), all of which were included in our review. The authors concluded that prenatal vitamin D reduced the risk of offspring recurrent wheeze (relative risk 0.812, 95% CI 0.67 to 0.98), but made no conclusions about the effects of vitamin D on asthma or other allergic outcomes. Another review by Shi and colleagues summarised evidence from 10 case-control and cohort studies and meta-analysed the results (Shi 2019). The authors concluded that higher vitamin D intake during pregnancy may be associated with a lower risk of asthma (odds ratio 0.78, 95% CI 0.69 to 0.89) and wheeze (odds ratio 0.65, 95% 0.54 to 0.79) in the offspring. A more recent review by Tareke and colleagues included four studies, all of which were included in our review (Tareke 2020). The authors concluded that there is currently no evidence that vitamin D in pregnancy decreases the risk of allergic diseases in the offspring. Of note, this review combined data from the primary endpoints (three years) and follow-up time points (six years) of two studies in the same meta-analysis, limiting the interpretability of the results. Our findings – which provide limited support for an effect of prenatal vitamin D on childhood wheeze and asthma, and little to no evidence for an effect of prenatal vitamin D on other allergic outcomes – are generally in line with the findings from these reviews.

We are also aware of several non-Cochrane reviews of vitamin D supplementation for preventing childhood asthma and associated factors that considered studies intervening in both pregnancy and infancy/early childhood. One review identified one intervention study that was included in our review which did not provide evidence for an effect of vitamin D on any allergic outcome (Yepes-Nuñez 2018). The review also identified four non-randomised cohort studies that evaluated associations of vitamin D status in pregnancy, breastfeeding, and infancy with allergic outcomes, with mixed results. One cohort study found associations of vitamin D during pregnancy with a lower risk of wheeze in the offspring, but no associations of vitamin D in infancy with childhood wheeze/asthma; one cohort study found associations of vitamin D in infancy with increased risk of childhood allergic rhinitis and wheeze/asthma; and two case-control studies showed no associations of vitamin D in pregnant or breastfeeding women with child food allergies or wheeze/asthma. The review authors concluded with very low certainty that there was no evidence supporting an effect of vitamin D supplementation for the primary prevention of allergic diseases. Another review included three intervention studies, all of which were included in our review, and 33 cohort studies (Shen 2018). The authors did not perform a meta-analysis of the intervention study data but noted consistent direction of effects of vitamin D in preventing childhood asthma and/or wheeze in all three trials. Meta-analysis of estimates from cohort studies of maternal vitamin D intake, blood levels, or both, during pregnancy was performed, and the review authors concluded that maternal vitamin D intake, but not blood levels, was inversely associated with the risk of childhood asthma and/or wheeze in the offspring (odds ratio 0.79, 95% CI 0.63 to 0.99). A more recent review included six trials (Luo 2022), all of which were included in our review. The authors concluded that vitamin D supplementation is not associated with a reduced risk of allergic diseases, including asthma, wheeze, atopic dermatitis, allergic rhinitis, lower respiratory tract infections, and food allergies. Another recent review included five trials that intervened in pregnancy or infancy/early childhood (Sobczak 2023), all of which were included in our review. As in our review, the authors conducted separate meta-analyses for interventions in pregnancy and interventions in infancy/early childhood. They found that prenatal vitamin D reduced the incidence of wheeze but not asthma, and did not see any effect of vitamin D supplementation in infancy or early childhood on either outcome. Of note, both the Luo 2022 and Sobczak 2023 reviews included data from multiple endpoints/follow-up time points of the same study in the same meta-analysis, limiting the interpretability of the results. Though the conclusions in these reviews are mixed, they generally align with our findings that there may be an effect of maternal vitamin D supplementation on childhood asthma.

Other non-Cochrane reviews have also evaluated vitamin D supplementation for the prevention of respiratory infections, one of our secondary outcomes. One review evaluated prenatal vitamin D for preventing respiratory infections in the offspring and included three studies (Sulaiman 2022), all of which were included in our review. The authors found no evidence for an effect of maternal vitamin D on the risk of respiratory tract infections in the offspring.

A systematic review and meta-analysis of individual participant data evaluated the effects of vitamin D versus placebo on acute respiratory infections in participants aged zero to 95 years and included 25 studies (Martineau 2017; Martineau 2019), two of which were included in our review. The results of this review suggested an overall protective effect of vitamin D on acute respiratory tract infections, with subgroup analysis revealing that the effects of vitamin D were driven by participants aged one to 15 years, those treated daily or weekly, and those with baseline vitamin D status of less than 25 ng/mL. Another review evaluated the effects of both vitamin D versus placebo and higher-dose versus lower-dose vitamin D against acute respiratory tract infections in participants of all ages, and included 46 studies (Jolliffe 2021), five of which were included in our review. The authors found a protective effect of vitamin D for preventing acute respiratory infections when comparing vitamin D to placebo, with subgroup analysis of stratified aggregate data suggesting the effects were again limited to participants aged one to 15 years and those treated daily. They also found that the effects were driven by trials lasting less than 12 months. No effect was seen when comparing higher-dose vitamin D to lower-dose vitamin D. A more recent review also evaluated the effects of both vitamin D versus placebo and higher-dose versus lower-dose vitamin D against acute respiratory tract infections in participants of all ages and included 30 studies (Cho 2022), four of which are included in our review. The authors found no evidence for an effect of vitamin D against acute respiratory tract infections overall, or in analyses of children aged zero to 18 years, but found some evidence for a protective effect in studies where vitamin D was given daily and where the duration of supplementation was 11 weeks or shorter.

In our review, we found limited evidence supporting an effect of high-dose vitamin D compared to low/standard-dose vitamin D in infants or children on airway infections, but found little to no evidence for an effect of any vitamin D versus placebo in infants or children, or for any vitamin D supplementation in pregnant or breastfeeding women. Airway infection was a secondary outcome in our review, and we did not perform subgroup analysis based on dosing scheme (e.g. daily versus weekly), baseline vitamin D status, or study duration, which could explain the differences in our findings versus those of other reviews.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence supporting a protective effect of vitamin D supplementation in early life, including the prenatal period, on childhood asthma is limited. Moderate-certainty evidence suggests that high-dose vitamin D given to pregnant women likely helps to prevent childhood wheeze. The evidence is less certain for the effects of any vitamin D given to pregnant or breastfeeding women, and for both high-dose vitamin D or any vitamin D given to infants or children. Small sample sizes, indirectness of study design, heterogeneity in intervention effects, high risk of bias in included studies, and small numbers of studies per comparison limited our ability to draw conclusions with strong certainty about the effects of vitamin D on included outcomes, especially for interventions in infants and young children.

Studies included in this review were performed in generally healthy populations and compared supplementation with vitamin D to placebo/no supplementation or to lower doses of vitamin D. Studies mainly intervened in pregnant women or in infants; a few studies intervened both prenatally and postnatally or in children aged two to five years. Most studies did not recruit at-risk populations who might be most likely to benefit from vitamin D supplementation, such as people at risk of vitamin D deficiency, or with a family history of atopy or exposure to cigarette smoke.

Implications for research

The optimal timing, dose, and duration of vitamin D supplementation to prevent asthma remains unclear. It also remains unclear whether any effects persist through childhood, and whether a protective effect of vitamin D in asthma is greater in certain population subgroups, such as people at risk of vitamin D inadequacy or with a family history of allergic disease. Meta-analyses of individual participant data or stratified aggregate data from existing trials could help identify potential subgroups most likely to benefit from vitamin D supplementation and inform future trials. Larger, well-designed randomised controlled trials of vitamin D supplementation, conducted in populations with varying risk, involving different doses/dosing schemes of vitamin D, and longer follow-up times, are needed to address remaining unknowns about the efficacy of vitamin D supplementation for preventing childhood asthma. Additional trials evaluating the effects of vitamin D supplementation on atopic dermatitis, sensitisation to allergens, and airway inflammation, along with asthma and wheeze, are needed to determine if any protective effects of vitamin D are mediated through effects on atopy, inflammation, or both. Consistent reporting of maternal, infant, and child adverse events is also needed to fully evaluate the safety of vitamin D supplementation in pregnancy and early childhood.

ACKNOWLEDGEMENTS

The protocol for this review (Best 2019) was partially developed during the World Health Organization (WHO)/ Cochrane/ Cornell University Summer Institutes for Systematic Reviews in Nutrition for Global Policy Making hosted by the Division of Nutritional Sciences, Cornell University, Ithaca, NY, USA, in 2019. Work on this review continued during the Summer Institutes in 2022 and 2023.

The Background and Methods sections of this review are based on a standard template used by Cochrane Airways Group.

We would like to acknowledge the following members of our Advisory Group for their assistance in reviewing the protocol, providing insightful suggestions about PICO, and making sure the protocol was relevant to thought leaders, practitioners, and patients (in alphabetical order): (1) Andrew Bush, MD, Professor of Paediatrics and Paediatric Respirology, Imperial College, and Consultant Paediatric Chest Physician, Royal Brompton Hospital, for his expertise in paediatric asthma, (2) Kjersti Danielsen, MD, PhD, Specialist in Dermatology at University Hospital of North Norway HF and Nordnorsk Hudlegesenter in Tromsø, Norway, as well as Department of Community Medicine, UiT, the Arctic University of Norway, for her expertise in atopic dermatitis, and (3) Patsy M. Brannon, PhD, RD, Visiting Professor, Division of Nutritional Sciences at Cornell University, for her expertise in vitamin D metabolism.

We would like to acknowledge the following librarians for their assistance in developing and executing the search strategy (in alphabetical order): (1) Elizabeth Stovold, Information Specialist at

the Cochrane Airways Group, and (2) Kate Ghezzi-Kopel, Applied Health Sciences Librarian at Cornell University Mann Library.

We would like to acknowledge and thank all those who helped in assessing the search results for this review via Cochrane's Screen4Me workflow.

We would also like to acknowledge Samantha Huey, PhD, Postdoctoral Associate, Division of Nutritional Sciences at Cornell University, for sharing her experience with Cochrane reviews and providing valuable suggestions and advice during the data extraction and analysis phase of the review.

Last but not least, we would like to acknowledge Julie Leung, a Cochrane consumer and a mother to two children with severe atopic dermatitis, for her input on readability and the relevance of this review to people with atopic dermatitis and/or asthma.

This project was supported by the National Institute for Health and Care Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Airways Group. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health and Social Care.

Editorial contributions

The following people conducted the editorial process for this article.

Sign-off Editor (final editorial decision): Toby Lasserson, Acting Editor-in-Chief, Cochrane Library; **Sign-off Editor** (first editorial decision): Katharine C Pike, Bristol Royal Hospital for Children; **Managing Editor** (edited the article, collated peer-reviewer comments, and provided editorial guidance to authors): Marwah Anas El-Wegoud, Cochrane Central Editorial Service; **Editorial Assistant** (selected peer reviewers, conducted editorial policy checks and supported editorial team): Jacob Hester, Cochrane Central Editorial Service; **Copy Editor** (copy editing and production): Faith Armitage, Cochrane Central Production Service.

Peer-reviewers (provided comments and recommended an editorial decision): Gulsym Manaosva, PhD, MD, Honored Doctor of Ukraine, Professor. Department of Obstetrics and Gynecology. Odessa National Medical University. Ukraine (**clinical review**); Sina Gallo, Associate Professor, Nutritional Sciences, University of Georgia (**clinical review**); Clare Miles, Evidence Production and Methods Directorate (**methods review**); Sarah Louise Klingenberg, Cochrane Hepato-Biliary Group (**search review**); Joveena Johnson, PharmD intern (**consumer review**).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aglipay 2017

Study characteristics	
Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Country (country income level):** Canada (high income) **Latitude:** 43°N **Funding/Conflict of interest:** Grants from the Canadian Institutes of Health Research Institutes of Human Development, Child and Youth Health and Nutrition, Metabolism and Diabetes (MOP-114945) and the Thrasher Research Fund (award #9113). Drops provided: vitamin D formulations in-kind
Participants	**Population receiving intervention:** Children (1 to 5 years of age, without chronic disease) **N randomised:** 703 **Baseline age (mean):** 2.70 years (overall) **Baseline serum 25OHD, ng/ml (mean):** 36.9 ng/mL in comparator group, 35.9 ng/mL in supplementation group **Sex of offspring, n (%) female:** 296 (42.3%) **Race/ethnicity:** Mother's ethnicity: 67% European, 6% East Asian, 4% South Asian, 5% Southeast Asian, 2% Arab, 6% African, 3% Latin American, 6% mixed, 1% other; Father's ethnicity: 68% Euro-

Aglipay 2017 *(Continued)*

	pean, 4% east Asian, 6% South Asian, 3% Southeast Asian, 2% Arab, 8% African, 4% Latin American, 5% mixed, <1% other **Skin colour (as reported):** Offspring Fitzpatrick skin type: 89 Type I (pale white skin); 221 Type II (white skin); 229 Type III (light brown skin); 76 Type IV (moderate brown skin); 40 Type V (dark brown skin); 27 Type VI (deeply pigmented dark drown skin to black skin) **Familial hx of allergic disease (% as reported of type of allergy):** NR **Smoking exposure (as reported):** NR
Interventions	**Comparator (dose, frequency, duration):** 400 IU, daily, for range of 4 to 8 months **Intervention (dose, frequency, duration):** 2000 IU, daily, for range of 4 to 8 months **Co-interventions:** none **Adherence (% when available):** NR
Outcomes	**Child age at outcome ascertainment:** Children followed for a mean of 6.2 months in comparator group; 6.3 months in intervention group. **Outcomes assessed:** wheeze (reported only in abstract), upper respiratory tract infections (URTI), adverse events **Assessment method (physician dx, laboratory measurement, parental report, medical records etc):** wheeze ascertained by parental report, URTI is laboratory-confirmed **Asthma/wheeze definition:** parental report of asthma plus confirmation from the child's medical record of 2 or more episodes of wheeze requiring the prescription of inhaled asthma-controlling medications.
Notes	We reached out to the study authors requesting data on wheeze. The authors responded with some clarifying questions about our request. We answered these questions but the authors did not respond again or provide the requested data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: *Sequence generation stratified by practice site was performed centrally at the Applied Health Research Centre (AHRC) at St. Michael's Hospital using a computer random number generator*
Allocation concealment (selection bias)	Low risk	Quote: *Allocation concealment is achieved by having the Pharmacy Department prepare the vitamin D preparations in sealed, serially numbered bottles identical in appearance and weight, with the drops similar in consistency and taste*
Blinding of participants and personnel (performance bias)	Low risk	Quote: *Participants and their parents, physicians, lab personnel, data analysts and investigators were blind*
Blinding of outcome assessment (detection bias)	Low risk	Quote: *Participants and their parents, physicians, lab personnel, data analysts and investigators were blind*
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: *Three hundred and forty-nine children (49.6%) were randomised to the high-dose (2000 IU/day) group and 354 children (50.4%) to the standard-dose (400 IU/day) group. Four participants (0.6%) had no primary outcome data and were excluded from the analysis, all from the standard-dose group. Six hundred ninety-nine participants were included in the primary analysis: 349 from the high-dose group and 350 from the standard-dose group.*

Aglipay 2017 *(Continued)*

Selective reporting (reporting bias)	High risk	Judgement comment: some secondary outcomes specified in the trial protocol were not reported in any of the available publications
Other bias	Low risk	Judgement comment: no other outstanding bias noticed.

Chawes 2016

Study characteristics	
Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Country (country income level):** Denmark (high income) **Latitude:** 56 Degrees N **Funding/Conflict of interest:** Dr Bisgaard reports receiving consulting fees from Chiesi.
Participants	**Population receiving intervention:** Pregnant women **N randomised:** 623 **Baseline age (mean):** 32.3 (maternal age at offspring birth) **Baseline serum 25OHD, ng/ml (mean):** 31 **Sex of offspring, n (%) female:** 283 (49%) **Race/ethnicity:** 96% White **Skin colour (as reported):** NR **Familial hx of allergic disease (% as reported of type of allergy):** maternal asthma = 26% **Smoking exposure (as reported):** smoking during pregnancy = 8%
Interventions	**Comparator (dose, frequency, duration):** placebo plus prenatal supplement of 400 IU/day, week 24 of pregnancy through 1 week postpartum **Intervention (dose, frequency, duration):** 2400 IU/day plus prenatal supplement of 400 IU/day, week 24 of pregnancy through 1 week postpartum **Co-interventions:** All the women also participated in a concomitant factorial designed, double-blind RCT of 2.4 g per day of long-chain n-3 polyunsaturated fatty acids (PUFAs) during pregnancy **Adherence (% when available):** 74% consumed > 80% of doses
Outcomes	**Child age at outcome ascertainment:** 3 years **Outcomes assessed:** asthma, wheeze, eczema, lower respiratory tract infections, upper respiratory tract infections (episodes per year), allergic sensitization (skin prick and IgE), airway inflammation (FeNO), adverse events **Assessment method (physician dx, laboratory measurement, parental report, medical records etc):** wheeze, asthma, eczema, allergy, lower respiratory tract infection, and number of upper respiratory tract infections per year, diagnosed by study paediatricians **Asthma/wheeze definition:** persistent wheeze (for children under 3 years of age)- required all the following: (1) recurrent wheeze (verified diary recordings of ≥ 5 episodes of troublesome lung symptoms [cough, wheeze, and/or dyspnoea] lasting ≥ 3 days within 6 months), (2) typical symptoms of asthma

Chawes 2016 *(Continued)*

	(eg, exercise-induced symptoms, prolonged nocturnal cough, or persistent cough outside common cold), (3) need for intermittent bronchodilator, and (4) response to a 3-month trial of inhaled corticosteroids and relapse upon cessation. Asthma diagnosed in children ≥ 3 years of age using same criteria as persistent wheeze
Notes	Reached out to authors on (1) the number of children with any RTI at age 3 (or any time point that is appropriate), (2) the number of children with URTI, (3) and the total number of children that were examined in each comparison group. No response from authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement comment: women were randomised using a computer-generated list of random numbers, supplied by an external investigator who had no further involvement in the RCT.
Allocation concealment (selection bias)	Low risk	Judgement comment: blinding and randomisation were carried out by the Capital Region Pharmacy.
Blinding of participants and personnel (performance bias)	Low risk	Judgement comment: the intervention code was unblinded when the youngest child reached age 3 years or in case of a medical emergency. Two women in each group who were unblinded were excluded from analyses.
Blinding of outcome assessment (detection bias)	Low risk	Judgement comment: the study paediatricians acted as general practitioners for the cohort and were solely responsible for diagnosis and treatment of persistent wheeze, asthma, allergy, and eczema, adhering to predefined algorithms and blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: the missingness rate is low (follow-up rate is 94% by year 3). In addition, the missing participants were well-balanced across arms (21 vs 22 women withdrawn in the vitD vs placebo group, and 2 vs 1 children excluded in the vitD vs placebo group).
Selective reporting (reporting bias)	Low risk	Judgement comment: the primary and secondary outcomes are pre-registered and reported as specified.
Other bias	Unclear risk	Judgement comment: this is a concomitant factorial designed, double-blinded RCT of vitamin D and fish oil but the fish oil report is omitted here. The authors tested for interaction of fish oil randomisation group and vitamin D supplementation and found no effect on wheeze (P value > 0.05), but it is unclear whether this holds for other outcomes.

El-Heis 2022

Study characteristics

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Country (country income level):** United Kingdom (high income) **Latitude:** 50.9 degrees North; 51.7 degrees North; 53.4 degrees North **Funding/Conflict of interest:** Study funded by Arthritis Research UK, Medical Research Council (MRC), Bupa Foundation, National Institute for Health Research (NIHR) Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, and

El-Heis 2022 *(Continued)*

	NIHR Musculoskeletal Biomedical Research Unit, University of Oxford. One study author received reimbursement for speaking at conferences sponsored by companies selling nutritional products, and is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec and Danone.
Participants	**Population receiving intervention:** pregnant women **N randomised:** 1134 total, 703 with offspring assessed for atopic dermatitis **Baseline age (mean):** 31.1 in placebo group, 31.0 in intervention group **Baseline serum 25OHD, ng/mL (mean):** 17.9 in placebo group, 18.4 in intervention group **Sex of offspring, n (%) female:** 175 (49.9%) in placebo group, 156 (44.3%) in intervention group **Race/ethnicity:** 95.8% White ethnic origin in placebo group, 95.2% White ethnic origin in intervention group **Skin colour (as reported):** NR **Familial hx of allergic disease (% as reported of type of allergy):** NR **Smoking exposure (as reported):** smoking in early pregnancy: 7% in placebo group, 5.3% in intervention group
Interventions	**Comparator (dose, frequency, duration):** placebo **Intervention (dose, frequency, duration):** 1000 IU/d **Co-interventions:** allowed to self-administrate antenatal multivitamins containing up to 400 IU/day of vitamin D **Adherence (% when available):** > 75% adherence in 72% of placebo and 71% of intervention arm **Asthma/wheeze definition:** NA
Outcomes	**Child age at outcome ascertainment:** 12, 24, and 48 months of age **Outcomes assessed:** atopic dermatitis **Assessment method:** atopic eczema diagnosis based on the U.K. Working Party Criteria for the Definition of Atopic Dermatitis, assessment done by trained research nurses who performed a standardized questionnaire and examination
Notes	Secondary analysis of MAVIDOS study, atopic dermatitis outcome not included in original trial registry.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement comment: study treatment was randomly assigned in a 1:1 ratio by a computer-generated sequence in randomly permuted blocks of ten, starting randomly midway through the block.
Allocation concealment (selection bias)	Low risk	Judgement comment: treatment packs were sequentially numbered and dispensed by study pharmacists.
Blinding of participants and personnel (performance bias)	Low risk	Judgement comment: both the participants and research team were masked to treatment allocation throughout the study duration.

