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Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health (Review)

Tan ML, Abrams SA, Osborn DA

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[Intervention Review]

Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health

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ABSTRACT

Background

Vitamin D deficiency is common worldwide, contributing to nutritional rickets and osteomalacia which have a major impact on health, growth, and development of infants, children and adolescents. Vitamin D levels are low in breast milk and exclusively breastfed infants are at risk of vitamin D insufficiency or deficiency.

Objectives

To determine the effect of vitamin D supplementation given to infants, or lactating mothers, on vitamin D deficiency, bone density and growth in healthy term breastfed infants.

Search methods

We used the standard search strategy of Cochrane Neonatal to 29 May 2020 supplemented by searches of clinical trials databases, conference proceedings, and citations.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs in breastfeeding mother-infant pairs comparing vitamin D supplementation given to infants or lactating mothers compared to placebo or no intervention, or sunlight, or that compare vitamin D supplementation of infants to supplementation of mothers.

Data collection and analysis

Two review authors assessed trial eligibility and risk of bias and independently extracted data. We used the GRADE approach to assess the certainty of evidence.

Main results

We included 19 studies with 2837 mother-infant pairs assessing vitamin D given to infants (nine studies), to lactating mothers (eight studies), and to infants versus lactating mothers (six studies). No studies compared vitamin D given to infants versus periods of infant sun exposure.

Vitamin D supplementation given to infants: vitamin D at 400 IU/day may increase 25-OH vitamin D levels (MD 22.63 nmol/L, 95% CI 17.05 to 28.21; participants = 334; studies = 6; low-certainty) and may reduce the incidence of vitamin D insufficiency (25-OH vitamin D < 50

nmol/L) (RR 0.57, 95% CI 0.41 to 0.80; participants = 274; studies = 4; low-certainty). However, there was insufficient evidence to determine if vitamin D given to the infant reduces the risk of vitamin D deficiency (25-OH vitamin D < 30 nmol/L) up till six months of age (RR 0.41, 95% CI 0.16 to 1.05; participants = 122; studies = 2), affects bone mineral content (BMC), or the incidence of biochemical or radiological rickets (all very-low certainty). We are uncertain about adverse effects including hypercalcaemia. There were no studies of higher doses of infant vitamin D (> 400 IU/day) compared to placebo.

Vitamin D supplementation given to lactating mothers: vitamin D supplementation given to lactating mothers may increase infant 25-OH vitamin D levels (MD 24.60 nmol/L, 95% CI 21.59 to 27.60; participants = 597; studies = 7; low-certainty), may reduce the incidences of vitamin D insufficiency (RR 0.47, 95% CI 0.39 to 0.57; participants = 512; studies = 5; low-certainty), vitamin D deficiency (RR 0.15, 95% CI 0.09 to 0.24; participants = 512; studies = 5; low-certainty) and biochemical rickets (RR 0.06, 95% CI 0.01 to 0.44; participants = 229; studies = 2; low-certainty). The two studies that reported biochemical rickets used maternal dosages of oral D3 60,000 IU/day for 10 days and oral D3 60,000 IU postpartum and at 6, 10, and 14 weeks. However, infant BMC was not reported and there was insufficient evidence to determine if maternal supplementation has an effect on radiological rickets (RR 0.76, 95% CI 0.18 to 3.31; participants = 536; studies = 3; very low-certainty). All studies of maternal supplementation enrolled populations at high risk of vitamin D deficiency. We are uncertain of the effects of maternal supplementation on infant growth and adverse effects including hypercalcaemia.

Vitamin D supplementation given to infants compared with supplementation given to lactating mothers: infant vitamin D supplementation compared to lactating mother supplementation may increase infant 25-OH vitamin D levels (MD 14.35 nmol/L, 95% CI 9.64 to 19.06; participants = 269; studies = 4; low-certainty). Infant vitamin D supplementation may reduce the incidence of vitamin D insufficiency (RR 0.61, 95% CI 0.40 to 0.94; participants = 334; studies = 4) and may reduce vitamin D deficiency (RR 0.35, 95% CI 0.17 to 0.72; participants = 334; studies = 4) but the evidence is very uncertain. Infant BMC and radiological rickets were not reported and there was insufficient evidence to determine if maternal supplementation has an effect on infant biochemical rickets. All studies enrolled patient populations at high risk of vitamin D deficiency. Studies compared an infant dose of vitamin D 400 IU/day with varying maternal vitamin D doses from 400 IU/day to > 4000 IU/day. We are uncertain about adverse effects including hypercalcaemia.

Authors' conclusions

For breastfed infants, vitamin D supplementation 400 IU/day for up to six months increases 25-OH vitamin D levels and reduces vitamin D insufficiency, but there was insufficient evidence to assess its effect on vitamin D deficiency and bone health. For higher-risk infants who are breastfeeding, maternal vitamin D supplementation reduces vitamin D insufficiency and vitamin D deficiency, but there was insufficient evidence to determine an effect on bone health. In populations at higher risk of vitamin D deficiency, vitamin D supplementation of infants led to greater increases in infant 25-OH vitamin D levels, reductions in vitamin D insufficiency and vitamin D deficiency compared to supplementation of lactating mothers. However, the evidence is very uncertain for markers of bone health. Maternal higher dose supplementation (≥ 4000 IU/day) produced similar infant 25-OH vitamin D levels as infant supplementation of 400 IU/day. The certainty of evidence was graded as low to very low for all outcomes.