El-Heis 2022 *(Continued)*

Blinding of outcome assessment (detection bias)	Low risk	Quote: *Case definition was based on the UK Working Party diagnostic criteria for the definition of atopic eczema, assessed by trained research nurses who were blinded to intervention and control allocation and who performed a standardized questionnaire and examination.*
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: atopic eczema assessment was planned at only one study site (703 children). Baseline characteristics of mothers of children assessed for atopic dermatitis were similar to overall characteristics of MAVIDOS participants. There was moderate loss to follow-up (N = 635 at 12 mo, 610 at 24 mo, 449 at 48 mo), but this was balanced across intervention and comparator groups and baseline characteristics of participants at each follow-up point were similar across groups and time points, so this is unlikely to bias the results.
Selective reporting (reporting bias)	High risk	Judgement comment: atopic dermatitis was not a pre-registered outcome of the original MAVIDOS trial (MAVIDOS trial registry: ISRCTN82927713).
Other bias	Low risk	Judgement comment: no other outstanding bias noticed.

Galdo 2018

Study characteristics	
Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Country (country income level):** Spain (high income) **Latitude:** 41 degrees N **Funding/Conflict of interest:** Supported by a grant from Spanish Ministry of Health (EC11-476)
Participants	**Population receiving intervention:** infants **N randomised:** 198 **Baseline age (mean):** NR, intervention started just after birth **Baseline serum 25OHD:** 72.7% of the infants had severe or moderate vitamin D deficiency at birth **Sex of offspring, n (%) female:** NR **Race/ethnicity:** NR **Skin colour (as reported):** NR **Familial hx of allergic disease (% as reported of type of allergy):** NR **Smoking exposure (as reported):** NR
Interventions	**Comparator (dose, frequency, duration):** 400 IU/day up to one year of age **Intervention (dose, frequency, duration):** 1000 IU/day up to one year of age **Co-interventions:** NR **Adherence (% when available):** NR
Outcomes	**Child age at outcome ascertainment:** 1 year of age

Galdo 2018 *(Continued)*

	Outcomes assessed: lower respiratory tract infections (acute bronchitis, recurrent bronchitis), upper respiratory tract infections **Assessment method:** NR **Asthma/wheeze definition:** NA
Notes	Abstract only. Reached out to authors on (1) the number of children with any RTI during the first year of life (or any time point that is appropriate), (2) the number of children with lower RTI, (3) and the total number of children that were examined in each comparison group; (4) the number of children with adverse events, and the total number of children for both groups. No response from authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: reported in abstract form only, does not include details of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Judgement comment: reported in abstract form only, does not include details of allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk	Judgement comment: reported as a randomised double-blind trial, which we take to mean blinding of participants and investigators.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement comment: reported only in abstract form, insufficient details to determine if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: reported in abstract form only, does not describe total number randomised vs assessed.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: reported in abstract form only, no trial registry cited, not clear whether all planned outcomes are reported.
Other bias	Unclear risk	Judgement comment: reported in abstract form only, unable to assess other potential biases.

Golan-Tripto 2020

Study characteristics

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Country (country income level):** Israel (high income) **Latitude:** 31 degrees N **Funding:** Funded by the Soroka JNF UK Clinical Research Scholars Program
Participants	**Population receiving intervention:** preterm infants (32+6 to 36+6 weeks of gestation) **N randomised:** 50 **Baseline age (mean):** < 72 hours

Golan-Tripto 2020 *(Continued)*

	Baseline serum 25OHD, ng/ml (mean): median 10.6 in comparator group, 13.6 in intervention group **Sex of offspring, n (%) female:** 29 (58%) **Race/ethnicity:** 44% Jewish in comparator group, 64% Jewish in intervention group **Skin colour (as reported):** NR **Familial hx of allergic disease (% as reported of type of allergy):** 32% with first degree relative with asthma **Smoking exposure (as reported):** exposure to smoking in 36% of comparator and 40% of intervention group, maternal smoking during pregnancy in 8% of comparator and 16% of intervention group
Interventions	**Comparator (dose, frequency, duration):** 400 IU, daily, for 12 months **Intervention (dose, frequency, duration):** 800 IU, daily, for 12 months **Co-interventions:** none **Adherence (% when available):** 57% and 108% at 6 and 12 months in comparator group, 42% and 47% at 6 and 12 months in intervention group
Outcomes	**Child age at outcome ascertainment:** 12 months **Outcomes assessed:** airway infection, adverse events **Assessment method:** assessed by parental questionnaire **Asthma/wheeze definition:** NA
Notes	Reached out to authors on (1) the number of children with any RTI during the first year of life (or any time point that is appropriate), (2) the number of children with any URTI, (3) the number of children with any LRTI, (4) the number of children with wheezing, (5) the total number of children that were examined in each comparison group, and (6) adverse events. Authors responded with a table of clinical outcomes in the intervention vs comparator group but noted that they did not separate between respiratory diseases (URTI/LRTI/wheezing or cough). They also responded that they did not have adverse events in either groups, except for one patient in the comparator group with high levels of 25(OH) vitamin D at the age of 6 months (136 nmol/L), but without any clinical adverse events.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: *This was a randomised double-blind trial.* Judgement Comment: no mention of how randomisation was achieved.
Allocation concealment (selection bias)	Low risk	Judgement comment: the intervention and placebo vitD drops were identical in their appearance, colour, and smell. The supplement preparations were generated in an independent pharmaceutic lab. The pharmacy removed the original label and relabelled the bottle with a kit number, batch number, and expiration date.
Blinding of participants and personnel (performance bias)	Low risk	Judgement comment: this was a double-blinded (investigator and participant) trial.
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement comment: it was not clear if the outcome assessors knew about the treatment assignments.

Golan-Tripto 2020 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: *Unfortunately, the dropout rate was high in this study. Only 11 subjects (11 of 25, 44%) in the intervention group and 14 in the control group (14 of 25, 56%) fully completed the study.*
Selective reporting (reporting bias)	High risk	Judgement comment: outcomes not reported using prespecified analysis method and not all prespecified outcomes were reported
Other bias	High risk	Judgement comment: very small sample size to examine respiratory outcomes at 1 year of age (14 in the intervention arm, 11 in the placebo arm). In addition, it is unclear why there is a large difference in compliance (much lower compliance in the intervention arm) across the two arms. Besides, there was a larger increase in serum vitamin D in control group than high vitamin D group.

Goldring 2013

Study characteristics	
Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Country (country income level):** England (high income) **Latitude:** 51.5 degrees N **Funding/Conflict of interest:** Supported by Grant number 09/36 from Asthma UK.
Participants	**Population receiving intervention:** Pregnant women **N randomised:** 180 **Baseline age (mean):** NR **Baseline serum 25OHD <10 ng/ml, n (%):** 71 (45%) **Sex of offspring, n (%) female:** 73 (46%) **Race/ethnicity:** Asian: 40 (25%); Middle Eastern: 41 (26%); Black: 39 (25%); White: 38 (24%) **Skin colour (as reported):** Maternal Fitzpatrick skin score grade 3-6, n (%): 89 (65.4%); Offspring Fitzpatrick skin score grade 3-6, n (%): 92 (69.2%) **Familial hx of allergic disease (% as reported of type of allergy):** At least one parent with allergic disease, n (%): 79 (55%) **Smoking exposure (as reported):** 5 (3%)
Interventions	**Comparator (dose, frequency, duration):** No treatment **Intervention (dose, frequency, duration):** Daily vitamin D group (800 IU daily starting at 27 weeks gestation until delivery (mean gestational age 39 weeks)); Bolus group (2000 IU, single dose at 27 weeks gestation) **Co-interventions:** none **Adherence (% when available):** NR
Outcomes	**Child age at outcome ascertainment:** Age 3 years

Goldring 2013 *(Continued)*

	Outcomes assessed: Wheeze, atopic dermatitis, airway infection (URTI and LRTI), allergic sensitization, airway inflammation
	Assessment method: Validated health questionnaire and clinical assessment; Medical records (wheeze, atopic dermatitis, food allergy); History of LRTI; Parent-reported URTI; eNO measured; Allergic sensitisation using skin prick test; Serum total IgE and eosinophil count measured
	Asthma/wheeze definition: ≥ 2 episodes of reported wheezing since birth, with wheeze defined by ISAAC questionnaire
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement comment: randomisation sequence generated by computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Judgement comment: independent researcher generated sequence and treatment was allocated from the hospital pharmacy.
Blinding of participants and personnel (performance bias)	High risk	Quote: *Participants were not blind to treatment allocation.*
Blinding of outcome assessment (detection bias)	Low risk	Quote: *Investigators blind to original treatment allocation assessed offspring at three years of age using a validated health questionnaire and clinical assessment.*
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: low risk of bias (ROB) for wheeze (88% retention). Unclear ROB for secondary outcomes (% EOS, IgE and eNO) as retention was much lower for these outcomes and reasons for missing data not given.
Selective reporting (reporting bias)	Low risk	Judgement comment: all outcomes were prespecified; primary analyses compared control group vs combined bolus and daily vitamin D groups; secondary analyses compared control vs bolus and control vs daily vitamin D groups separately
Other bias	Low risk	Judgement comment: no other sources of bias noted.

Grant 2015

Study characteristics

Methods	**Study design:** Randomized controlled trial
	Study grouping: parallel arm
	Country (country income level): New Zealand (high income)
	Latitude: 36 degrees S
	Funding/Conflict of interest: Sponsored by the Health Research Council of New Zealand and a University of New Zealand Faculty Research Development Grant
Participants	**Population receiving intervention:** pregnant women/infant pairs

Grant 2015 *(Continued)*

	N randomised: 260 pregnant women, 249 infants **Baseline age (mean):** 28 in comparator group, 27 in the lower-dose vitamin D group, 26 in higher-dose vitamin D group **Baseline serum 25OHD, ng/ml (mean):** 22 ng/mL in comparator group 23 ng/mL in lower-dose vitamin D group, 22 ng/mL in higher-dose vitamin D group **Sex of offspring, n (%) female:** 48% in comparator group, 51% in lower-dose group, 56% in higher-dose group **Race/ethnicity:** Comparator group: 38% European, 24% Maori, 46% Pacific, 25% other; lower dose group: 31% European, 26% Maori, 51% Pacific, 23% other; higher-dose group: 33% European, 22% Maori, 50% Pacific, 27% other **Skin colour (as reported):** NR **Familial hx of allergic disease (% as reported of type of allergy):** NR **Smoking exposure (as reported):** current smoking during pregnancy: 21% in comparator group, 16% in lower dose group, 20% in higher dose group
Interventions	**Comparator (dose, frequency, duration):** placebo for the mothers, daily, 27 weeks gestation through delivery/placebo for the infants, daily, birth to 6 months **Intervention (dose, frequency, duration):** lower dose: 1000 IU/d for mothers 27 weeks gestation through delivery/400 IU/d for the infants, birth to 6 months; higher dose: 2000 IU/d for mothers 27 weeks gestation through delivery/800 IU/d for the infants, birth to 6 months **Co-interventions:** none **Adherence (% when available):** 95% in comparator, 96% in lower dose group, 93% in higher dose group
Outcomes	**Child age at outcome ascertainment:** 18 months **Outcomes assessed:** asthma, airway infection (acute respiratory tract infection), allergic sensitization (IgE and skin prick), adverse events **Assessment method:** asthma diagnosis from medical records, airway infection from primary care audit (used for meta-analysis), parental report and hospital visits **Asthma/wheeze definition:** any doctor diagnosis of asthma in primary care medical record
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement comment: allocation to the 3 study arms was by restricted randomisation within blocks of variable size using a computer-generated randomisation list.
Allocation concealment (selection bias)	Low risk	Judgement comment: the allocation sequence was concealed from research staff involved in recruitment. The study statistician randomly allocated a treatment to each participant and labelled identical study medicine bottles such that study staff and participants were unaware of the treatment status.
Blinding of participants and personnel (performance bias)	Low risk	Quote: *Study participants and research staff remained unaware of treatment allocations throughout the recruitment, enrolment, treatment and data ac-*

Grant 2015 *(Continued)*

		quisition phases, including the completion of the primary care audit to age 18 months.
Blinding of outcome assessment (detection bias)	Low risk	Quote: *Study participants and research staff remained unaware of treatment allocations throughout the recruitment, enrolment, treatment and data acquisition phases, including the completion of the primary care audit to age 18 months.*
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: for respiratory infection, attrition was low and comparable between groups, but it is unclear why it wasn't available for some. Attrition was greater for IgE and skin prick, and the mothers of children in whom IgE and skin prick were not available were older (28 vs. 25 years, P < 0.001) but did not otherwise differ with respect to season of enrolment, demographics, health, vitamin D intake or sunlight exposure. Nor were there differences in cord blood 25(OH)D concentration or infant feeding (Table S2). No imputation for missing data.
Selective reporting (reporting bias)	Low risk	Judgement comment: reported results from both parental report and audited healthcare records for respiratory infections and any other infectious or non-infectious illnesses
Other bias	Low risk	Judgement comment: no other potential biases noted

Hibbs 2018

Study characteristics	
Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Country (country income level):** USA (high income) **Latitude:** 41 degrees N (Cleveland); 32 degrees N (Charleston); 41 degrees N (Bronx) **Funding/Conflict of interest:** National Heart, Lung and Blood Institute and Office of Dietary Supplements (grant R01HL109293)
Participants	**Population receiving intervention:** Preterm infants **N randomised:** 300 **Baseline age, Adjusted gestational age, median:** Range: 35.3-35.4 (Comparator group: 35.4; Intervention group: 35.3) **Baseline serum 25OHD, ng/ml (median):** Range: 19.1-21.0 (Comparator: 21.0; Intervention: 19.1) **Sex of offspring, n (%) female:** 133 (44%) **Race/ethnicity:** Black race: Maternal: 242 (97%), Paternal: 246 (98%); Hispanic ethnicity: Maternal: 19 (8%), Paternal: 19 (8%) **Skin colour (as reported):** NR **Familial hx of allergic disease (% as reported of type of allergy):** Food allergy: 91 (37%); Hay fever or pollen allergy: 161 (65%); Eczema: 166 (66%); Asthma: 249 (64%) **Smoking exposure (as reported):** 95 (38%)

Hibbs 2018 *(Continued)*

Interventions	**Comparator (dose, frequency, duration):** "Diet-limited Supplementation"; Dose: 0 IU (placebo); Frequency: daily?; Duration: **Intervention (dose, frequency, duration):** "Sustained vitamin D Supplementation"; Dose: 400 IU; Frequency: Daily; Duration: daily until 6 months' adjusted age or until they were taking at least 200 IU/d of vitamin D from formula or human milk fortifier. **Co-interventions:** none **Adherence (% when available):** Comparator group: among participants who received their final bottle of study drug, rate of return of all bottles was 60 of 133 (45.1%); Treatment group: among participants who received their final bottle of study drug, rate of return of all bottles was 75 of 141 (53.2%)
Outcomes	**Child age at outcome ascertainment:** 12 months adjusted age **Outcomes assessed: Asthma**, wheeze, atopic dermatitis, respiratory infection, airway inflammation **Assessment method:** Wheeze: parent reported; URTI/LRTI: parent reported; Allergies: parent reported; Eczema: parent reported Asthma: parent reported; Airway inflammation: Eosinophil counts **Asthma/wheeze definition:** recurrent wheezing - parental report of ≥ 2 wheezing episodes since the last interview or reports of single wheezing episodes at multiple study visits; asthma - parental report of symptoms with diagnosis based on positive result on the Asthma Predictive Index (API)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: *Infants were randomised with randomly permuted blocks, sizes 2 to 6, using computer-generated random numbers. Randomization was stratified by site and whether the infant had received any of their own mother's milk within 24 hours of randomisation.*
Allocation concealment (selection bias)	Low risk	Quote: *Families, clinical caregivers, and study staff were blinded to assignment and block size... Patients received open-label multivitamin until they were consuming 200 IU/d of cholecalciferol from formula or human milk fortifier, after which they received masked study drug (liquid cholecalciferol or a placebo, dispensed in an amber bottle). Parents, clinical caregivers, and study staff with patient contact were masked.*
Blinding of participants and personnel (performance bias)	Low risk	Quote: *Families, clinical caregivers, and study staff were blinded to assignment and block size.*
Blinding of outcome assessment (detection bias)	Low risk	Quote: *Families, clinical caregivers, and study staff were blinded to assignment and block size.*
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: attrition and reasons for attrition do not differ between the groups, and the number missing is relatively small.
Selective reporting (reporting bias)	Low risk	Judgement comment: reported outcomes match the clinical trial registration.
Other bias	Low risk	Judgement comment: no other potential biases noted.

Kalra 2012

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel arm **Country (country income level):** India (lower-middle) **Latitude:** 27 degrees N **Funding/Conflict of interest:** study was partially funded by an Indian Council for Medical Research grant (3/2/2006/PG-MPD-7). None of the authors report any conflicts of interest.
Participants	**Population receiving intervention:** pregnant women **N randomised:** 299 **Baseline age (mean):** 26.7 (mean for those who returned for follow-up) **Baseline serum 25OHD, ng/ml (mean):** median 12.7 in low vitamin D comparator group, 12.8 in high vitamin D intervention group **Sex of offspring, n (%) female:** NR, but stated no difference between treatment groups **Race/ethnicity:** 83% Hindu, 14% Muslim **Skin colour (as reported):** NR **Familial hx of allergic disease (% as reported of type of allergy):** NR **Smoking exposure (as reported):** NR
Interventions	**Comparator (dose, frequency, duration):** 60,000 IU vitamin D, bolus dose, at second trimester **Intervention (dose, frequency, duration):** 120,000 IU vitamin D, bolus doses, at second and third trimesters **Co-interventions:** 1 g of elemental Ca daily **Adherence (% when available):** NR
Outcomes	**Child age at outcome ascertainment:** 3, 6 and 9 months **Outcomes assessed:** lower respiratory tract infections, adverse events **Assessment method:** parental report of symptoms consistent with LRTI **Asthma/wheeze definition:** NA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: *Pregnant women were randomly assigned (by the use of random number tables).*
Allocation concealment (selection bias)	Unclear risk	Judgement comment: no mention in the paper of methods to conceal allocation

Kalra 2012 *(Continued)*

Blinding of participants and personnel (performance bias)	High risk	Judgement comment: investigators who measured the anthropometry and did the follow-up were blinded to the treatment category. However, the mothers may have known which group they were in as it was easy to tell if they had one dose or two doses (if some mothers knew other women in the other arm and talked to them about their vitamin D doses).
Blinding of outcome assessment (detection bias)	Low risk	Judgement comment: investigators who measured the anthropometry and did the follow-up were blinded to the treatment category.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: even though the loss to follow-up rate was high (~70%) as shown in Table 2, the baseline characteristics among those who were followed up were balanced across groups. Thus, it seems that the missing participants are random across groups (e.g. prefer to deliver at a nearby hospital vs. this clinic) and not biased by the outcome.
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no protocol or clinical trial registry number cited to assess what the prespecified primary outcomes and time points were.
Other bias	Low risk	Judgement comment: no other outstanding biases observed.

Litonjua 2016

Study characteristics	
Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Country (country income level):** US (high income) **Latitude:** Three locations - Boston (latitude 42 degrees N), St Louis (latitude 39 degrees N), Southern California (latitude 35 degrees N) **Funding/Conflict of interest:** sponsored by the National Heart, Lung, and Blood Institute and the National Center for Advancing Translational Sciences
Participants	**Population receiving intervention:** pregnant women **N randomised:** 876 **Baseline age (mean):** 27.4 **Baseline serum 25OHD, ng/ml (mean):** 22.9 **Sex of offspring, n (%) female:** 45% in control group, 51% in intervention group **Race/ethnicity:** maternal: 43% Black, 14% White Hispanic, 26% White non-Hispanic, 17% other **Skin colour (as reported):** NR **Familial hx of allergic disease (% as reported of type of allergy):** 41% asthma, 64% allergic rhinitis, 32% eczema **Smoking exposure (as reported):** NR
Interventions	**Comparator (dose, frequency, duration):** placebo + multivitamin containing 400 IU vitamin D, daily, 10-18 weeks gestational age through delivery (mean ~24 weeks) **Intervention (dose, frequency, duration):** 4000 IU + multivitamin containing 400 IU vitamin D, daily, 10-18 weeks gestational age through delivery (mean ~24 weeks)

Litonjua 2016 *(Continued)*

	Co-interventions: daily multivitamin containing 400 IU vitamin D **Adherence (% when available):** mean adherence of 71.3 % in control group, 70% in intervention group
Outcomes	**Child age at outcome ascertainment:** 3 years (6-year follow-up data also reported, but 3-year data are used in this study because this is what was specified in trial registry) **Outcomes assessed:** asthma, atopic dermatitis, airway infection (LRTI), allergic sensitization (IgE and skin prick) **Assessment method (physician dx, laboratory measurement, parental report, medical records etc):** asthma, atopic dermatitis, airway infection assessed by parental report of doctor diagnosis **Asthma/wheeze definition:** asthma - parental report of physician-diagnosed asthma, recurrent wheeze - occurrence of at least 1 of the following 5 conditions: (1) parental report of wheeze after child's second birthday preceded by at least 1 report of wheeze prior to second birthday; (2) report of child's use of asthma controller medication (defined as report of use of steroid inhalers or nebulisers, leukotriene modifiers, or steroid pills or liquids) after the second birthday, preceded by a report of wheeze before the second birthday; (3) 2 or more distinct parental reports of wheeze after the second birthday; (4) at least 1 parental report of wheeze and use of asthma controller medications at distinct visits, both after the second birthday; or (5) 2 distinct reports of use of asthma controller medications after the second birthday.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: *A system that automates the random assignment of treatment groups to study identification numbers; stratified permuted blocks with randomly varied block sizes of 4 and 6, and 1 block allocation list per stratum (study site and racial/ethnic group). That is, separate permuted block randomisation lists were maintained for each racial/ ethnic group (e.g., Caucasian/Non-Hispanics, Caucasian/Hispanic, African-American, and Other) within each study site.*
Allocation concealment (selection bias)	Low risk	Quote: *Participants who consent and are deemed eligible to participate will be randomised by the Data Coordinating Center (DCC) to either of the 2 arms of the trial and will be sequentially assigned a six-digit Study Identification Number (Study ID).*
Blinding of participants and personnel (performance bias)	Low risk	Judgement comment: all investigators, clinical staff and participants were masked to trial outcome data until the end of the trial. The authors acknowledge that laboratory technicians may be able to infer treatment arm based on serum 25(OH)D assay results, but these results were sent only to the DCC and thus the authors anticipated that blinding of investigators, clinical staff and participants to both treatment intervention and trial outcome would be maintained until the end of the trial.
Blinding of outcome assessment (detection bias)	Low risk	Judgement comment: all investigators, clinical staff and participants were masked to trial outcome data until the end of the trial. The authors acknowledge that laboratory technicians may be able to infer treatment arm based on serum 25(OH)D assay results, but these results were sent only to the DCC and thus the authors anticipated that blinding of investigators, clinical staff and participants to both treatment intervention and trial outcome would be maintained until the end of the trial.
Incomplete outcome data (attrition bias)	Low risk	Judgement comment: the missing data seem to be balanced across study arms with similar reasons.

Litonjua 2016 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Judgement comment: the study reported the findings for the primary and secondary outcomes in the prespecified way.
Other bias	Low risk	Judgement comment: no other potential biases stood out.

Manaseki-Holland 2012

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel arm **Country (country income level):** Afghanistan (lower-middle income) **Latitude:** 35 degrees N **Funding/Conflict of interest:** Wellcome Trust and British Council
Participants	**Population receiving intervention:** infants **N randomised:** 3046 **Baseline age (mean):** 6.5 months **Baseline serum 25OHD, ng/ml (mean):** NR **Sex of offspring, n (%) female:** 78% **Race/ethnicity:** 70% Tajik, 23% Pashton, 2% Uzbek, 4% Hazara, 1% other or unknown **Skin colour (as reported):** NR **Familial hx of allergic disease (% as reported of type of allergy):** NR **Smoking exposure (as reported):** 31% had one or more indoor smokers in the family
Interventions	**Comparator (dose, frequency, duration):** placebo, quarterly for 18 months (6 total doses) **Intervention (dose, frequency, duration):** 100,000 IU, quarterly for 18 months (6 total doses) **Co-interventions:** none **Adherence (% when available):** NR
Outcomes	**Child age at outcome ascertainment:** estimated mean of 2 years (children assessed every 2 weeks for 18 months starting at mean age of 6.5 months) **Outcomes assessed:** pneumonia, adverse events **Assessment method (physician dx, laboratory measurement, parental report, medical records etc):** pneumonia diagnosed by chest radiograph **Asthma/wheeze definition:** NA
Notes	Reports incidence rates for pneumonia and the number of first/only episodes of pneumonia but not the number of participants assessed. Reached out to authors on the number of participants who were assessed for pneumonia (N) within each treatment group, but never heard back.

Manaseki-Holland 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: *An independent statistician randomised unique identification numbers individually in fixed blocks of 20 to the vitamin D or placebo group by use of a random number generator with the SAS routine.*
Allocation concealment (selection bias)	Low risk	Quote: *By use of the randomisation list, a pharmacist in the Department of Pharmacy prepared... vitamin D (cholecalciferol) in olive oil... or placebo (olive oil) in sealed 2 mL plastic syringes labelled with the unique identification numbers. The vitamin D 3 and the placebo were the same colour (pale yellow), taste, and quantity (0.5 mL) and therefore the study staff and the families did not know to which group the children were assigned.*
Blinding of participants and personnel (performance bias)	Low risk	Quote: *the study staff and the families did not know to which group the children were assigned.*
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement comment: it is unclear whether physicians, nurses, midwives, and fieldworkers were blind to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: death and dropout rates were similar in vitamin D and placebo groups and not related to outcomes (except for 10 children who died from septicaemia/pneumonia).
Selective reporting (reporting bias)	Low risk	Judgement comment: the primary endpoint was reported in full, with both intent to treat and per-protocol analysis.
Other bias	Low risk	Judgement comment: no other apparent sources of bias.

Morris 2021

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Country (country income level):** Bangladesh (low income) **Latitude:** latitude 24 degrees N **Funding/Conflict of interest:** sponsored by the Bill and Melinda Gates Foundation
Participants	**Population receiving intervention:** pregnant women **N randomised:** 1300 **Baseline age (mean):** 22-23 across intervention groups **Baseline serum 25OHD, ng/ml (mean):** 27.2, 27.6, 28.4, 27.4 and 26.4 in placebo, low-dose, mid-dose, high-dose 1 and high-dose 2 groups **Sex of offspring, n (%) female:** 582 (49.6%) **Race/ethnicity:** NR **Skin colour (as reported):** NR

Morris 2021 *(Continued)*

	Familial hx of allergic disease (% as reported of type of allergy): NR **Smoking exposure (as reported):** NR
Interventions	**Comparator (dose, frequency, duration):** placebo, weekly, from second trimester through 26 weeks post-partum **Intervention (dose, frequency, duration):** low-dose: 4200 IU, weekly, from second trimester through 26 weeks post-partum; mid-dose: 16000 IU, weekly, from second trimester through 26 weeks post-partum; high-dose 1: 28000 IU, weekly, for second trimester through birth, followed by placebo, weekly, from birth to 26 weeks postpartum; high-dose 2: 28000 IU, weekly, from second trimester through 26 weeks post-partum **Co-interventions:** calcium (500 mg per day), iron (66 mg per day), and folic acid (350 µg per day) were provided to all participants throughout the intervention phase **Adherence (% when available):** 96% of participants across arms received at least 90% of scheduled doses
Outcomes	**Child age at outcome ascertainment:** 6 months **Outcomes assessed:** airway infection (total, URTI, LRTI) **Assessment method (physician dx, laboratory measurement, parental report, medical records etc):** airway infection reported clinically and microbiologically **Asthma/wheeze definition:** NA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: *The allocation sequence was generated by the trial statistician (ARW) using a computer-generated random number sequence according to a simple randomisation scheme (i.e., no stratification or blocking)*
Allocation concealment (selection bias)	Low risk	Quote: *The random number list was provided to the Toronto Institute for Pharmaceutical Technology (TIPT), the pharmaceutical company that has produced and packaged the supplements in individual participant supplement packs, each of which is labelled with a unique participant identifier. The pre-labelled supplement packets containing both prenatal and postpartum supplements (in separate vials) are sequentially allocated to participants according to their order of enrolment. Participants, investigators, field personnel, study laboratory staff, and data analysts are blinded to vitamin D or placebo group allocation. The allocation scheme will be made available to the Data and Safety Monitoring Board (DSMB) in cases in which individual participants need to be unmasked because of suspected supplement-related adverse events (i.e., hypercalcemia or clinical features suggestive of vitamin D toxicity). Concealment of trial-group assignments was ensured with the use of pre-labelled and sequentially numbered but otherwise identical supplement vials, which were provided to participants in accordance with the assignment sequence.*
Blinding of participants and personnel (performance bias)	Low risk	Quote: *Participants, investigators, field personnel, study laboratory staff, and data analysts are blinded to vitamin D or placebo group allocation. The allocation scheme will be made available to the Data and Safety Monitoring Board (DSMB) in cases in which individual participants need to be unmasked because of suspected supplement-related adverse events (i.e., hypercalcemia or clinical features suggestive of vitamin D toxicity).*

Morris 2021 *(Continued)*

Blinding of outcome assessment (detection bias)	Low risk	Quote: *Participants, investigators, field personnel, study laboratory staff, and data analysts are blinded to vitamin D or placebo group allocation.* Judgement comment: this was the case for the primary trial MDIG published in 2018, which evaluated infant growth outcomes at 9 and 12 months of age. The MDARI study, which was nested within the MDIG study, evaluated respiratory infections at 6 months of age, so we assume blinding held for this assessment as well.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: there were few exclusions and withdrawals and numbers analysed match the remaining number of participants at bottom of flow diagram (Figure 1).
Selective reporting (reporting bias)	Low risk	Judgement comment: the study outcomes reported, including definitions, match those from the published study protocol.
Other bias	Low risk	Judgement comment: no other potential biases noted.

Rosendahl 2018

Study characteristics	
Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group **Country (country income level):** Finland (high income) **Latitude:** 60° N **Funding/Conflict of interest:** Foundation for Pediatric Research, Finska Läkaresällskapet, the Finnish Medical Foundation, Governmental Subsidy for Clinical Research, the Päivikki and Sakari Sohlberg Foundation, Stiftelsen Dorothea Olivia, Karl Walter och Jarl Walter Perkléns minne, the Academy of Finland, the Sigrid Jusénlius Foundation, the Folkh€alsan Research Foundation, the Novo Nordisk Foundation, the Orion Research Foundation, Barncancerfonden, and Allergy Research Foundation.
Participants	**Population receiving intervention:** Infants born 37-42 weeks gestation **N randomised:** 987 **Baseline age (mean):** NR but the intervention was started at 2 weeks of age **Baseline serum 25OHD, ng/ml (mean):** Maternal during pregnancy: 32.8 in comparator group, 32.6 in treatment group; cord blood at birth: 32.7 in comparator group, 32.5 in treatment group **Sex of offspring, n (%) female;** 485 (50%) **Race/ethnicity:** NR (but mothers were of northern European ethnicity) **Skin colour (as reported):** NR **Familial hx of allergic disease (% as reported of type of allergy):** Maternal asthma: 7%, allergic rhinitis: 31%, atopic eczema: 17%, food allergy: 16%; paternal asthma: 8%, allergic rhinitis: 36%, atopic eczema: 11%, food allergy: 14% **Smoking exposure (as reported):** Maternal smoking: 4%, paternal smoking: 15%
Interventions	**Comparator (dose, frequency, duration):** 400 IU, daily, from 2 weeks to 24 months **Intervention (dose, frequency, duration):** 1200 IU, daily, from 2 weeks to 24 months

Rosendahl 2018 *(Continued)*

	Co-interventions: none **Adherence (% when available):** NR
Outcomes	**Child age at outcome ascertainment:** Asthma: 12 months of age, wheeze: 12 months of age, allergic sensitization: 12 months of age, airway infection: 12 months of age **Outcomes assessed:** Asthma, wheeze, atopic dermatitis, airway infection, sensitization to allergens **Assessment method (physician dx, laboratory measurement, parental report, medical records etc):** Physician diagnosis for asthma; parental report for wheeze and atopic dermatitis, and airway infection; IgE levels (laboratory measurement) for sensitization to allergens **Asthma/wheeze definition:** asthma - physician diagnosis; ever wheeze - parental report of a positive answer to the question, “Has your child ever had wheezing or difficulty in breathing in the preceding 12 months?”
Notes	Reported the number of respiratory infections and incidence rates. Also reported IgE-based sensitisation to food and aero allergens separately. We reached out to authors on the number of participants in each group who experienced (1) at least 1 respiratory infection, (2) at least 1 upper respiratory infection, and (3) at least 1 episode of pneumonia diagnosed by physician, as well as the number assessed for each outcome (n, N). We also asked for the union of the allergens for IgE-based sensitisation, and the number of participants assessed for hypercalcaemia. Authors responded to all requests with numbers/proportions, which we used in meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: *Randomization to the 2 vitamin D supplementation groups was performed in blocks of 50 by a pharmacist at Helsinki University Hospital Pharmacy.* Judgement comment: unclear what the sequence generation process was.
Allocation concealment (selection bias)	Low risk	Quote: *Study preparations, identical in appearance, contained vitamin D dissolved in medium-chain triglyceride oil (Orion Pharmaceuticals, Espoo, Finland) and were administered orally with 5 drops for both groups. Randomization to the 2 vitamin D supplementation groups was performed in blocks of 50 by a pharmacist at Helsinki University Hospital Pharmacy.*
Blinding of participants and personnel (performance bias)	Low risk	Quote: *The study was double blinded, with participants and investigators masked to group assignment.*
Blinding of outcome assessment (detection bias)	Low risk	Quote: *The study was double blinded, with participants and investigators masked to group assignment.*
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: the data on allergic diseases and allergic sensitization at 12 months were available for 79% and 74% of children, respectively. There was insufficient information about attrition to know if the reason for attrition is related to the outcomes.
Selective reporting (reporting bias)	Low risk	Judgement Comment: allergy outcomes are pre-registered secondary outcomes in study protocol.
Other bias	Low risk	Judgement comment: no other sources of bias noted.

Rueter 2020

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Country (country income level):** Australia (high income) **Latitude:** 32 degrees South **Funding/Conflict of interest:** Telethon–New Children's Hospital Research Fund, Australia; Asthma Foundation of Western Australia, Australia; and the Princess Margaret Hospital Foundation, Australia.
Participants	**Population receiving intervention:** infants **N randomised:** 195 **Baseline age (mean):** 12.8 days in comparator group, 13.2 days in treatment group **Baseline serum 25OHD, ng/ml (mean):** NR (reports maternal late gestation vitamin D: 30.4 in comparator group, 30.7 in treatment group) **Sex of offspring, n (%) female:** 91 (47%) **Race/ethnicity:** maternal white race: 83% **Skin colour (as reported):** NR **Familial hx of allergic disease (% as reported of type of allergy):** 100% (recruited infants with a parent or sibling with allergic disease - maternal: 77%; paternal: 75%; sibling: 21%) **Smoking exposure (as reported):** NR
Interventions	**Comparator (dose, frequency, duration):** placebo, daily, until 6 months of age **Intervention (dose, frequency, duration):** 400 IU, daily, until 6 months of age **Co-interventions:** none **Adherence (% when available):** NR
Outcomes	**Child age at outcome ascertainment:** outcomes reported at 3 months, 6 months, 1 year and 2.5 years (data from 6-month time point used for meta-analysis) **Outcomes assessed:** wheeze, eczema, allergic sensitization (skin prick), adverse events **Assessment method (physician dx, laboratory measurement, parental report, medical records etc):** Diagnosis of wheeze (virus induced and nonviral) was made by a medical doctor; diagnosis of atopic dermatitis made according to the guidelines of the American Academy of Dermatology Association by typical skin lesions **Asthma/wheeze definition:** wheeze (at primary endpoint of 6 months)- diagnosed by medical doctor. Wheeze and/or asthma (composite outcome assessed at 1-year and 2.5-year follow-up visits) - physician-diagnosed based on structured history and clinical assessment
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Rueter 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	Judgement comment: the pharmacy created a randomisation plan from an online source (www.randomization.com). The randomisation was stratified according to a history of maternal allergic disease and participant sex.
Allocation concealment (selection bias)	Low risk	Judgement comment: the study used central allocation (pharmacy-controlled randomisation) and the intervention/placebo oil were packaged to appear identical so that the investigators and participants could not foresee assignments.
Blinding of participants and personnel (performance bias)	Low risk	Quote: *Both the intervention (vitamin D) and control (placebo) oils were packaged to appear identical and to maintain the blind. Pharmacy staff had no contact with participants, and all research staff remained blind to the allocations until analyses were completed.*
Blinding of outcome assessment (detection bias)	Low risk	Quote: T*he researchers involved in data collection and analysis remained blind to these test results throughout the trial.*
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: missing data were balanced in numbers across groups with similar reasons.
Selective reporting (reporting bias)	High risk	Judgement comment: wheeze was not prespecified as an outcome in the trial registry. Allergic disease (defined as eczema and/or food allergy) and allergic sensitisation (skin prick to food and aero allergens) were specified as secondary outcomes at 6 months, 1 year, and 2.5 years.
Other bias	Low risk	No other sources of bias were noted.

Sahoo 2017

Study characteristics	
Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Country (country income level):** India (lower-middle income) **Latitude:** 26.9 degrees N **Funding/Conflict of interest:** Grant support from Department of Biotechnology (BT/PR/13985/SPD/11/1297/2010), intramural grant from Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Indian Council for Medical Research grant (manpower development scheme)
Participants	**Population receiving intervention:** pregnant women **N randomised:** 300 **Baseline age (mean):** median age: 25 (mean NR) **Baseline serum 25OHD, ng/mL (mean)** Median 28.5 in comparator group, 30.3 in group receiving intervention 1, 24.3 in group receiving intervention 2 **Sex of offspring, n (%) female:** NR **Race/ethnicity:** NR

Sahoo 2017 *(Continued)*

	Skin colour (as reported): NR **Familial hx of allergic disease (% as reported of type of allergy):** NR **Smoking exposure (as reported):** 0% smokers
Interventions	**Comparator (dose, frequency, duration):** 400 IU, daily, from 14-20 weeks through delivery **Intervention (dose, frequency, duration):** Intervention 1: 60,000 IU, once every 4 weeks, from 14-20 weeks through delivery; Intervention 2: 60,000 IU, once every 8 weeks, from 14-20 weeks through delivery **Co-interventions:** none **Adherence (% when available):** NR
Outcomes	**Child age at outcome ascertainment:** 12-16 months of age **Outcomes assessed:** wheeze, atopic dermatitis **Assessment method (physician dx, laboratory measurement, parental report, medical records etc):** parental report for wheeze and airway infection, examination of infants for evidence of visible eczema for atopic dermatitis **Asthma/wheeze definition:** wheeze - "Any history of wheeze, need for nebulization and their frequency any time since birth were noted"
Notes	Also reported the mean frequency of respiratory infections per group, which we assumed to mean the number of episodes per person. Reached out to authors for the number/proportion of participants that experienced any respiratory infection but never heard back.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: *Randomization was done by a computer-generated sequence in randomly permuted blocks of hundred.*
Allocation concealment (selection bias)	Low risk	Quote: *All the medications were dispensed in sequentially numbered, identical, opaque, sealed packs (carrying the name of the participant) by a research assistant, who was blinded to intervention.*
Blinding of participants and personnel (performance bias)	Low risk	Quote: *The allocation sequence was also concealed from all participants; the researcher enrolling and assessing mothers, the researcher assessing offspring and DXA scan images, and performing data analysis.*
Blinding of outcome assessment (detection bias)	Low risk	Quote: *The allocation sequence was also concealed from all participants; the researcher enrolling and assessing mothers, the researcher assessing offspring and DXA scan images, and performing data analysis.*
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: the reasons for missing data are balanced across groups.
Selective reporting (reporting bias)	High risk	Judgement comment: the trial was registered retrospectively and the protocol does not mention offspring atopic dermatitis or wheeze in the outcomes (CTRI/2012/02/002395).
Other bias	Low risk	Judgement comment: no other sources of bias noted.

Salas 2018

Study characteristics	
Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Country (country income level):** USA (high income) **Latitude:** 33.5 degrees N **Funding/Conflict of interest:** Kaul Pediatric Research Institute Senior Investigator Award and the National Institutes of Health (NIH), grant number NIH U10 HD34216.
Participants	**Population receiving intervention:** Premature infants **N randomised:** 100 **Baseline age (mean):** Median gestational age: 26 weeks in comparator group, 26 weeks in group receiving intervention 1, 25 weeks in group receiving intervention 2 (means NR) **Baseline serum 25OHD, ng/mL (mean):** median 18 in comparator group, 13 in group receiving intervention 1, 16 in group receiving intervention 2 (means NR) **Sex of offspring, n (%) female:** 40 (57%) **Race/ethnicity:** Black race: 35 (50%) **Skin colour (as reported):** NR **Familial hx of allergic disease (% as reported of type of allergy):** NR **Smoking exposure (as reported):** NR
Interventions	**Comparator (dose, frequency, duration):** placebo, daily, from day 1 of enteral feeding to postnatal day 28 **Intervention (dose, frequency, duration):** Intervention 1: 200 IU, daily, from day 1 of enteral feeding to postnatal day 28; intervention 2: 800 IU, daily, from day 1 of enteral feeding to postnatal day 28 **Co-interventions:** none **Adherence (% when available):** 100% (with some LTF due to death)
Outcomes	**Child age at outcome ascertainment:** 2 years **Outcomes assessed:** Asthma **Assessment method (physician dx, laboratory measurement, parental report, medical records etc):** diagnosed by use of asthma medications up to 3 months prior to follow-up **Asthma/wheeze definition:** asthma - structured questionnaire for parents or primary caregivers that included questions about the use of asthma medications up to 3 months prior to follow-up
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Salas 2018 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: *Research pharmacy staff not involved in patient care were responsible for performing block randomisation using computerized random sequence generation*
Allocation concealment (selection bias)	Low risk	Quote: *Research pharmacy staff not involved in patient care were responsible for... determining participant allocation to one of the supplementation groups... and masking the individuals administering the assigned supplementation.*
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement comment: no information on blinding of participants or participant families.
Blinding of outcome assessment (detection bias)	Low risk	Quote: *Certified examiners who were unaware of group allocation assessed the outcomes.*
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: there were 10 participants that were alive at the two-year follow-up who did not complete assessment, and surrogate measures based on medical records were used to minimise risk of bias due to missing data.
Selective reporting (reporting bias)	High risk	Judgement comment: the outcome "Use of asthma medication", which was used to define asthma cases, was not prespecified in the trial protocol available at ClinicalTrials.gov.
Other bias	Low risk	Judgement comment: study appears to be free of other sources of bias

Yadav 2022

Study characteristics	
Methods	**Study design:** Open-label randomised controlled trial **Study grouping:** Parallel group **Country (country income level):** India (low-middle) **Latitude:** 26.2 N **Funding/Conflict of interest:** The cost of the investigations was born by the institute (All India Institute of Medical Sciences). The drug was supplied by Cipla, India.
Participants	**Population receiving intervention:** Infants **N randomized:** 102 **Baseline age (mean):** 63 hours **Baseline serum 25OHD, ng/mL (mean):** 13.6 ng/mL **Sex of offspring, n (%) female:** 50 (49%) **Race/ethnicity:** NR **Skin colour (as reported):** NR **Familial hx of allergic disease (% as reported of type of allergy):** NR **Smoking exposure (as reported):** NR

Yadav 2022 *(Continued)*

Interventions	**Comparator (dose, frequency, duration):** 400 IU/d for 14 weeks **Intervention (dose, frequency, duration):** 800 IU/d for 14 weeks **Co-interventions:** Mothers received calcium (500 mg/day) with vitamin D3 (250 IU/day) beyond the 1st trimester in the antepartum period, and calcium (1000mg/day) with vitamin D3 (500 IU/day) for 6 weeks in the postpartum period; exclusive breastfeeding recommended for all infants **Adherence (% when available):** > 95% for infants followed through 14 weeks
Outcomes	**Child age at outcome ascertainment:** 14 weeks **Outcomes assessed:** Respiratory tract infections (included upper respiratory tract infection, lower respiratory infection, bronchiolitis, and community-acquired pneumonia), adverse events **Assessment method (physician dx, laboratory measurement, parental report, medical records etc):** RTIs, adverse events assessed by study investigators **Asthma/wheeze definition:** NA
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: *An investigator generated the randomization sequence from a website (www.randomization. com)*
Allocation concealment (selection bias)	Low risk	Quote: *The randomization sequence was concealed using sequentially numbered, opaque, sealed envelopes.*
Blinding of participants and personnel (performance bias)	High risk	Quote: *This study is an open-label, randomized controlled trial... The principal investigator and parents were not blinded.*
Blinding of outcome assessment (detection bias)	High risk	Judgement comment: Although the laboratory personnel and statistician were blinded to intervention allocation, our outcome of interest, respiratory tract infections, was assessed by the study investigators, who were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: *We enrolled 102 infants (51 in each group). One infant in the intervention group and two infants in the control group were lost to follow-up.* Judgement comment: low attrition, balanced across intervention and comparator groups
Selective reporting (reporting bias)	Low risk	Judgement comment: All outcomes that were listed in trial registry and described in paper methods were reported. The paper also reported anthropometry and rickets outcomes, which were not included in the trial registry, but this is unlikely to bias the results for respiratory tract infections (the outcome of interest in this study).
Other bias	Low risk	No other sources of bias noted.

Zhou 2018

Study characteristics

Zhou 2018 *(Continued)*

Methods	**Study design:** Randomised controlled trial **Study grouping:** parallel group **Country (country income level):** China (middle-upper) **Latitude:** 29 degrees N (Yongkang, central part of Zhejiang province **Funding/Conflict of interest:** sponsored by the Wenzhou science and technology project
Participants	**Population receiving intervention:** Infants **N randomised:** 400 **Baseline age (mean):** 7.8 months **Baseline serum 25OHD, ng/mL (mean):** 17.4 ng/mL in control and 17 ng/mL in intervention groups **Sex of offspring, n (%) female:** 159 (48%) **Race/ethnicity:** NR **Skin colour (as reported):** NR **Familial hx of allergic disease (% as reported of type of allergy):** NR **Smoking exposure (as reported):** NR
Interventions	**Comparator (dose, frequency, duration):** 400 IU, daily, for 4 months **Intervention (dose, frequency, duration):** 1200 IU, daily, for 4 months **Co-interventions:** none **Adherence (% when available):** poor compliance (not defined) reported in 5 infants in control group and 7 infants in intervention group
Outcomes	**Child age at outcome ascertainment:** 11.8 months (estimated based on mean baseline age + 4 months) **Outcomes assessed:** wheeze, adverse events, lower respiratory tract infections (pneumonia) **Assessment method (physician dx, laboratory measurement, parental report, medical records etc):** wheeze assessed by medical staff **Asthma/wheeze definition:** wheeze - monitored daily by medical staff for wheeze-like symptoms once presenting for influenza-like illness
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: insufficient information to determine how randomisation was done.
Allocation concealment (selection bias)	Unclear risk	Judgement comment: unclear how allocation was concealed.

Zhou 2018 *(Continued)*

Blinding of participants and personnel (performance bias)	High risk	Quote: *This study was a multicenter, randomised, open, controlled clinical trial*
Blinding of outcome assessment (detection bias)	High risk	Judgement comment: this study was not blinded and assessments of wheeze and adverse events, which were made by medical staff, were subjective and could have been influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: *Participants were excluded from analysis due to poor compliance, without stating a definition of poor compliance. However, the numbers were equal in both groups and are unlikely to effect the outcome data. Lost to follow up appear balanced between the groups.*
Selective reporting (reporting bias)	High risk	Judgement comment: wheeze was not specified as an outcome (primary or secondary) in the clinical trials registry.
Other bias	Low risk	Judgement comment: the study appears to be free of other sources of bias.

dx: diagnosis; (**F)eNO**: (fractional) exhaled nitric oxide; **hx**: history; **IgE**: immunoglobulin E; **ISAAC:** International Study of Asthma and Allergies in Childhood; **IU**: international units; **LTF**: lost to follow-up; **LRTI**: lower respiratory tract infection; **NHLBI**: National Heart, Lung and Blood Institute; **NA:** not applicable; **NR**: not reported; **ODS**: US National Institutes of Health Office of Dietary Supplements; **RCT:** randomised controlled trial; **RTI**: respiratory tract infection; **25(OH)D:** 25-hydroxyvitamin D; **URTI**: upper respiratory tract infection

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Fioranelli 2016	Ineligible population: this study evaluated the effects of vitamin D in children with pre-existing atopic dermatitis
Ganmaa 2020	Ineligible population: this study evaluated the effect of vitamin D in school children aged 6 to 13 years
IRCT20110807007244N7	Outcomes not measured: this study evaluated the effect of vitamin D in pregnant women at risk of preterm delivery on the incidence of non-specific respiratory distress syndrome in their infants. To the best of our knowledge, this trial did not measure or plan to measure asthma, wheeze, atopic dermatis, respiratory tract infections, allergic sensitisation, or airway inflammation.
IRCT2014052617843N2	Ineligible population: this trial evaluated the effect of vitamin D in children with pre-existing, confirmed respiratory infections
Jadhav 2021	Ineligible population: this study evaluated the effects of vitamin D in children with pre-existing respiratory infections
JRCTs031200376	Ineligible population: this study evaluated the effects of vitamin D in children with respiratory syncytial viral (RSV) infection
Lara-Corrales 2018	Ineligible population: this study evaluated the effects of vitamin D in children with pre-existing atopic dermatitis
Manaseki-Holland 2012b	Ineligible study design: editorial on vitamin D for the treatment of childhood pneumonia
Mansuroglu 2017	Ineligible study design: this study evaluated the association of vitamin D levels in the blood and wheezing in the context of a randomised trial of *recommendations* to take vitamin D

Study	Reason for exclusion
NCT01337635	Ineligible population: this study evaluated the effects of vitamin D in children with pre-existing atopic dermatitis
NCT01921894	Ineligible population: this study evaluated the effect of vitamin D in children aged 6 to 14 years with pre-existing asthma
NCT02617771	Ineligible population: this study evaluated the effect of vitamin D in children with a history of recurrent respiratory tract infections
NCT03257215	Ineligible population: this study evaluated the effect of vitamin D in children with pre-existing atopic dermatitis
NCT04579640	Ineligible population: this study evaluated the effect of vitamin D in participants aged 16 years and older
NCT05043116	Ineligible population: this study evaluated the effects of vitamin D in children with pre-existing asthma/asthma-like symptoms
Pettifor 2016	Ineligible study design: editorial on vitamin D for the prevention and management of lower respiratory tract infections in children
Rueter 2017	Ineligible study design: methods study that compared chemiluminescent immunoassay (CLIA) and liquid chromatography - tandem mass spectometry assay (LC-MS/MS) methods for measuring total 25-hydroxyvitamin D (25(OH)D) levels in the context of a randomised trial of vitamin D supplementation (Rueter 2020).
Seth 2021	Review (screened for references): a review of paediatric inner-city asthma and risk factors related to poverty and urban environments
Sidbury 2008	Ineligible population: this study evaluated the effect of vitamin D in children aged 2 to 13 with pre-existing atopic dermatitis
Singh 2019	Ineligible population: this study evaluated the effect of vitamin D in children diagnosed with pneumonia
UMIN000001975	Ineligible population: this study evaluated the effect of vitamin D in children with atopic dermatitis
UMIN000004159	Ineligible population: this study evaluated the effect of vitamin D in children with atopy
Zeghoud 1994	Outcomes not measured: this study evaluated the effect of vitamin D supplementation in infants on infant serum vitamin D and calcium. To the best of our knowledge, this trial did not measure or plan to measure asthma, wheeze, atopic dermatitis, respiratory tract infections, allergic sensitisation, or airway inflammation.
Zeghoud 1997	Ineligible study design: this study evaluated serum vitamin D, parathyroid hormone, calcium, phosphates, and alkaline phosphatase activity in neonates to determine thresholds for vitamin D deficiency
Zerofsky 2014	Ineligible population: this study evaluated the effects of vitamin D during pregnancy on maternal outcomes only. To the best of our knowledge, no outcomes were evaluated in the offspring.
Zerofsky 2016	Ineligible population: this study evaluated the effects of vitamin D during pregnancy on maternal outcomes only. To the best of our knowledge, no outcomes were evaluated in the offspring.
Zhang 2011	Ineligible population: this study evaluated the effect of vitamin D on vitamin D levels in lactating women. To the best of our knowledge, no outcomes were evaluated in the offspring.

Study	Reason for exclusion
Zhao 2019	Ineligible population: this study evaluated the effects of vitamin D in early pregnancy on maternal outcomes only. To the best of our knowledge, no outcomes were evaluated in the offspring.
Ziegler 2014	Outcomes not assessed: this study evaluated the effect of vitamin D in breastfed infants on plasma 25-hydroxyvitamin D (25(OH)D) concentration and non-specified illness incidence and growth. To the best of our knowledge, this trial did not measure or plan to measure asthma, wheeze, atopic dermatitis, respiratory tract infections, allergic sensitisation, or airway inflammation.
Ziegler 2017	Outcomes not assessed: this study evaluated the effect of vitamin D in breastfed infants on bone mineral content and measures of bone turnover. To the best of our knowledge, this trial did not measure or plan to measure asthma, wheeze, atopic dermatitis, respiratory tract infections, allergic sensitisation, or airway inflammation.

25(OH)D: 25-hydroxyvitamin D

Characteristics of studies awaiting classification *[ordered by study ID]*

CTRI/2012/09/002958

Methods	Randomised controlled trial
Participants	Lactating women and breastfed offspring
Interventions	**Comparator:** double placebo (mother and infant) started within 7 days of delivery and until 9 months **Intervention, mother:** 120,000 IU/month vitamin D3 to mother started within 7 days of delivery and until 9 months **Intervention, offpring:** 400 IU/day vitamin D3 to offpring started within 7 days of delivery and until 9 months
Outcomes	Respiratory infection
Notes	Needed data for respiratory illness are not reported. We contacted the authors and never heard back.

Flores-Aldana 2023

Methods	Randomised controlled trial with 4 treatment groups
Participants	Healthy preschool-age children 12–30 months old of both sexes, recruited from eight public day-care centres in Cuernavaca, Mexico
Interventions	400 IU/d ergocalciferol vs 800 IU/d ergocalciferal vs 1000 IU/d cholecalciferol vs multivitamin without vitamin D
Outcomes	Airway infections
Notes	Trial registry mentions collecting data on airway infections but data not reported

Hauger 2019

Methods	Randomised controlled trial
Participants	White 4- to 8-year-old children
Interventions	800 IU vitamin D per day vs 400 IU vitamin D per day vs daily placebo
Outcomes	Markers of innate immune defence, including blood leukocyte counts
Notes	Contacted authors requesting disaggregation of data for children aged 4-5; no response.

Kumar 2011

Methods	Randomised controlled trial
Participants	Low birthweight infants born at term
Interventions	**Comparator:** placebo given weekly from age 7 days to 6 months **Intervention:** 1400 IU/week vitamin D from age 7 days to 6 months
Outcomes	Hospital admission or death, any severe morbidity
Notes	Reports a composite morbidity outcome that includes pneumonia; cannot disaggregate the data

NCT01229189

Methods	Randomised controlled trial
Participants	Pregnant women/infant pairs
Interventions	Maternal 4000 IU vitamin D per day/infant 400 IU vitamin D per day vs maternal 4000 IU/d/infant placebo vs maternal placebo/infant placebo
Outcomes	Maternal and neonatal complications, including infant pneumonia
Notes	Trial registry only

NCT01705314

Methods	Randomised controlled trial
Participants	Children and adolescents between the ages of 3 and 17 years
Interventions	**Comparator:** Placebo weekly for 8 months **Intervention:** 14,000 IU/week vitamin D for 8 months
Outcomes	Influenza infection, non-influenza respiratory viral infection, influenza-like illness
Notes	Authors were contacted to request disaggregation of data for ages 3-5; no response

NCT02046577

Methods	Double-blind, randomised, placebo-controlled, parallel-arm study
Participants	Children aged 18 to 36 months
Interventions	Placebo weekly vs 5600 IU vitamin D weekly vs 11,200 IU vitamin D weekly for 6 months
Outcomes	Incidence of acute respiratory tract infections
Notes	Trial registry only

NCT02210884

Methods	Randomised controlled trial
Participants	Breastfeeding women aged 18 to 45 years
Interventions	Placebo weekly versus 15,000 IU Vitamin D3 weekly, duration not specified
Outcomes	Incidence of infant acute respiratory tract infections
Notes	Trial registry only

Oberhelman 2013

Methods	Randomised controlled trial
Participants	Lactating mother/infant pairs
Interventions	Maternal supplementation with 150,000 IU vitamin D once vs 5000 IU vitamin D per day
Outcomes	Upper respiratory infections were reported as adverse events
Notes	Contacted authors for more information on upper respiratory infections; no response.

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12616000659404

Study name	PREVARID - PREVention of Acute Respiratory Infections with Vitamin D
Methods	Randomised double-blinded placebo-controlled parallel study.
Participants	"Children will be eligible for enrolment if they are NZ residents, are < 2 years old at the time of their ALRI hospital admission and reside in the Auckland District Health Board catchment area."
Interventions	5000 IU vitamin D per week, administered as 5 drops orally per week, for 12 months, vs placebo (coconut oil) control

ACTRN12616000659404 *(Continued)*

Outcomes	Number of acute respiratory infections during the 12 months following enrolment
Starting date	July 2016
Contact information	Cameron Grant, cc.grant@auckland.ac.nz
Notes	

Binks 2023

Study name	Vitamin D supplementation to prevent acute respiratory infections among Indigenous children in the Northern Territory: a randomised controlled trial
Methods	Double-blind parallel-arm randomised controlled study
Participants	Pregnant women aged over 17 to less than or equal to 40 years, with current gestation of 28 to 34 weeks, of Aboriginal and/or Torres Strait Islander descent, resident in urban Darwin, Alice Springs or one of the participating communities at the time of enrolment and intending to stay in a study community until the infants is 12 months of age
Interventions	Mother: total 14,000 IU/week (equivalent 2000 IU/day), from 28-34 weeks gestation (inclusive) until delivery. Infant: 4200 IU/week (equivalent 600 IU/day), from birth until 4 months of age vs placebo for mother and placebo for infant
Outcomes	Acute respiratory infection episodes in first 12 months of life
Starting date	January 2019
Contact information	Michael Binks, michael.binks@menzies.edu.au
Notes	

ChiCTR2000032488

Study name	A multicenter randomised controlled study of vitamin D supplementation in pregnant women for the prevention of gestational diabetes
Methods	Randomised controlled trial
Participants	Pregnant women aged 18-45 years old who are at high risk of gestational diabetes mellitus, defined as a) pre-pregnancy or early pregnancy BMI >= 24 kg/m^2; b) family history of diabetes or gestational diabetes; c) gestational diabetes diagnosed in previous pregnancies; d) have a history of childbirth of macrosomia (>= 4000 g); e) glycosylated haemoglobin 5.7-6.4% or fasting blood glucose 6.1-7.0 mmol/L;
Interventions	800 IU vitamin D per day vs daily placebo, 8–14 weeks gestation through delivery
Outcomes	Gestational diabetes, elevated serum vitamin D, birthweight and gestational age, baby length and weight, baby allergic diseases
Starting date	July 2020

ChiCTR2000032488 *(Continued)*

Contact information	Yu Yunxian, yunxianyu@zju.edu.cn
Notes	

CTRI/2017/10/010274

Study name	Role of vitamin D3 intake and decrease in respiratory infections
Methods	Double-blind, randomised, parallel-arm, controlled trial
Participants	Children aged 3 to 6 years, healthy by parental report, recruited at Jallappaschool in Kolar, Karnataka, India
Interventions	"High dose (3000 IU daily for 3 Months, same Dose and Frequency for another 3 months after an Intervention free period of 6 Months) vs low dose (600 IU daily for 3 Months, same Dose and Frequency for another 3 months after a Drug free period of 6 Months)."
Outcomes	Number of parent-reported and class-teacher-detected acute respiratory tract infections
Starting date	January 2018
Contact information	Kanak N Venkateshwara Prasad, drknvp@gmail.com
Notes	

CTRI/2020/11/029281

Study name	Comparison of two doses of vitamin D in healthy term neonates
Methods	Double-blind, randomised, parallel-arm, controlled trial
Participants	Infants born at Nehru Hospital in Pgimer, Chandigarh, India, gestational age 37 weeks or more and appropriate for gestational age (as defined by Intergrowth 21 growth charts), aged 1 to 28 days
Interventions	High dose (800 IU daily, from hospital discharge through 14 weeks postnatal) vs low dose (400 IU daily, from hospital discharge through 14 weeks postnatal)
Outcomes	(Secondary outcome) episodes of respiratory illness
Starting date	November 2020
Contact information	Jogender Kumar, jogendrayadv@gmail.com
Notes	

Gerveieeha 2019

Study name	The effect of different amounts of vitamin D supplementation on serum calcidiol, anthropometric status, and body composition in overweight or obese nursing women

Gerveieeha 2019 *(Continued)*

Methods	Double-blind, randomised, placebo-controlled, parallel-group trial
Participants	Lactating and nursing healthy women with overweight or obesity, recruited after full term birth
Interventions	Placebo (lactose) vs 2000 IU daily vitamin D vs 4000 IU daily vitamin D for 12 weeks
Outcomes	Infant infections
Starting date	Registered April 2018
Contact information	Gity Sotodeh, gsotodeh@tums.ac.ir
Notes	Study protocol published

NCT01038453

Study name	Effects of Vitamin D Supplement Before and During Pregnancy on Complications, Birth Weight and Bone Mineral Density During Lactation
Methods	Double-blind, randomised, placebo-controlled, parallel-arm trial
Participants	Pregnant women aged 20-35 with pregnancy 25OHD levels < 50 nmol/L
Interventions	Placebo daily vs 35 µg vitamin D daily vs 70 µg vitamin D daily, baseline through 16 weeks after delivery
Outcomes	Infections of the newborn
Starting date	December 2009
Contact information	Gitte Bloch Rasmussen, gittebr@ki.au.dk
Notes	No full text found

NCT02112734

Study name	The VITALITY Trial
Methods	Double-blind, randomised, parallel-arm, placebo-controlled trial
Participants	Fully breastfed infants who are 6-12 weeks of age, not receiving vitamin D supplementation and live in metropolitan Melbourne, Australia.
Interventions	400 IU, daily, during first year of life vs placebo
Outcomes	The primary outcome is challenge-proven food allergy at 12 months of age. Secondary outcomes are food sensitisation (positive skin prick test), number of lower respiratory infections (through hospital linkage), moderately-severe and persistent eczema (by history and examination).
Starting date	December 2014
Contact information	Kirsten Perrett, kirsten.perrett@rch.org.au

NCT02112734 *(Continued)*

Notes	

NCT04302987

Study name	Vitamin D Intervention in Infants - 6 Years Follow-up (VIDI2)
Methods	Follow-up of the VIDI study, a randomised controlled trial
Participants	Participants in the original VIDI study who participated until the last study visit at the age of 2 years. The original study included infants born at term with a birth weight within 2 standard deviations of the mean for gestational age
Interventions	10 µg daily vs 30 µg daily from the age 2 weeks until 2 years
Outcomes	Morbidity due to allergic diseases, morbidity due to infectious diseases
Starting date	6-year follow-up assessment registered March, 2020
Contact information	Sture Andersson, sture.andersson@hus.fi
Notes	

NCT05694689

Study name	Randomized Trial of Enteral Vitamin D Supplementation in Infants < 28 Weeks Gestational Age or <1000 Grams Birth Weight
Methods	Quadruple-blind, randomised, parallel-arm, placebo-controlled trial
Participants	"Infants aged 24 Hours to 96 Hours, born <28 weeks gestational age or <1000 grams birth weight, at the University of Texas Medical Branch in Galveston, Texas"
Interventions	800 IU/day vs placebo until 400 IU/day provided as part of usual care, then 400 IU/day on top of usual care (totalling 800 IU/day) vs usual care (400 IU/d), birth to 28 days
Outcomes	Wheeze
Starting date	15 February 2023
Contact information	Sunil Jain, skjain@utmb.edu
Notes	

DATA AND ANALYSES

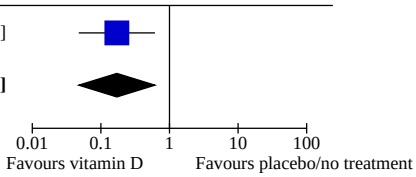
Comparison 1. Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Asthma	1	236	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.05, 0.61]
1.2 Wheeze	1	158	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.50, 2.54]
1.3 Atopic dermatitis	2	600	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.59, 1.33]
1.4 Adverse events	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.4.1 Infant elevated 25OHD	2	467	Risk Ratio (M-H, Fixed, 95% CI)	3.73 [0.50, 27.63]
1.4.2 Infant hypercalcaemia	2	1179	Risk Ratio (M-H, Fixed, 95% CI)	3.45 [0.20, 61.03]
1.4.3 Maternal hypercalcaemia	4	2714	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.21, 13.83]
1.4.4 Infant death	2	1478	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.18, 0.93]
1.4.5 Intrauterine death	4	2670	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.23, 0.90]
1.4.6 Congenital malformations	2	2263	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.36, 1.01]
1.4.7 Preterm delivery	2	2263	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [0.77, 3.47]
1.4.8 Maternal hypertension	2	2432	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.76, 2.05]
1.5 Any airway infection	3	1564	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.97, 1.04]
1.6 Lower respiratory tract infection	2	1325	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.82, 1.42]
1.7 Upper respiratory tract infection	2	1328	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.82, 2.04]
1.8 Allergic sensitisation – total IgE (continuous)	1	86	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.92, 0.32]
1.9 Allergic sensitisation – skin prick against common allergens	1	95	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.27, 1.44]
1.10 Airway inflammation – eosinophil counts (continuous)	1	80	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-1.21, 0.65]
1.11 Airway inflammation – exhaled nitric oxide (continuous)	1	62	Mean Difference (IV, Fixed, 95% CI)	-4.20 [-10.44, 2.04]

Analysis 1.1. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 1: Asthma

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Grant 2015	3	156	9	80	100.0%	0.17 [0.05 , 0.61]
Total		**156**		**80**	**100.0%**	**0.17 [0.05 , 0.61]**
Total events:	3		9			

Test for overall effect: Z = 2.71 (P = 0.007)

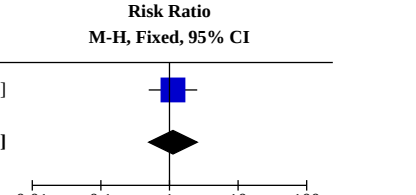


Heterogeneity: Not applicable

Analysis 1.2. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 2: Wheeze

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldring 2013	17	108	7	50	100.0%	1.12 [0.50 , 2.54]
Total		**108**		**50**	**100.0%**	**1.12 [0.50 , 2.54]**
Total events:	17		7			

Test for overall effect: Z = 0.28 (P = 0.78)

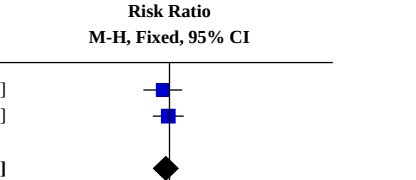


Heterogeneity: Not applicable

Analysis 1.3. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 3: Atopic dermatitis

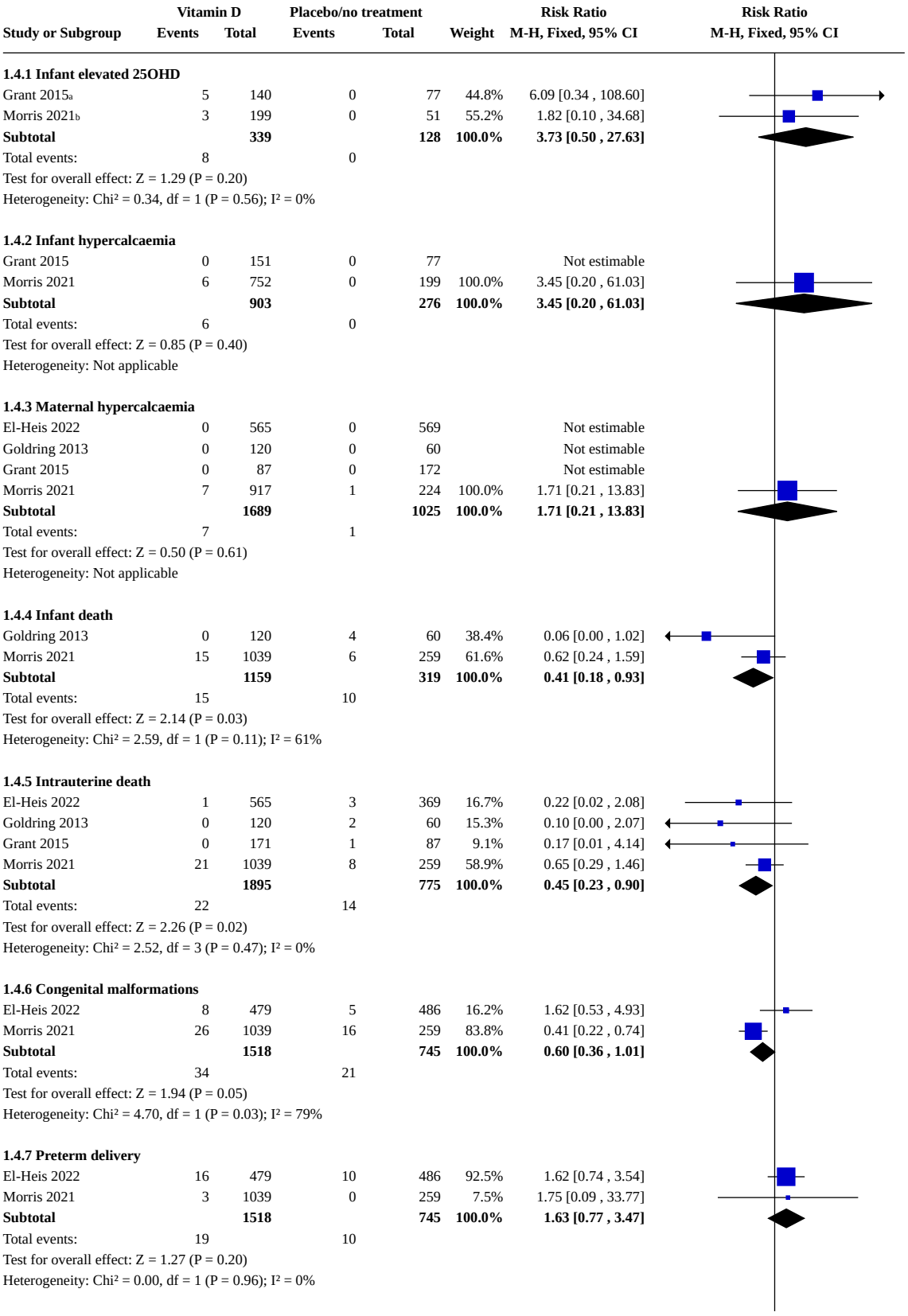
Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
El-Heis 2022	15	223	19	226	48.2%	0.80 [0.42 , 1.53]
Goldring 2013	30	102	15	49	51.8%	0.96 [0.57 , 1.61]
Total		**325**		**275**	**100.0%**	**0.88 [0.59 , 1.33]**
Total events:	45		34			

Test for overall effect: Z = 0.59 (P = 0.55)



Heterogeneity: $Chi^2 = 0.19$, df = 1 (P = 0.66); $I^2 = 0\%$

Analysis 1.4. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 4: Adverse events



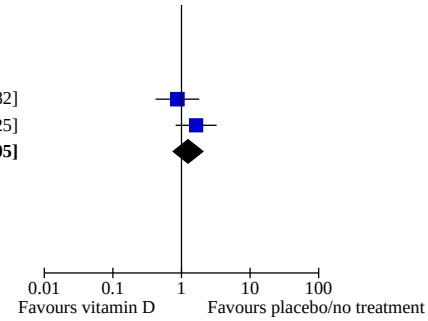
Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Infant elevated 25OHD						
Grant 2015[a]	5	140	0	77	44.8%	6.09 [0.34 , 108.60]
Morris 2021[b]	3	199	0	51	55.2%	1.82 [0.10 , 34.68]
Subtotal		**339**		**128**	**100.0%**	**3.73 [0.50 , 27.63]**
Total events:	8		0			
Test for overall effect: Z = 1.29 (P = 0.20)						
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
1.4.2 Infant hypercalcaemia						
Grant 2015	0	151	0	77		Not estimable
Morris 2021	6	752	0	199	100.0%	3.45 [0.20 , 61.03]
Subtotal		**903**		**276**	**100.0%**	**3.45 [0.20 , 61.03]**
Total events:	6		0			
Test for overall effect: Z = 0.85 (P = 0.40)						
Heterogeneity: Not applicable						
1.4.3 Maternal hypercalcaemia						
El-Heis 2022	0	565	0	569		Not estimable
Goldring 2013	0	120	0	60		Not estimable
Grant 2015	0	87	0	172		Not estimable
Morris 2021	7	917	1	224	100.0%	1.71 [0.21 , 13.83]
Subtotal		**1689**		**1025**	**100.0%**	**1.71 [0.21 , 13.83]**
Total events:	7		1			
Test for overall effect: Z = 0.50 (P = 0.61)						
Heterogeneity: Not applicable						
1.4.4 Infant death						
Goldring 2013	0	120	4	60	38.4%	0.06 [0.00 , 1.02]
Morris 2021	15	1039	6	259	61.6%	0.62 [0.24 , 1.59]
Subtotal		**1159**		**319**	**100.0%**	**0.41 [0.18 , 0.93]**
Total events:	15		10			
Test for overall effect: Z = 2.14 (P = 0.03)						
Heterogeneity: Chi² = 2.59, df = 1 (P = 0.11); I² = 61%						
1.4.5 Intrauterine death						
El-Heis 2022	1	565	3	369	16.7%	0.22 [0.02 , 2.08]
Goldring 2013	0	120	2	60	15.3%	0.10 [0.00 , 2.07]
Grant 2015	0	171	1	87	9.1%	0.17 [0.01 , 4.14]
Morris 2021	21	1039	8	259	58.9%	0.65 [0.29 , 1.46]
Subtotal		**1895**		**775**	**100.0%**	**0.45 [0.23 , 0.90]**
Total events:	22		14			
Test for overall effect: Z = 2.26 (P = 0.02)						
Heterogeneity: Chi² = 2.52, df = 3 (P = 0.47); I² = 0%						
1.4.6 Congenital malformations						
El-Heis 2022	8	479	5	486	16.2%	1.62 [0.53 , 4.93]
Morris 2021	26	1039	16	259	83.8%	0.41 [0.22 , 0.74]
Subtotal		**1518**		**745**	**100.0%**	**0.60 [0.36 , 1.01]**
Total events:	34		21			
Test for overall effect: Z = 1.94 (P = 0.05)						
Heterogeneity: Chi² = 4.70, df = 1 (P = 0.03); I² = 79%						
1.4.7 Preterm delivery						
El-Heis 2022	16	479	10	486	92.5%	1.62 [0.74 , 3.54]
Morris 2021	3	1039	0	259	7.5%	1.75 [0.09 , 33.77]
Subtotal		**1518**		**745**	**100.0%**	**1.63 [0.77 , 3.47]**
Total events:	19		10			
Test for overall effect: Z = 1.27 (P = 0.20)						
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						

Analysis 1.4. (Continued)

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%

1.4.8 Maternal hypertension						
El-Heis 2022	13	565	15	569	50.9%	0.87 [0.42 , 1.82]
Morris 2021	59	1039	9	259	49.1%	1.63 [0.82 , 3.25]
Subtotal		**1604**		**828**	**100.0%**	**1.25 [0.76 , 2.05]**
Total events:	72		24			

Test for overall effect: Z = 0.87 (P = 0.39)
Heterogeneity: Chi² = 1.50, df = 1 (P = 0.22); I² = 33%

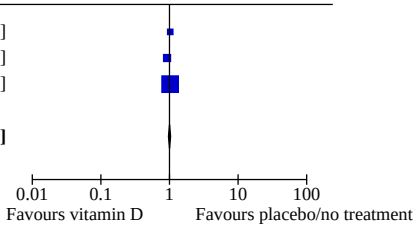


Footnotes
[a]Defined as serum 25OHD >100 ng/mL
[b]Defined as serum 25OHD >125 ng/mL

Analysis 1.5. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 5: Any airway infection

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldring 2013	104	104	49	50	13.2%	1.03 [0.98 , 1.08]
Grant 2015	142	156	79	80	20.7%	0.92 [0.87 , 0.97]
Morris 2021	854	940	208	234	66.1%	1.02 [0.97 , 1.07]
Total		**1200**		**364**	**100.0%**	**1.00 [0.97 , 1.04]**
Total events:	1100		336			

Test for overall effect: Z = 0.10 (P = 0.92)

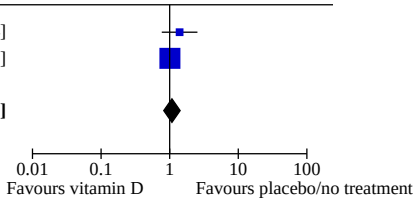


Heterogeneity: Chi² = 10.24, df = 2 (P = 0.006); I² = 80%

Analysis 1.6. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 6: Lower respiratory tract infection

Study or Subgroup	Vitamin D Events	Vitamin D Total	placebo/no treatment Events	placebo/no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldring 2013	31	101	11	50	18.3%	1.40 [0.77 , 2.54]
Morris 2021	166	940	41	234	81.7%	1.01 [0.74 , 1.37]
Total		**1041**		**284**	**100.0%**	**1.08 [0.82 , 1.42]**
Total events:	197		52			

Test for overall effect: Z = 0.54 (P = 0.59)

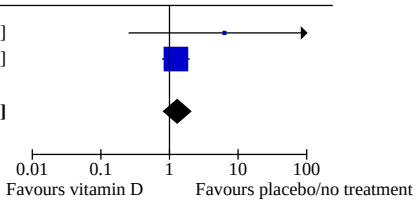


Heterogeneity: Chi² = 0.89, df = 1 (P = 0.34); I² = 0%

Analysis 1.7. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 7: Upper respiratory tract infection

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Goldring 2013	104	104	49	50	1.0%	6.33 [0.25 , 158.26]
Morris 2021	854	940	208	234	99.0%	1.24 [0.78 , 1.97]
Total		**1044**		**284**	**100.0%**	**1.29 [0.82 , 2.04]**
Total events:	958		257			

Test for overall effect: Z = 1.11 (P = 0.27)

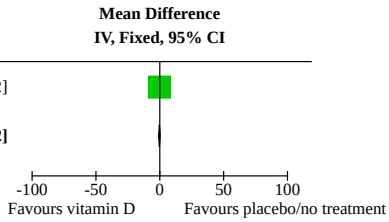


Heterogeneity: Chi² = 0.97, df = 1 (P = 0.33); I² = 0%

Analysis 1.8. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 8: Allergic sensitisation – total IgE (continuous)

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Placebo/no treatment Mean	Placebo/no treatment SD	Placebo/no treatment Total	Weight	Mean Difference IV, Fixed, 95% CI
Goldring 2013	3.44	1.52	59	3.74	1.29	27	100.0%	-0.30 [-0.92 , 0.32]
Total			**59**			**27**	**100.0%**	**-0.30 [-0.92 , 0.32]**

Test for overall effect: Z = 0.94 (P = 0.34)

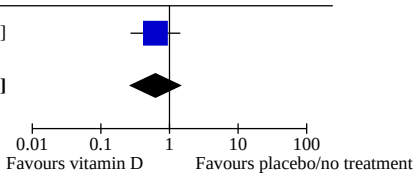


Heterogeneity: Not applicable

Analysis 1.9. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 9: Allergic sensitisation – skin prick against common allergens

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldring 2013[a]	11	68	7	27	100.0%	0.62 [0.27 , 1.44]
Total		**68**		**27**	**100.0%**	**0.62 [0.27 , 1.44]**
Total events:	11		7			

Test for overall effect: Z = 1.11 (P = 0.27)



Heterogeneity: Not applicable

Footnotes

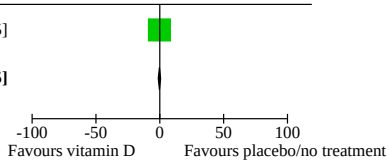
[a]Sensitization defined as at least one skin prick test result ≥ 3 mm above negative control (Glycerine)

Analysis 1.10. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 10: Airway inflammation – eosinophil counts (continuous)

Study or Subgroup	Vitamin D Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Goldring 2013[a]	2.75	1.99	53	3.03	2.01	27	100.0%	-0.28 [-1.21 , 0.65]
Total			**53**			**27**	**100.0%**	**-0.28 [-1.21 , 0.65]**

Test for overall effect: Z = 0.59 (P = 0.55)

Heterogeneity: Not applicable



Footnotes

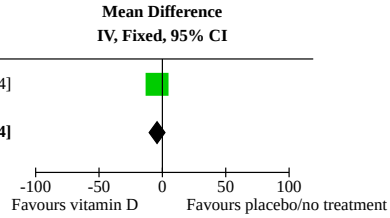
[a]Geometric mean and SD

Analysis 1.11. Comparison 1: Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women, Outcome 11: Airway inflammation – exhaled nitric oxide (continuous)

Study or Subgroup	Vitamin D Mean	SD	Total	Placebo/no treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Goldring 2013[a]	19.3	9.28	42	23.5	12.71	20	100.0%	-4.20 [-10.44 , 2.04]
Total			**42**			**20**	**100.0%**	**-4.20 [-10.44 , 2.04]**

Test for overall effect: Z = 1.32 (P = 0.19)

Heterogeneity: Not applicable



Footnotes

[a]exhaled nitric oxide, arithmetic mean and SD

Comparison 2. Any vitamin D versus placebo/no treatment in infants or young children

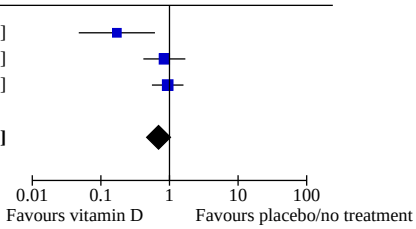
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Asthma	3	588	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.47, 1.03]
2.2 Wheeze	2	431	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.68, 1.16]
2.3 Atopic dermatitis	2	448	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.80, 1.28]
2.4 Adverse events	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.4.1 Infant elevated 25OHD	2	3263	Risk Ratio (M-H, Fixed, 95% CI)	5.61 [0.68, 45.93]
2.4.2 Infant hypercalcaemia	2	497	Risk Ratio (M-H, Fixed, 95% CI)	34.74 [2.11, 571.92]
2.4.3 Infant/child death	2	3146	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.80, 3.02]
2.5 Any airway infection	2	500	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.83, 1.01]
2.6 Lower respiratory tract infection	1	300	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.57, 1.29]
2.7 Upper respiratory tract infection	1	300	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.60, 1.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.8 Allergic sensitisation – specific IgE against common allergens (dichotomous)	1	228	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [0.60, 8.50]
2.9 Allergic sensitisation – skin prick against common allergens	1	136	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.63, 2.20]
2.10 Airway inflammation – elevated eosinophil counts (dichotomous)	1	226	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.65, 1.74]

Analysis 2.1. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 1: Asthma

	Vitamin D		Placebo/no treatment			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Grant 2015	3	156	9	80	27.7%	0.17 [0.05 , 0.61]	
Hibbs 2018	13	141	15	137	35.4%	0.84 [0.42 , 1.70]	
Salas 2018	19	45	13	29	36.8%	0.94 [0.55 , 1.60]	
Total		**342**		**246**	**100.0%**	**0.69 [0.47 , 1.03]**	
Total events:	35		37				

Test for overall effect: Z = 1.81 (P = 0.07)

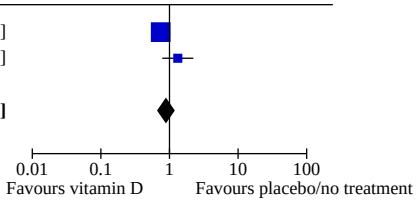


Heterogeneity: Chi² = 6.19, df = 2 (P = 0.05); I² = 68%

Analysis 2.2. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 2: Wheeze

	Vitamin D		Placebo/no treatment			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hibbs 2018	42	135	56	134	75.3%	0.74 [0.54 , 1.03]	
Rueter 2020	25	83	18	79	24.7%	1.32 [0.78 , 2.23]	
Total		**218**		**213**	**100.0%**	**0.89 [0.68 , 1.16]**	
Total events:	67		74				

Test for overall effect: Z = 0.86 (P = 0.39)



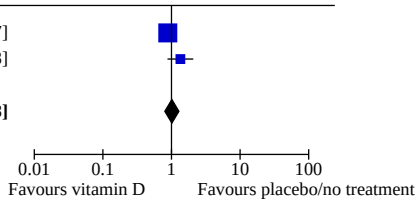
Heterogeneity: Chi² = 3.39, df = 1 (P = 0.07); I² = 71%

Analysis 2.3. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 3: Atopic dermatitis

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hibbs 2018	53	140	63	147	72.2%	0.88 [0.67 , 1.17]
Rueter 2020	33	83	23	78	27.8%	1.35 [0.87 , 2.08]
Total		**223**		**225**	**100.0%**	**1.01 [0.80 , 1.28]**
Total events:	86		86			

Test for overall effect: Z = 0.11 (P = 0.92)

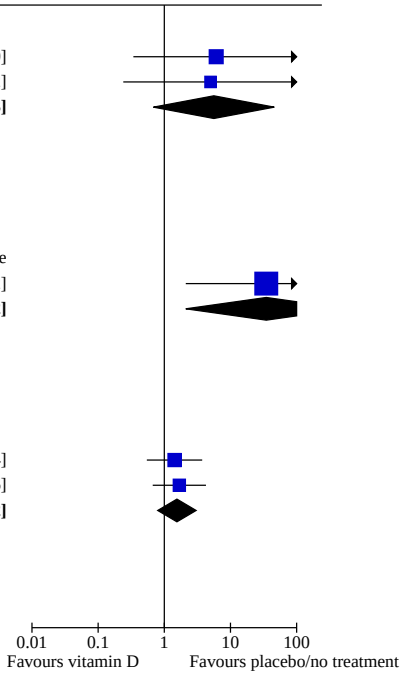
Heterogeneity: Chi² = 2.57, df = 1 (P = 0.11); I² = 61%



Analysis 2.4. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 4: Adverse events

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Infant elevated 25OHD						
Grant 2015	5	140	0	77	56.3%	6.09 [0.34 , 108.60]
Manaseki-Holland 2012	2	1524	0	1522	43.7%	4.99 [0.24 , 103.92]
Subtotal		**1664**		**1599**	**100.0%**	**5.61 [0.68 , 45.93]**
Total events:	7		0			
Test for overall effect: Z = 1.61 (P = 0.11)						
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%						
2.4.2 Infant hypercalcaemia						
Grant 2015	0	151	0	77		Not estimable
Hibbs 2018	17	135	0	134	100.0%	34.74 [2.11 , 571.92]
Subtotal		**286**		**211**	**100.0%**	**34.74 [2.11 , 571.92]**
Total events:	17		0			
Test for overall effect: Z = 2.48 (P = 0.01)						
Heterogeneity: Not applicable						
2.4.3 Infant/child death						
Manaseki-Holland 2012	10	1524	7	1522	52.3%	1.43 [0.54 , 3.74]
Salas 2018	15	64	5	36	47.7%	1.69 [0.67 , 4.26]
Subtotal		**1588**		**1558**	**100.0%**	**1.55 [0.80 , 3.02]**
Total events:	25		12			
Test for overall effect: Z = 1.29 (P = 0.20)						
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						

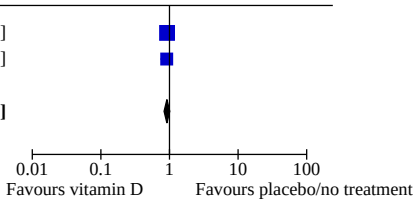
Test for subgroup differences: Chi² = 5.47, df = 2 (P = 0.06), I² = 63.4%



Analysis 2.5. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 5: Any airway infection

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Grant 2015	142	156	79	80	56.9%	0.92 [0.87 , 0.97]
Hibbs 2018[a]	72	132	79	132	43.1%	0.91 [0.74 , 1.12]
Total		**288**		**212**	**100.0%**	**0.92 [0.83 , 1.01]**
Total events:	214		158			

Test for overall effect: Z = 1.78 (P = 0.08)



Heterogeneity: Chi² = 0.03, df = 1 (P = 0.85); I² = 0%

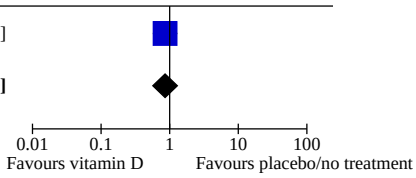
Footnotes

[a]Medically attended respiratory infections at 12 months, as reported in eTable3- Outcome Reporting by Time-Point

Analysis 2.6. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 6: Lower respiratory tract infection

Study or Subgroup	Vitamin D Events	Vitamin D Total	placebo/no treatment Events	placebo/no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hibbs 2018[a]	33	153	37	147	100.0%	0.86 [0.57 , 1.29]
Total		**153**		**147**	**100.0%**	**0.86 [0.57 , 1.29]**
Total events:	33		37			

Test for overall effect: Z = 0.74 (P = 0.46)



Heterogeneity: Not applicable

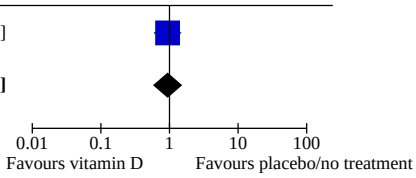
Footnotes

[a]Based on parental report, reported under adverse events

Analysis 2.7. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 7: Upper respiratory tract infection

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hibbs 2018[a]	84	153	83	147	100.0%	0.94 [0.60 , 1.48]
Total		**153**		**147**	**100.0%**	**0.94 [0.60 , 1.48]**
Total events:	84		83			

Test for overall effect: Z = 0.27 (P = 0.79)



Heterogeneity: Not applicable

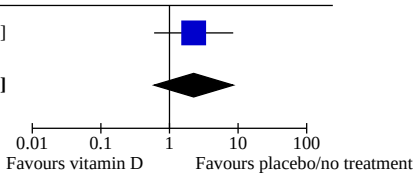
Footnotes

[a]Based on parental report, reported under adverse events

Analysis 2.8. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 8: Allergic sensitisation – specific IgE against common allergens (dichotomous)

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hibbs 2018[a]	7	116	3	112	100.0%	2.25 [0.60 , 8.50]
Total		**116**		**112**	**100.0%**	**2.25 [0.60 , 8.50]**
Total events:	7		3			

Test for overall effect: Z = 1.20 (P = 0.23)



Heterogeneity: Not applicable

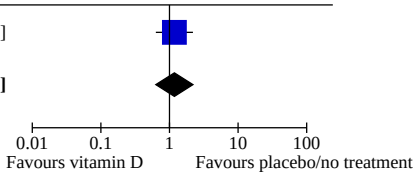
Footnotes

[a]Union of IgE against common allergens, sensitization defined as specific IgE level of 0.35 KUA/L or higher for at least one allergen

Analysis 2.9. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 9: Allergic sensitisation – skin prick against common allergens

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rueter 2020[a]	17	69	14	67	100.0%	1.18 [0.63 , 2.20]
Total		**69**		**67**	**100.0%**	**1.18 [0.63 , 2.20]**
Total events:	17		14			

Test for overall effect: Z = 0.52 (P = 0.60)



Heterogeneity: Not applicable

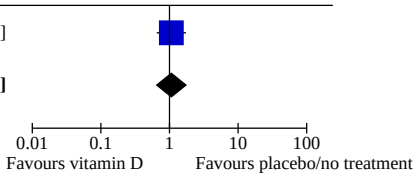
Footnotes

[a]Sensitization defined as at least one skin prick test result ≥ 3 mm above negative control

Analysis 2.10. Comparison 2: Any vitamin D versus placebo/no treatment in infants or young children, Outcome 10: Airway inflammation – elevated eosinophil counts (dichotomous)

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hibbs 2018[a]	26	114	24	112	100.0%	1.06 [0.65 , 1.74]
Total		**114**		**112**	**100.0%**	**1.06 [0.65 , 1.74]**
Total events:	26		24			

Test for overall effect: Z = 0.25 (P = 0.80)



Heterogeneity: Not applicable

Footnotes

[a]Eosinophils > 4%

Comparison 3. High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women

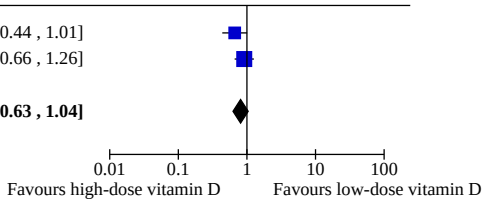
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Asthma	2	1355	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.63, 1.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Asthma (6-year follow-up data)	2	1249	Risk Ratio (IV, Fixed, 95% CI)	1.21 [0.92, 1.59]
3.3 Wheeze	3	1439	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.64, 0.98]
3.4 Atopic dermatitis	3	1439	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.75, 1.11]
3.5 Adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.5.1 Infant elevated 25OHD	2	928	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [0.12, 72.78]
3.5.2 Maternal hypercalcaemia	2	1176	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.5.3 Maternal death	2	1499	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.5.4 Intrauterine death	2	1499	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.48, 2.06]
3.5.5 Congenital malformations	2	1460	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.53, 1.34]
3.5.6 Preterm delivery < 32 weeks	2	1460	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.26, 1.61]
3.5.7 Pre-eclampsia	2	1499	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.71, 1.49]
3.5.8 Maternal hospitalisation	2	1499	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.74, 1.39]
3.6 Any airway infection	3	1441	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.82, 1.11]
3.7 Lower respiratory tract infection	3	1441	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.82, 1.11]
3.8 Allergic sensitisation – total IgE (continuous)	1	538	Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.51, 0.03]
3.9 Allergic sensitisation – specific IgE against common allergens (dichotomous)	2	1110	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.87, 1.18]
3.10 Allergic sensitisation – skin prick against common allergens	1	577	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.68, 2.17]

Analysis 3.1. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 1: Asthma

Study or Subgroup	High-dose vitamin D Events	Total	Low-dose vitamin D Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chawes 2016	32	278	47	271	42.2%	0.66 [0.44 , 1.01]
Litonjua 2016[a]	60	405	65	401	57.8%	0.91 [0.66 , 1.26]
Total		**683**		**672**	**100.0%**	**0.81 [0.63 , 1.04]**
Total events:	92		112			

Test for overall effect: Z = 1.64 (P = 0.10)



Heterogeneity: Chi² = 1.42, df = 1 (P = 0.23); I² = 29%

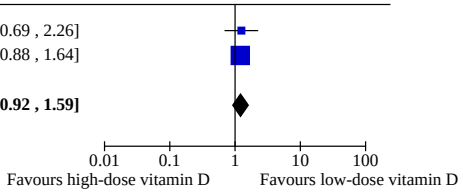
Footnotes

[a]Parental report of doctor-diagnosed asthma

Analysis 3.2. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 2: Asthma (6-year follow-up data)

Study or Subgroup	High-dose vitamin D Events	Total	Low/standard-dose vitamin D Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Chawes 2016[a]	23	274	18	268	21.3%	1.25 [0.69 , 2.26]
Litonjua 2016[b]	74	361	59	346	78.7%	1.20 [0.88 , 1.64]
Total		**635**		**614**	**100.0%**	**1.21 [0.92 , 1.59]**
Total events:	97		77			

Test for overall effect: Z = 1.38 (P = 0.17)



Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%

Footnotes

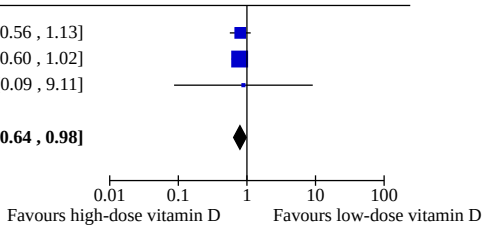
[a]Data reported at 6-year follow-up (3 years after the original study endpoint)

[b]Data reported at 6 year follow up (3 years after the original study endpoint)

Analysis 3.3. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 3: Wheeze

Study or Subgroup	High-dose vitamin D Events	Total	Low-dose vitamin D Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chawes 2016	47	295	57	286	37.2%	0.80 [0.56 , 1.13]
Litonjua 2016[a]	76	405	96	401	61.9%	0.78 [0.60 , 1.02]
Sahoo 2017	2	36	1	16	0.9%	0.89 [0.09 , 9.11]
Total		**736**		**703**	**100.0%**	**0.79 [0.64 , 0.98]**
Total events:	125		154			

Test for overall effect: Z = 2.18 (P = 0.03)



Heterogeneity: Chi² = 0.02, df = 2 (P = 0.99); I² = 0%

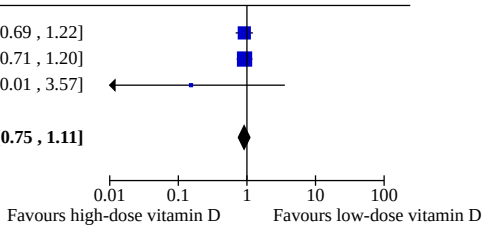
Footnotes

[a]Parental report of doctor-diagnosed recurrent wheeze

Analysis 3.4. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 4: Atopic dermatitis

Study or Subgroup	High-dose vitamin D Events	Total	Low-dose vitamin D Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chawes 2016	68	295	72	286	44.4%	0.92 [0.69 , 1.22]
Litonjua 2016	83	405	89	401	54.3%	0.92 [0.71 , 1.20]
Sahoo 2017	0	36	1	16	1.2%	0.15 [0.01 , 3.57]
Total		**736**		**703**	**100.0%**	**0.91 [0.75 , 1.11]**
Total events:	151		162			

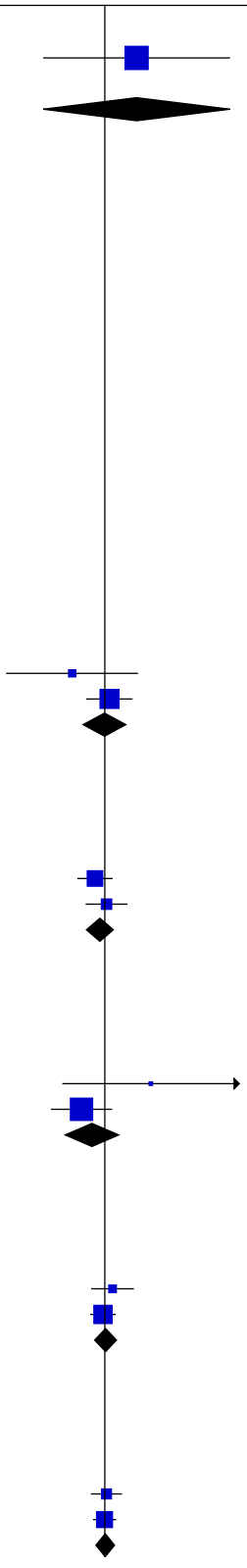
Test for overall effect: Z = 0.95 (P = 0.34)



Heterogeneity: Chi² = 1.24, df = 2 (P = 0.54); I² = 0%

Analysis 3.5. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 5: Adverse events

Study or Subgroup	High-dose vitamin D Events	Total	Low-dose vitamin D Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 Infant elevated 25OHD						
Litonjua 2016	1	440	0	436	100.0%	2.97 [0.12 , 72.78]
Sahoo 2017	0	36	0	16		Not estimable
Subtotal		**476**		**452**	**100.0%**	**2.97 [0.12 , 72.78]**
Total events:	1		0			
Test for overall effect: Z = 0.67 (P = 0.50)						
Heterogeneity: Not applicable						
3.5.2 Maternal hypercalcaemia						
Litonjua 2016	0	440	0	436		Not estimable
Sahoo 2017	0	200	0	100		Not estimable
Subtotal		**640**		**536**		**Not estimable**
Total events:	0		0			
Test for overall effect: Not applicable						
Heterogeneity: Not applicable						
3.5.3 Maternal death						
Chawes 2016	0	315	0	308		Not estimable
Litonjua 2016	0	440	0	436		Not estimable
Subtotal		**755**		**744**		**Not estimable**
Total events:	0		0			
Test for overall effect: Not applicable						
Heterogeneity: Not applicable						
3.5.4 Intrauterine death						
Chawes 2016	1	315	3	308	21.5%	0.33 [0.03 , 3.12]
Litonjua 2016	13	440	11	436	78.5%	1.17 [0.53 , 2.59]
Subtotal		**755**		**744**	**100.0%**	**0.99 [0.48 , 2.06]**
Total events:	14		14			
Test for overall effect: Z = 0.03 (P = 0.98)						
Heterogeneity: Chi² = 1.10, df = 1 (P = 0.29); I² = 9%						
3.5.5 Congenital malformations						
Chawes 2016	17	297	23	287	62.5%	0.71 [0.39 , 1.31]
Litonjua 2016	15	440	14	436	37.5%	1.06 [0.52 , 2.17]
Subtotal		**737**		**723**	**100.0%**	**0.84 [0.53 , 1.34]**
Total events:	32		37			
Test for overall effect: Z = 0.72 (P = 0.47)						
Heterogeneity: Chi² = 0.69, df = 1 (P = 0.41); I² = 0%						
3.5.6 Preterm delivery < 32 weeks						
Chawes 2016	2	297	0	287	4.4%	4.83 [0.23 , 100.22]
Litonjua 2016	5	440	11	436	95.6%	0.45 [0.16 , 1.29]
Subtotal		**737**		**723**	**100.0%**	**0.64 [0.26 , 1.61]**
Total events:	7		11			
Test for overall effect: Z = 0.95 (P = 0.34)						
Heterogeneity: Chi² = 2.14, df = 1 (P = 0.14); I² = 53%						
3.5.7 Pre-eclampsia						
Chawes 2016	16	315	12	308	24.1%	1.30 [0.63 , 2.71]
Litonjua 2016	36	440	38	436	75.9%	0.94 [0.61 , 1.45]
Subtotal		**755**		**744**	**100.0%**	**1.03 [0.71 , 1.49]**
Total events:	52		50			
Test for overall effect: Z = 0.14 (P = 0.89)						
Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² = 0%						
3.5.8 Maternal hospitalisation						
Chawes 2016	26	315	24	308	35.4%	1.06 [0.62 , 1.80]
Litonjua 2016	44	440	44	436	64.6%	0.99 [0.67 , 1.47]
Subtotal		**755**		**744**	**100.0%**	**1.02 [0.74 , 1.39]**

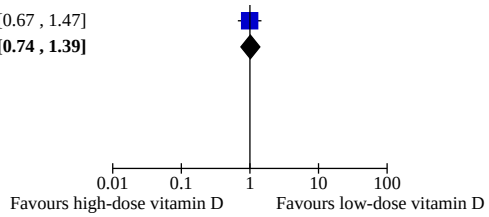


Analysis 3.5. (Continued)

Litonjua 2016	44	440	44	436	64.6%	0.99 [0.67 , 1.47]
Subtotal		**755**		**744**	**100.0%**	**1.02 [0.74 , 1.39]**
Total events:	70		68			

Test for overall effect: Z = 0.09 (P = 0.93)

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%

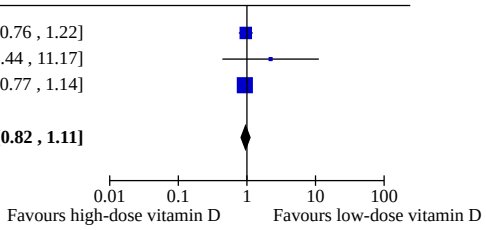


Analysis 3.6. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 6: Any airway infection

	High-dose vitamin D		Low-dose vitamin D			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Chawes 2016	94	292	95	284	40.8%	0.96 [0.76 , 1.22]	
Kalra 2012[a]	4	28	2	31	0.8%	2.21 [0.44 , 11.17]	
Litonjua 2016	129	405	137	401	58.4%	0.93 [0.77 , 1.14]	
Total		**725**		**716**	**100.0%**	**0.95 [0.82 , 1.11]**	
Total events:	227		234				

Test for overall effect: Z = 0.60 (P = 0.55)

Heterogeneity: Chi² = 1.10, df = 2 (P = 0.58); I² = 0%



Footnotes

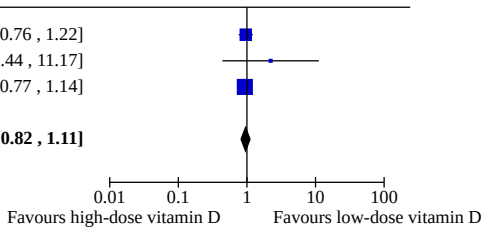
[a]Pneumonia

Analysis 3.7. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 7: Lower respiratory tract infection

	High-dose vitamin D		Low-dose vitamin D			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Chawes 2016	94	292	95	284	40.8%	0.96 [0.76 , 1.22]	
Kalra 2012	4	28	2	31	0.8%	2.21 [0.44 , 11.17]	
Litonjua 2016	129	405	137	401	58.4%	0.93 [0.77 , 1.14]	
Total		**725**		**716**	**100.0%**	**0.95 [0.82 , 1.11]**	
Total events:	227		234				

Test for overall effect: Z = 0.60 (P = 0.55)

Heterogeneity: Chi² = 1.10, df = 2 (P = 0.58); I² = 0%

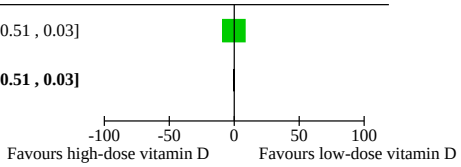


Analysis 3.8. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 8: Allergic sensitisation – total IgE (continuous)

	High-dose vitamin D			Low-dose vitamin D				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Litonjua 2016	3.38	1.61	276	3.62	1.62	262	100.0%	-0.24 [-0.51 , 0.03]	
Total			**276**			**262**	**100.0%**	**-0.24 [-0.51 , 0.03]**	

Test for overall effect: Z = 1.72 (P = 0.08)

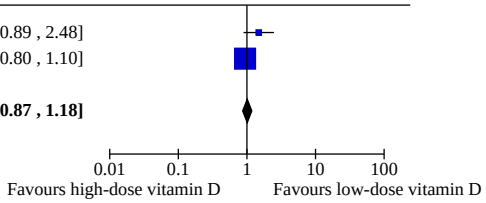
Heterogeneity: Not applicable



Analysis 3.9. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 9: Allergic sensitisation – specific IgE against common allergens (dichotomous)

Study or Subgroup	High-dose vitamin D Events	Total	Low-dose vitamin D Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chawes 2016[a]	34	289	22	278	12.9%	1.49 [0.89 , 2.48]
Litonjua 2016[b]	146	279	147	264	87.1%	0.94 [0.80 , 1.10]
Total		**568**		**542**	**100.0%**	**1.01 [0.87 , 1.18]**
Total events:	180		169			

Test for overall effect: Z = 0.13 (P = 0.89)



Heterogeneity: Chi² = 3.04, df = 1 (P = 0.08); I² = 67%

Footnotes

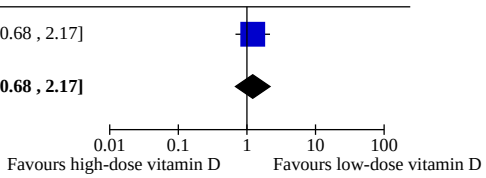
[a]Union of IgE against raw milk, pasteurised eggs, dogs, or cats, sensitisation defined as specific IgE level of 0.35 kUA/L or higher for at least one allergen

[b]Union of IgE against 13 common allergens, sensitisation defined as a specific IgE level ≥ 0.35 IU/ml for at least one allergen

Analysis 3.10. Comparison 3: High versus low/standard dose (≤ 400 IU/day) vitamin D in pregnant or breastfeeding women, Outcome 10: Allergic sensitisation – skin prick against common allergens

Study or Subgroup	High-dose vitamin D Events	Total	Low-dose vitamin D Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chawes 2016[a]	24	294	19	283	100.0%	1.22 [0.68 , 2.17]
Total		**294**		**283**	**100.0%**	**1.22 [0.68 , 2.17]**
Total events:	24		19			

Test for overall effect: Z = 0.66 (P = 0.51)



Heterogeneity: Not applicable

Footnotes

[a]Sensitisation defined as at least one skin prick test result 2 mm or larger

Comparison 4. High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children

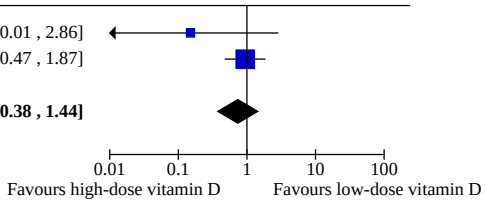
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Asthma	2	201	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.38, 1.44]
4.2 Wheeze	2	1095	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.51, 0.90]
4.3 Atopic dermatitis	1	769	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.05]
4.4 Adverse events	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.4.1 Infant elevated 25OHD	3	1124	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.81]
4.4.2 Infant hypercalcaemia	3	1773	Risk Ratio (M-H, Fixed, 95% CI)	2.94 [0.12, 70.50]
4.5 Any airway infection	6	2385	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.90, 0.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.6 Lower respiratory tract infection	3	1427	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.67, 1.18]
4.7 Upper respiratory tract infection	3	1798	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.80, 1.31]
4.8 Allergic sensitisation – specific IgE against common allergens (dichotomous)	1	723	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.72, 1.39]

Analysis 4.1. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 1: Asthma

Study or Subgroup	High-dose vitamin D Events	Total	Low-dose vitamin D Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Grant 2015[a]	0	76	3	80	25.9%	0.15 [0.01 , 2.86]
Salas 2018[b]	9	22	10	23	74.1%	0.94 [0.47 , 1.87]
Total		**98**		**103**	**100.0%**	**0.74 [0.38 , 1.44]**
Total events:	9		13			

Test for overall effect: Z = 0.90 (P = 0.37)



Heterogeneity: Chi² = 1.61, df = 1 (P = 0.20); I² = 38%

Footnotes

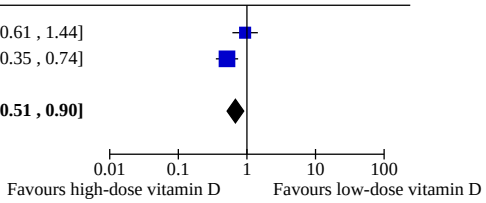
[a]Intervention given to mother/infant pairs; data shown are for 800 IU/d infant (2000 IU/d mothers) vs 400 IU/d infant (1000 IU/d mothers) intervention groups

[b]Data shown are for 800 IU/d vs 200 IU/d intervention groups

Analysis 4.2. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 2: Wheeze

Study or Subgroup	High-dose vitamin D Events	Total	Low-dose vitamin D Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rosendahl 2018	37	383	39	380	39.0%	0.94 [0.61 , 1.44]
Zhou 2018	31	164	62	168	61.0%	0.51 [0.35 , 0.74]
Total		**547**		**548**	**100.0%**	**0.68 [0.51 , 0.90]**
Total events:	68		101			

Test for overall effect: Z = 2.72 (P = 0.007)



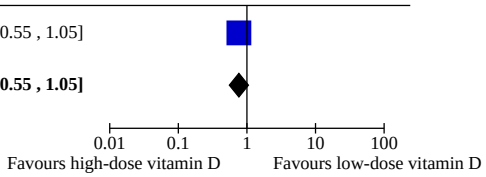
Heterogeneity: Chi² = 4.44, df = 1 (P = 0.04); I² = 77%

Analysis 4.3. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 3: Atopic dermatitis

Study or Subgroup	High-dose vitamin D Events	Total	Low-dose vitamin D Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rosendahl 2018	56	388	72	381	100.0%	0.76 [0.55 , 1.05]
Total		**388**		**381**	**100.0%**	**0.76 [0.55 , 1.05]**
Total events:	56		72			

Test for overall effect: Z = 1.65 (P = 0.10)

Heterogeneity: Not applicable



Analysis 4.4. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 4: Adverse events

Study or Subgroup	High-dose vitamin D Events	Total	Low-dose vitamin D Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.4.1 Infant elevated 25OHD						
Golan-Tripto 2020	0	25	1	25	100.0%	0.33 [0.01 , 7.81]
Rosendahl 2018	0	486	0	489		Not estimable
Yadav 2022	0	50	0	49		Not estimable
Subtotal		**561**		**563**	**100.0%**	**0.33 [0.01 , 7.81]**
Total events:	0		1			

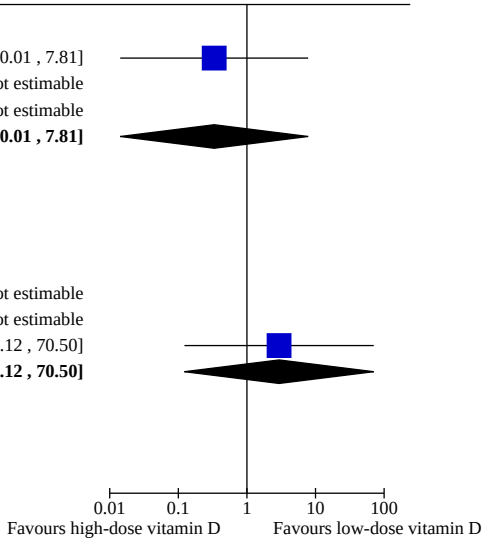
Test for overall effect: Z = 0.68 (P = 0.49)

Heterogeneity: Not applicable

4.4.2 Infant hypercalcaemia						
Aglipay 2017	0	349	0	350		Not estimable
Rosendahl 2018	0	486	0	489		Not estimable
Yadav 2022	1	50	0	49	100.0%	2.94 [0.12 , 70.50]
Subtotal		**885**		**888**	**100.0%**	**2.94 [0.12 , 70.50]**
Total events:	1		0			

Test for overall effect: Z = 0.67 (P = 0.51)

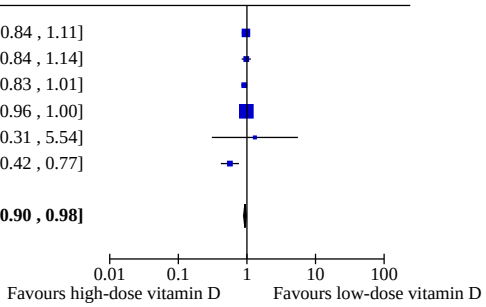
Heterogeneity: Not applicable



Analysis 4.5. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 5: Any airway infection

Study or Subgroup	High-dose vitamin D Events	Total	Low-dose vitamin D Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aglipay 2017	184	349	193	354	22.2%	0.97 [0.84 , 1.11]
Galdo 2018	79	104	73	94	8.9%	0.98 [0.84 , 1.14]
Grant 2015[a]	66	76	76	80	8.6%	0.91 [0.83 , 1.01]
Rosendahl 2018[b]	431	448	440	449	51.0%	0.98 [0.96 , 1.00]
Yadav 2022	4	50	3	49	0.4%	1.31 [0.31 , 5.54]
Zhou 2018[c]	43	164	78	168	8.9%	0.56 [0.42 , 0.77]
Total		**1191**		**1194**	**100.0%**	**0.94 [0.90 , 0.98]**
Total events:	807		863			

Test for overall effect: Z = 3.00 (P = 0.003)



Heterogeneity: Chi² = 28.46, df = 5 (P < 0.0001); I² = 82%

Footnotes

[a]Intervention given to mother/infant pairs; data shown are for 800 IU/d infant (2000 IU/d mothers) vs 400 IU/d infant (1000 IU/d mothers) intervention groups

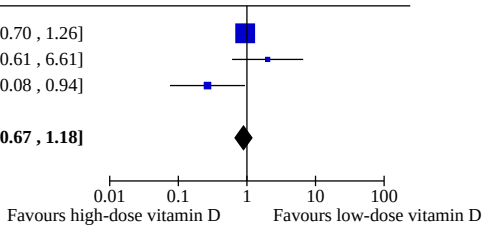
[b]Acute airway infections, obtained from email correspondence with authors

[c]PCR confirmed influenza A

Analysis 4.6. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 6: Lower respiratory tract infection

Study or Subgroup	High-dose vitamin D Events	Total	Low-dose vitamin D Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Galdo 2018[a]	48	104	46	94	76.2%	0.94 [0.70 , 1.26]
Rosendahl 2018[b]	8	448	4	449	6.3%	2.00 [0.61 , 6.61]
Zhou 2018[c]	3	168	11	164	17.5%	0.27 [0.08 , 0.94]
Total		**720**		**707**	**100.0%**	**0.89 [0.67 , 1.18]**
Total events:	59		61			

Test for overall effect: Z = 0.80 (P = 0.42)



Heterogeneity: Chi² = 5.46, df = 2 (P = 0.07); I² = 63%

Footnotes

[a]Acute bronchitis

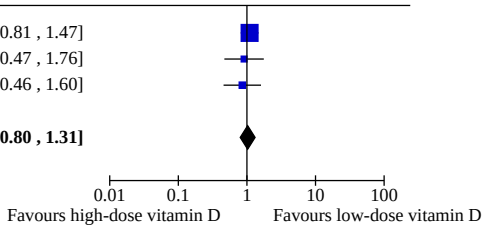
[b]Pneumonia, obtained from email correspondence with the authors

[c]Pneumonia

Analysis 4.7. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 7: Upper respiratory tract infection

Study or Subgroup	High-dose vitamin D Events	Total	Low-dose vitamin D Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Aglipay 2017	198	349	193	354	67.7%	1.09 [0.81 , 1.47]
Galdo 2018	79	104	73	94	15.1%	0.91 [0.47 , 1.76]
Rosendahl 2018[a]	426	448	430	449	17.2%	0.86 [0.46 , 1.60]
Total		**901**		**897**	**100.0%**	**1.02 [0.80 , 1.31]**
Total events:	703		696			

Test for overall effect: Z = 0.19 (P = 0.85)



Heterogeneity: Chi² = 0.63, df = 2 (P = 0.73); I² = 0%

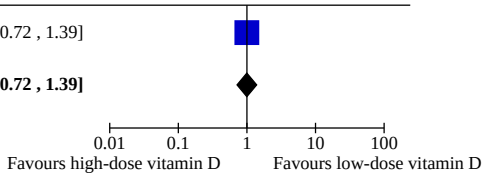
Footnotes

[a]Data obtained from email correspondence with the authors

Analysis 4.8. Comparison 4: High versus low/standard dose (≤ 400 IU/day) vitamin D in infants or young children, Outcome 8: Allergic sensitisation – specific IgE against common allergens (dichotomous)

Study or Subgroup	High-dose vitamin D Events	Total	Low-dose vitamin D Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rosendahl 2018[a]	60	365	59	358	100.0%	1.00 [0.72 , 1.39]
Total		**365**		**358**	**100.0%**	**1.00 [0.72 , 1.39]**
Total events:	60		59			

Test for overall effect: Z = 0.02 (P = 0.99)



Heterogeneity: Not applicable

Footnotes

[a]Union of IgE against food and aero allergens, sensitisation defined as a specific IgE concentration of ≥ 0.35 kU/L for at least one allergen

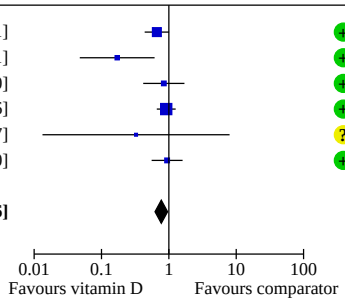
Comparison 5. Exploratory analysis – studies combined regardless of comparator or participants receiving the intervention

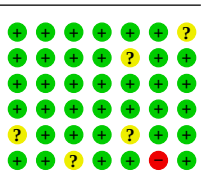
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Asthma – as defined by trial authors	6	2708	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.62, 0.96]
5.2 Wheeze – as defined by trial authors	8	3123	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.68, 0.91]

Analysis 5.1. Comparison 5: Exploratory analysis – studies combined regardless of comparator or participants receiving the intervention, Outcome 1: Asthma – as defined by trial authors

Study or Subgroup	Vitamin D Events	Vitamin D Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chawes 2016[a]	32	278	47	271	30.2%	0.66 [0.44 , 1.01]
Grant 2015[b]	3	156	9	80	7.6%	0.17 [0.05 , 0.61]
Hibbs 2018[c]	13	141	15	137	9.7%	0.84 [0.42 , 1.70]
Litonjua 2016[a]	60	405	65	401	41.5%	0.91 [0.66 , 1.26]
Rosendahl 2018[d]	0	387	1	378	1.0%	0.33 [0.01 , 7.97]
Salas 2018[e]	19	45	13	29	10.0%	0.94 [0.55 , 1.60]
Total		**1412**		**1296**	**100.0%**	**0.77 [0.62 , 0.96]**
Total events:	127		150			

Test for overall effect: Z = 2.37 (P = 0.02)





Heterogeneity: Chi² = 7.78, df = 5 (P = 0.17); I² = 36%

Footnotes

[a]Intervention given to pregnant mothers, comparator group received placebo plus daily multivitamin containing 400 IU vitamin D

[b]Intervention given to pregnant mother/infant pairs, comparator group recieved placebo. Analysis combines higher and lower dose intervention groups.

[c]Intervention given to infants, comparator group received placebo

[d]Intervention given to infants, comparator group recieved 400 IU vitamin D per day

[e]Intervention given to infants, comparator group received placebo. Analysis combines higher and lower dose intervention groups.

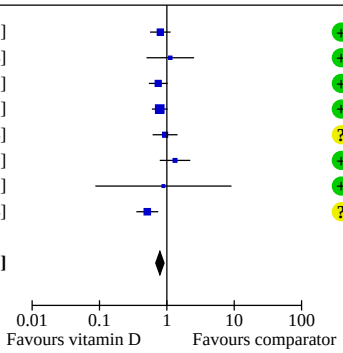
Risk of bias legend

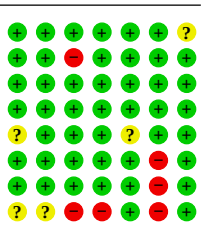
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other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

Analysis 5.2. Comparison 5: Exploratory analysis – studies combined regardless of comparator or participants receiving the intervention, Outcome 2: Wheeze – as defined by trial authors

Study or Subgroup	Vitamin D Events	Vitamin D Total	Comparator Events	Comparator Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chawes 2016[a]	47	295	57	286	17.0%	0.80 [0.56 , 1.13]
Goldring 2013[b]	17	108	7	50	2.8%	1.12 [0.50 , 2.54]
Hibbs 2018[c]	42	135	56	134	16.5%	0.74 [0.54 , 1.03]
Litonjua 2016[a]	76	405	96	401	28.3%	0.78 [0.60 , 1.02]
Rosendahl 2018[d]	37	383	39	380	11.5%	0.94 [0.61 , 1.44]
Rueter 2020[e]	25	83	18	79	5.4%	1.32 [0.78 , 2.23]
Sahoo 2017[f]	2	36	1	16	0.4%	0.89 [0.09 , 9.11]
Zhou 2018[d]	31	164	62	168	18.0%	0.51 [0.35 , 0.74]
Total		**1609**		**1514**	**100.0%**	**0.79 [0.68 , 0.91]**
Total events:	277		336			

Test for overall effect: Z = 3.30 (P = 0.0010)





Heterogeneity: Chi² = 10.42, df = 7 (P = 0.17); I² = 33%

Footnotes

[a]Intervened in pregnant women, comparator group received low dose vitamin D (placebo plus daily mulitvitamin containing 400 IU vitamin D)
[b]Intervened in pregnant women, comparator group received no treatment
[c]Intervened in infants, comparator group recieved placebo
[d]Intervened in infants, comparator group received low dose vitamin D (400 IU vitamin D per day)
[e]Intervened in infants, comparator group received placebo. Data represent combined wheeze and asthma outcomes
[f]Intervened in pregnant women, comparator group received low dose vitamin D (400 IU vitamin D per day)

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

ADDITIONAL TABLES

Table 1. Key characteristics of studies included in each comparison

Study	Country (latitude)	Population (N)	Intervention	Comparator	Duration of intervention	Age at outcome assessment	Outcomes evaluated	Asthma/wheeze case definition
Comparison 1. Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women								
El-Heis 2022	United Kingdom (3 locations - 50.9°N, 51.7°N, 53.4°N)	Pregnant women (1134)	1000 IU/d	Daily placebo	Week 14 of pregnancy through delivery	12, 24, and 48 months	Atopic dermatitis	NA
Goldring 2013	England (51.5°N)	Pregnant Women (180)	Group 1: 800 IU/d Group 2: 200,000 IU bolus (single dose)	No treatment	Week 27 of pregnancy through delivery (for intervention Group 1)	3 years	Wheeze, atopic dermatitis, airway infection, allergic sensitisation, airway inflammation	Recurrent Wheeze: medical record documentation of ≥2 episodes of wheezing since birth
Grant 2015	New Zealand (36°S)	Pregnant women/infant pairs (260 mothers, 249 infants)	Group 1: 1000 IU/d for mothers/400 IU/d for infants Group 2: 2000 IU/d for mothers/800 IU/d for infants	Daily placebo for mothers/daily placebo for infants	Week 27 of pregnancy through delivery for mother, birth through 6 months for infants	18 months	Asthma, airway infection, allergic sensitisation	Asthma: doctor diagnosis from primary care medical record
Morris 2021	Bangladesh (24°N)	Pregnant women (1300)	Low-dose: 4200 IU weekly; mid-dose: 16,000 IU weekly; high-dose 1: 28,000 IU weekly, for second trimester through birth, followed by placebo, weekly, from birth to 26 weeks postpartum; high-dose 2: 28,000 IU week-	Placebo	2nd trimester through 26 weeks postpartum	6 months	Airway infection	NA

Table 1. Key characteristics of studies included in each comparison *(Continued)*

			ly, from second trimester through 26 weeks post-partum					
Comparison 2. Any vitamin D versus placebo/no treatment in infants or young children								
Grant 2015	New Zealand (36°S)	Pregnant women/infant pairs (260 mothers, 249 infants)	Group 1: 1000 IU/d for mothers/400 IU/d for infants Group 2: 2000 IU/d for mothers/800 IU/d for infants	Daily placebo for mothers/daily placebo for infants	Week 27 of pregnancy through delivery for mother, birth through 6 months for infants	18 months	Asthma, airway infection, allergic sensitisation	Asthma: doctor diagnosis from primary care medical record
Hibbs 2018	USA (two locations - 41°N, 32°N)	Preterm infants (300)	400 IU/d until 6 months adjusted age or until they were taking at least 200 IU/d from formula or human milk fortifier	Daily placebo	Birth through 6 months adjusted age	12 months adjusted age	Wheeze, atopic dermatitis, airway infection, allergic sensitisation	Recurrent wheeze: parental report of ≥ 2 episodes of wheezing since last interview or reports of wheezing at multiple visits. Asthma: positive result on Asthma Predictive Index, based on parental report.
Manaseki-Holland 2012	Afghanistan (35°N)	Infants (3046)	100,000 IU quarterly	Placebo quarterly	18 months (6 total doses)	2 years	Airway infection	NA
Rueter 2020	Australia (32°S)	Infants (195)	400 IU/d	Daily placebo	From ~2 weeks to 6 months	Wheeze: 6 months (primary endpoint); combined outcome of wheeze and/or asthma: 2.5 years (follow-up)	Wheeze, atopic dermatitis, allergic sensitisation	Wheeze (undefined): diagnosed by medical doctor, criteria not defined; Combined outcome of wheeze and/or asthma: diagnosed by medical doctor based on structured history and clinical assessment
Salas 2018	USA (33.5°N)	Premature infants (100)	Group 1: 200 IU/d Group 2: 800 IU/d	Daily placebo	Day 1 of enteral feeding	2 years	Asthma	Asthma: parental report of use of asthma medications in previous 3 months

Table 1. Key characteristics of studies included in each comparison *(Continued)*

					to postnatal day 28			
Comparison 3. High versus low dose (≤ 400 IU/d) vitamin D in pregnant or breastfeeding women								
Chawes 2016	Denmark (56°N)	Pregnant women (623)	2800 IU/d (2400 IU/d plus daily prenatal supplement with 400 IU/d)	400 IU/d (daily placebo plus daily prenatal supplement with 400 IU/d)	Week 24 of pregnancy through 1 week postpartum	Wheeze ascertained 0-3 years; asthma ascertained at 3 years (primary endpoint) and 6 years (follow-up)	Asthma, wheeze, atopic dermatitis, airway infection, allergic sensitisation, airway inflammation	Recurrent wheeze: physician diagnosis, defined as meeting all of the following: (1) recurrent wheeze, (2) typical symptoms of asthma, (3) need for intermittent bronchodilator, and (4) response to a 3-month trial of inhaled corticosteroids and relapse upon cessation. Asthma: same as above but in children 3+ years of age.
Kalra 2012	India (27°N)	Pregnant women (299)	120,000 IU bolus dose at 2nd and 3rd trimesters	60,000 bolus dose at 2nd trimester	28 weeks	3, 6 and 9 months	Airway infection	NA
Litonjua 2016	USA (three locations - 42°N, 39°N, 34°N)	Pregnant women (876)	4400 IU/d (4000 IU/d plus multivitamin containing 400 IU/d)	400 IU/d (daily placebo plus daily multivitamin containing 400 IU/d)	Week 10-18 of pregnancy through delivery	3 years (primary endpoint) 6 years (follow-up)	Asthma, atopic dermatitis, airway infection, allergic sensitisation	Combined outcome of asthma/ recurrent wheeze: parental report of physician-diagnosed asthma or recurrent wheeze defined as ≥ 2 distinct parental reports of wheeze and/or child's use of asthma controller medication, with at least 1 or the reports falling after the child's second birthday
Sahoo 2017	India (26.9°N)	Pregnant women (300)	Group 1: 60,000 IU bolus every 4 weeks Group 2: 60,000 IU bolus every 8 weeks	400 IU/d	Week 14-20 of pregnancy through delivery	12-16 months	Wheeze, atopic dermatitis	Ever wheeze: "any history of wheeze"
Comparison 4. High versus low dose (≤ 400 IU/d) vitamin D in infants or young children								
Aglipay 2017	Canada (43°N)	Children (703)	2000 IU/d	400 IU/d	Range of 4-8 months	Mean 3.2 years	Wheeze (reported only in abstract)[a],	Parental report of asthma plus confirmation from the child's medical record of 2 or more episodes of wheeze requiring the prescrip-

Table 1. Key characteristics of studies included in each comparison *(Continued)*

							airway infection	tion of inhaled asthma-controlling medications.
Galdo 2018	Spain (41°N)	Infants (198)	1000 IU/d	400 IU/d	Birth to one year of age	12 months	Airway infection	NA
Golan-Tripto 2020	Israel (31°N)	Premature infants (50)	800 IU/d	400 IU/d	12 months	12 months	Airway infection	NA
Rosendahl 2018	Finland (60°N)	Infants (987)	1200 IU/d	400 IU/d	From 2 weeks to 24 months	12 months	Asthma, wheeze, atopic dermatitis, airway infection, allergic sensitisation	Ever Wheeze: positive answer to "Has your child ever had wheezing or difficulty breathing in the past 12 months?" Asthma: physician diagnosis, criteria not described
Salas 2018	United States (33.5°N)	Premature infants (64)	Group 2: 800 IU/d	Group 1: 200 IU/d	Day 1 of enteral feeding to postnatal day 28	2 years	Asthma	Asthma: parental report of use of asthma medications in previous 3 months
Yadav 2022	India (26.2°N)	Infants (102)	800 IU/d	400 IU/d	14 weeks	14 weeks	Airway infection	NA
Zhou 2018	China (29°N)	Infants (400)	1200 IU/d	400 IU/d	Duration of 4 months, starting at mean age of 7.8 months	Mean age of 11.8 months	Wheeze, airway infection	Wheeze (undefined): assessed by medical staff, criteria not defined

NA: not applicable (study did not evaluate asthma and/or wheeze).
[a]Only reported adjusted risk ratio. We reached out to the authors requesting data on wheeze, but the authors did not respond, so these data are not included in the meta-analysis for wheeze (comparison 4).

Table 2. Adverse events evaluated in only one study, by comparison

Outcome	Study	Vitamin D (n/N)	Comparator (n/N)	RR [95% CI]
Comparison 1. Any vitamin D versus placebo/no treatment in pregnant or breastfeeding women				
Maternal - nausea/vomiting	El-Heis 2022[a]	6/565	7/596	0.90 [0.31, 2.67]
Maternal - diarrhoea	El-Heis 2022[a]	6/565	4/569	1.58 [0.45, 5.58]
Maternal - abdominal pain	El-Heis 2022[a]	16/565	16/569	1.05 [0.53, 2.09]
Maternal - headache	El-Heis 2022[a]	8/565	9/569	0.94 [0.36, 2.41]
Maternal - severe postpartum haemorrhage	El-Heis 2022[a]	65/565	96/569	0.68 [0.51, 0.91]
Maternal - instrumental delivery	El-Heis 2022[a]	25/565	35/569	0.72 [0.44, 1.19]
Maternal - infection	El-Heis 2022[a]	17/565	17/569	1.01 [0.52, 1.95]
Maternal - death	Morris 2021[b]	1/1039	1/259	0.25 [0.02, 3.97]
Maternal - hospitalisation	Morris 2021[b]	87/1039	26/259	0.83 [0.55, 1.26]
Maternal - hypercalciuria	Morris 2021[b]	1/800	1/199	0.25 [0.02, 3.96]
Maternal - urolithiasis/nephrolithiasis	Morris 2021[b]	105/1039	26/259	1.01 [0.67, 1.51]
Maternal - any clinical encounter	Morris 2021[b]	375/1039	80/259	1.17 [0.96, 1.43]
Infant - foetal growth retardation	El-Heis 2022[a]	0/479	0/486	Not estimable
Infant - hypercalciuria	Morris 2021[b]	1/697	0/151	0.65 [0.03, 15.96]
Infant - birthweight < 2500 grams at 37 weeks gestation	Morris 2021[b]	156/1039	30/259	1.30 [0.90, 1.87]
Infant - hospitalisation	Morris 2021[b]	156/1039	40/259	0.97 [0.71, 1.34]
Infant - any clinical encounter	Morris 2021[b]	346/1039	89/259	0.97 [0.80, 1.17]
Comparison 2. Any vitamin D versus placebo/no treatment in infants or young children				
Infant - elevated alkaline phosphatase	Hibbs 2018	3mo: 10/135 6mo: 3/134	3mo: 4/134 6mo: 8/141	3mo: 2.48 [0.80, 7.72] 6mo: 0.39 [0.11, 1.46]
Infant - any serious adverse event (not defined)	Hibbs 2018	36/153	38/147	0.91 [0.61, 1.35]
Comparison 3. High versus low dose (≤ 400 IU/d) vitamin D in pregnant or breastfeeding women				
Maternal - antibiotic use during pregnancy	Chawes 2016	52/315	97/308	0.52 [0.39, 0.71]

Table 2. Adverse events evaluated in only one study, by comparison *(Continued)*

Maternal - emergency caesarean section	Chawes 2016	44/315	35/308	1.23 [0.81, 1.86]
Maternal - gestational diabetes	Chawes 2016	5/315	9/308	0.54 [0.18, 1.60]
Maternal - infection	Chawes 2016	82/315	97/308	0.83 [0.64, 1.06]
Maternal - HELLP syndrome	Litonjua 2016	2/440	1/436	1.98 [0.18, 21.78]
Infant/child - death	Chawes 2016	0/297	0/287	Not estimable
Infant - hospitalisation	Chawes 2016	32/297	28/287	1.10 [0.68, 1.79]
Infant - neonatal demise	Litonjua 2016	3/440	3/436	0.99 [0.20, 4.88]
Infant - neonatal ICU admission	Litonjua 2016	36/440	28/436	1.27 [0.79, 2.05]
Infant - hypercalcaemia	Sahoo 2017	0/36	0/16	Not estimable
Comparison 4. High versus low dose (≤ 400 IU/d) vitamin D in infants or young children				
Infant - hospitalisation	Yadav 2022	0/50	0/49	Not estimable
Infant - vomiting/diarrhoea	Zhou 2018	2/164	2/168	1.02 [0.15, 7.19]

[a]Adverse events for El-Heis 2022 reported in Cooper 2016; N evaluated for adverse events not reported so N for maternal outcomes was assumed to be N randomised and N for infant outcomes was assumed to be N live births.
[b]Adverse events for Morris 2021 reported in Roth 2018.

APPENDICES

Appendix 1. Search strategy

Source	Search strategy
1. Airways register, Skin register	1 MESH DESCRIPTOR Adolescent EXPLODE ALL AND INREGISTER
	2 MESH DESCRIPTOR Child EXPLODE ALL AND INREGISTER
	3 MESH DESCRIPTOR Infant EXPLODE ALL AND INREGISTER
	4 MESH DESCRIPTOR Pregnant Women AND INREGISTER
	5 MESH DESCRIPTOR Pregnancy EXPLODE ALL AND INREGISTER
	6 MESH DESCRIPTOR Prenatal Care AND INREGISTER
	7 MESH DESCRIPTOR Lactation AND INREGISTER
	8 (Pregnan* or infant* or maternal or baby or babies or newborn* or neonat* or toddler* or child* or preschool* or schoolchild* or boy* or girl* or pre-school* or teen* or adolescen* or pre-teen* or youth* or young person* or young people or in utero or lactating women or lactating woman):ti,ab,kw AND INREGISTER
	9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 AND INREGISTER

(Continued)

	10 MESH DESCRIPTOR Vitamin D EXPLODE ALL AND INREGISTER 11 MESH DESCRIPTOR Vitamin D Deficiency EXPLODE ALL AND INREGISTER 12 (vitamin d* or colecalciferol or ergocalciferol$):ti,ab,kw AND INREGISTER 13 #10 OR #11 OR #12 AND INREGISTER 14 #13 AND #9 AND INREGISTER
2. CENTRAL (via the Cochrane Library)	1 MESH DESCRIPTOR Adolescent EXPLODE ALL AND CENTRAL:TARGET 2 MESH DESCRIPTOR Child EXPLODE ALL AND CENTRAL:TARGET 3 MESH DESCRIPTOR Infant EXPLODE ALL AND CENTRAL:TARGET 4 MESH DESCRIPTOR Pregnant Women AND CENTRAL:TARGET 5 MESH DESCRIPTOR Pregnancy EXPLODE ALL AND CENTRAL:TARGET 6 MESH DESCRIPTOR Prenatal Care AND CENTRAL:TARGET 7 MESH DESCRIPTOR Lactation AND CENTRAL:TARGET 8 (Pregnan* or infant* or maternal or baby or babies or newborn* or neonat* or toddler* or child* or preschool* or schoolchild* or boy* or girl* or pre-school* or teen* or adolescen* or pre-teen* or youth* or young person* or young people or in utero or lactating women or lactating woman):ti,ab,kw AND CENTRAL:TARGET 9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 10 MESH DESCRIPTOR Vitamin D EXPLODE ALL AND CENTRAL:TARGET 11 MESH DESCRIPTOR Vitamin D Deficiency EXPLODE ALL AND CENTRAL:TARGET 12 (vitamin d* or colecalciferol or ergocalciferol$):ti,ab,kw AND CENTRAL:TARGET 13 #10 OR #11 OR #12 14 #13 AND #9
3. MEDLINE	1 adolescent/ or exp child/ or exp infant/ 2 Pregnant Women/ 3 exp Pregnancy/ 4 Prenatal Care/ 5 Lactation/ 6 (Pregnan$ or infant$ or maternal or baby or babies or newborn$ or neonat$ or toddler$ or child$ or preschool$ or schoolchild$ or boy$ or girl$ or pre-school$ or teen$ or adolescen$ or preteen$ or youth$ or young person$ or young people or in utero or lactating women or lactating woman).ti,ab. 7 or/1-6 8 exp Vitamin D/ 9 exp Vitamin D Deficiency/ 10 (Vitamin D* or Colecalciferol or Ergocalciferol$).ti,ab. 11 or/8-10 12 7 and 11

(Continued)

	13 (controlled clinical trial or randomized controlled trial).pt. 14 (randomized or randomised).ab,ti. 15 placebo.ab,ti. 16 dt.fs. 17 randomly.ab,ti. 18 trial.ab,ti. 19 groups.ab,ti. 20 or/13-19 21 Animals/ 22 Humans/ 23 21 not (21 and 22) 24 20 not 23 25 12 and 24
4. Embase	1 adolescent/ or exp child/ 2 pregnant woman/ 3 exp pregnancy/ 4 prenatal care/ 5 Lactation/ 6 (Pregnan$ or infant$ or maternal or baby or babies or newborn$ or neonat$ or toddler$ or child$ or preschool$ or schoolchild$ or boy$ or girl$ or pre-school$ or teen$ or adolescen$ or preteen$ or youth$ or young person$ or young people or in utero or lactating women or lactating woman).ti,ab. 7 or/1-6 8 exp vitamin D/ 9 vitamin D deficiency/ 10 (vitamin d* or colecalciferol or ergocalciferol$).ti,ab. 11 or/8-10 12 7 and 11 13 Randomized Controlled Trial/ 14 randomization/ 15 controlled clinical trial/ 16 Double Blind Procedure/ 17 Single Blind Procedure/ 18 Crossover Procedure/ 19 (clinica$ adj3 trial$).tw. 20 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).tw.

(Continued)

	21 exp Placebo/ 22 placebo$.ti,ab. 23 random$.ti,ab. 24 ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).tw. 25 (crossover$ or cross-over$).ti,ab. 26 or/13-25 27 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ 28 human/ or normal human/ or human cell/ 29 27 and 28 30 27 not 29 31 26 not 30 32 12 and 31
5. ClinicalTrials.gov	Study type - Interventional Intervention - vitamin d Outcome - asthma OR wheeze OR eczema OR dermatitis
6. WHO ICTRP	Title - asthma OR wheeze OR eczema OR dermatitis Intervention - vitamin d Recruitment status - ALL

Appendix 2. Data extraction elements

Source:

- Study ID (surname of first author and year when the main report of study was published, e.g. Smith 2001)
- Reference citation
- Study author contact details
- Publication type (e.g. full report, abstract, letter)

Methods:

- Method of sequence generation
- Method of allocation
- Method of concealment
- Unit of allocation (by individuals or clusters)
- Trial start date
- Trial end date
- Information collection method (e.g. questionnaire, medication, medical record)
- Duration of participation (from recruitment to last follow-up)
- Ethical approval needed/obtained for study (Y/N/Unclear)

Participants:

- Population description (from which study participants are drawn)
- Setting (number of sites; locations (including latitude); and social context)

- Types of populations (e.g. pregnant women, lactating women, offspring)
- Inclusion criteria
- Period of gestation during which intervention was received (optional)
- Exclusion criteria
- Method of recruitment of participants
- Informed consent obtained (Y/N/Unclear)
- Total no. allocated to each group
- No. of infants born if pregnant women were randomised (optional)
- Baseline imbalances for mothers
- Baseline imbalances for children
- Baseline age (both maternal age and gestational age for prenatal interventions) (median with interquartile range, or mean with standard deviation)
- Age at outcome ascertainment (mean and range)
- Sex
- Race/Ethnicity
- 25(OH)D concentration at baseline (median with interquartile range, or mean with standard deviation)
- For prenatal intervention, offspring 25(OH)D concentration at birth or earliest available (in addition to maternal baseline and endline 25(OH)D concentration)
- Baseline body-mass-index (BMI) (median with interquartile range, or mean with standard deviation)
- Prevalence of parental (biological) history of asthma and/or atopic dermatitis and/or allergy
- Comorbidities
- Other relevant sociodemographics
- Subgroups measured
- Subgroups reported
- Loss to follow-up with reasons

Intervention groups (separate numbered table for each group):

- Group name
- No. randomised to group (specify whether no. people or clusters)
- Description of intervention (include sufficient detail for replication, e.g. content, dose, components)
- Duration of treatment period
- Delivery (e.g. mechanism, medium, intensity, fidelity)
- Providers (e.g. no., profession, training)
- Co-interventions
- Compliance

Outcomes (separate numbered table for each outcome):

- Outcome name
- Primary or secondary
- Outcome definition (with diagnostic criteria if relevant)
- Targeted population for this outcome (e.g. children, mother)
- Unit of measurement
- Scales: upper and lower limits (indicate whether high or low score is favourable)
- Time points measured
- Time points reported
- Person measuring/reporting
- Laboratory method of measurement

Results (separate numbered table per outcome):

- Sample size
- Unadjusted effect estimate(s) and measure of variability

Other:

- Study funding sources
- Possible conflicts of interest (for study authors)

Appendix 3. Additional domains for assessment of risk of bias

Below are the additional domains for risk of bias (items 1 to 4 for cluster-randomised trials, and items 5 to 6 for trials with more than 2 intervention arms).

1. Recruitment bias - (1) high risk of bias: when individuals were recruited into the trial after the clusters had been randomised and the types of participants recruited could be different based on whether the cluster is an "intervention" or "control" cluster; (2) low risk of bias: if individuals had been recruited before the clusters were randomised; or (3) unclear risk of bias: if there is insufficient information to make a judgment of low or high risk.
2. Baseline imbalance - (1) high risk of bias: if there is a baseline characteristic(s) imbalance between randomised groups; (2) low risk of bias: if stratified or pair-matched randomisation was used for clusters, or reporting of the baseline of clusters showed no imbalance; or (3) unclear risk of bias: if there is insufficient information to make a judgment of low or high risk.
3. Loss of clusters - (1) high risk of bias: if complete cluster(s) is lost from a trial, or there are enough missing outcomes for individuals within the cluster(s) that could induce clinically relevant bias; (2) low risk of bias: if there are no missing data, or missing data are not enough to induce clinically relevant bias; or (3) unclear risk of bias: if there is insufficient information to make a judgment of low or high risk.
4. Incorrect analysis of clustering - (1) high risk of bias: if the analysis did not take clustering into account; (2) low risk of bias: if clustering was correctly accounted for in statistical models; or (3) unclear risk of bias: if there is insufficient information to make a judgment of low or high risk.
5. Selective reporting of intervention arms - (1) high risk of bias: if there was selective reporting of comparisons of intervention arms for some outcomes; (2) low risk of bias: if data were presented for each of the groups for all prespecified outcomes; or (3) unclear risk of bias: if there is insufficient information to make a judgment of low or high risk.
6. Interaction between different interventions - (1) high risk of bias: if the trial reported an interaction between the different active interventions (e.g., synergy); (2) low risk of bias: if there was no interaction between active interventions; or (3) unclear risk of bias: if there is insufficient information to make a judgment of low or high risk.

HISTORY

Protocol first published: Issue 8, 2019

CONTRIBUTIONS OF AUTHORS

JX, CMB, PAC, and BP drafted and edited the protocol. JX and CMB developed the search strategy in consultation with librarians. JX, BP and CMB obtained copies of studies. BP, JX, CMB, JB, AV, and BS determined which studies to include. BP, JX, CMB, JB, AV, and BS extracted data from studies, entered data into RevMan, and carried out the analysis. BP, JX, CMB, JB, AV, and BS interpreted the results in consultation with RC and PAC. BP drafted and edited the final review with input from all authors. PAC will update the review.

Contributions of the editorial team

Sally Spencer (Co-ordinating Editor) edited the review; advised on methodology, interpretation and content; approved the review prior to publication.

Lindsay Robertson: advised on methodology, interpretation and content.

Emma Dennett (Deputy Co-ordinating Editor): checked the data entry prior to the full write-up of the review.

Kayleigh Kew (Freelance editor): advised on methodology, interpretation and content; edited the review.

Emma Jackson (Managing Editor): co-ordinated the editorial process; conducted peer review; edited the review.

Elizabeth Stovold (Information Specialist): designed the search strategy; ran the searches

DECLARATIONS OF INTEREST

BP: National Institute of Diabetes and Digestive and Kidney Diseases (Grant / Contract)

PAC: none known.

CB: none known.

JB: none known.

BS: none known.

AV: none known.

JX: none known.

RC: SANOFI US SERVICES INC. (Independent Contractor - Consultant; Independent Contractor - Data Safety and Monitoring).

SOURCES OF SUPPORT

Internal sources

- All authors, Other

  The authors declare that no such funding was received for this systematic review

External sources

- National Institute for Health and Care Research (NIHR), UK

  Cochrane Airways was supported by the National Institute for Health and Care Research (NIHR), via Cochrane Infrastructure funding

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We conducted this review according to the published protocol (Best 2019), and made clarifications where language in the original protocol was unclear. Clarifications to the protocol included further defining "diseased populations" for exclusion criteria as those with pre-existing conditions (e.g. women with gestational diabetes, children with atopic dermatitis), clarifying that the intervention was vitamin D in the form of D_2 and D_3 (not other forms of vitamin D, e.g. 25(OH)D, 1,25(OH)2D), clarifying that we only included trials of vitamin D supplementation (i.e. we excluded trials of vitamin D fortification), and clarifying that subgroup analyses were performed on the study level and subgroups were mutually exclusive.

There were a few differences between the protocol and the review. We included studies that compared vitamin D to no supplementation (rather than placebo), following an approach used in a previous Cochrane review of vitamin D (Huey 2020). Our primary outcomes originally included persistent/recurrent wheeze, but because of how wheeze was reported across studies meeting our criteria for inclusion, we relabelled this as simply 'wheeze'. We revised our secondary objectives to include respiratory tract infections, allergic sensitisation, and airway inflammation in addition to atopic dermatitis, reflecting our secondary outcomes, all of which were specified in the original protocol. If an outcome was defined or reported differently between studies, we conducted a meta-analysis that combined studies with compatible definitions (e.g. continuous versus dichotomous serum immunoglobulin E (IgE) data) and described the results from studies with incompatible outcomes narratively. We had planned to perform separate meta-analysis on unadjusted and adjusted estimates, but in this review we only performed meta-analysis on unadjusted study results because of heterogeneity in variables adjusted for and inconsistency in reporting. We had also planned to perform a number of subgroup and sensitivity analyses, including meta-regression, but given the small number of studies included in each comparison, we limited the analysis to the main analyses. For adverse events, we recorded all events reported by included studies, and meta-analysed any event reported by at least two studies. Due to the inconsistency in adverse events reporting across included studies, we narratively summarised adverse events in the summary of findings tables. Meta-analyses were conducted using RevMan version 4.1.0.3 rather than RevMan version 5.3.

INDEX TERMS

Medical Subject Headings (MeSH)

*Asthma [prevention & control]; Bias; *Breast Feeding; *Dietary Supplements; Randomized Controlled Trials as Topic; Respiratory Sounds; *Vitamin D [administration & dosage]; Vitamin D Deficiency [complications] [prevention & control]; *Vitamins [administration & dosage]

MeSH check words

Child; Child, Preschool; Female; Humans; Infant; Pregnancy