PLAIN LANGUAGE SUMMARY

Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health

Review question: do vitamin D supplements for breastfed infants or their mothers prevent vitamin D deficiency and improve bone health?

Background: vitamin D deficiency is common worldwide with infants at higher risk due to pigmentation, covering, avoidance of sun exposure or the latitude of where they live. Vitamin D is important for bone health, helping prevent nutritional rickets and fractures. Vitamin D levels are low in breast milk and exclusively breastfed infants are at risk of low vitamin D levels.

Study characteristics: evidence is up-to-date as of May 2020. We identified 19 studies with 2837 mother-infant pairs assessing vitamin D given to infants (nine studies), to breastfeeding mothers (eight studies), and to infants versus breastfeeding mothers (six studies). No studies compared vitamin D given to infants versus periods of infant sun exposure.

Key results: for breastfed infants, vitamin D supplements may increase vitamin D levels and reduce the incidence of mildly low vitamin D levels, but there was insufficient information to determine if there was a reduction in vitamin D deficiency or in signs of poor bone health (low bone mineral content, nutritional rickets or fractures). For breastfed infants at higher risk of vitamin D deficiency, vitamin D supplementation for the mother may increase infant vitamin D levels and may prevent vitamin D deficiency. There was not enough information to determine if there are benefits for bone health. In populations at higher risk of vitamin D deficiency, vitamin D supplementation of infants may be better than vitamin D supplementation of the mother whilst breastfeeding for preventing vitamin D deficiency. However, the evidence is very uncertain for markers of bone health. High-dose maternal supplementation (≥ 4000 IU per day) achieved similar infant vitamin D levels as infant supplementation with 400 IU per day.

Certainty of evidence: the evidence is currently very uncertain for supplementation of vitamin D for breastfeeding mothers or supplementation of their infants in populations at low risk of vitamin D deficiency. In populations at high risk of vitamin D deficiency, there is low-certainty evidence that vitamin D 400 IU per day given to the infant or higher doses given to the breastfeeding mother may prevent vitamin D deficiency, although effects on bone health are unclear.

Summary of findings 1. Vitamin D given to infants compared to placebo or no treatment for term breastfed infants to prevent vitamin D deficiency and improve bone health

Vitamin D given to infants compared to placebo or no treatment for term breastfed infants to prevent vitamin D deficiency and improve bone health

Patient or population: term breastfed infants to prevent vitamin D deficiency and improve bone health
Settings: community
Intervention: vitamin D given to infants compared to placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with vitaminD given to infants				
Bone mineral content at the end of intervention mg/cm Photon absorptiometry Follow-up: 6 months	The mean bone mineral content ranged across control groups from **64 to 101 mg/cm**	The mean bone mineral content at the end of intervention in the intervention groups was **3.93 higher** (2.42 lower to 10.27 higher)		56 (2 studies)	⊕⊝⊝⊝ **very low** [1,2,3]	
Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L Follow-up: 6 months	**451 per 1000**	**257 per 1000** (185 to 361)	**RR 0.57** (0.41 to 0.8)	274 (4 studies)	⊕⊕⊝⊝ **low** [1,4]	
Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L Follow-up: 6 months	**219 per 1000**	**90 per 1000** (35 to 230)	**RR 0.41** (0.16 to 1.05)	122 (2 studies)	⊕⊝⊝⊝ **very low** [1,3,5]	A single study reported deficiency in high-risk infants.
Nutritional rickets: biochemical Alkaline phosphatase, calcium and phosphate levels. Follow-up: 3 to 6 months	See comment	See comment	Not estimable	34 (2 studies)	⊕⊝⊝⊝ **very low** [1,6]	
Adverse effects (hypercalcaemia) Follow-up: 6 months	**118 per 1000**	**171 per 1000** (64 to 454)	**RR 1.45** (0.54 to 3.86)	98 (1 study)	⊕⊕⊝⊝ **low** [1,3]	
Serum 25-OH vitamin D level at latest time reported nmol/L Follow-up: 6 months	The mean serum 25-OH vitamin D level ranged across control groups from	The mean serum 25-OH vitamin D level at latest time reported to six months of age in the intervention groups was		356 (7 studies)	⊕⊕⊝⊝ **low** [1,7]	

	45.3 to 72.1 nmol/L	**22.63 higher** (17.05 to 28.21 higher)

*__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.

[1] Downgraded one level for serious risk of bias as no study of good methodology
[2] Downgraded one level for serious inconsistency as high level of heterogeneity between studies
[3] Downgraded one level for serious uncertainty as wide confidence intervals included the null
[4] Downgraded one level for serious indirectness as vitamin D insufficiency may not be predictive of bone health
[5] Downgraded one level for serious inconsistency as low level of heterogeneity between studies (risk difference used)
[6] Downgraded two levels for very serious uncertainty as no events (analysis underpowered).
[7] Downgraded one level for serious indirectness as average vitamin D levels may not be predictive of bone health

Summary of findings 2. Vitamin D given to lactating mothers compared to placebo or no treatment for term breastfed infants to prevent vitamin D deficiency and improve bone health

Vitamin D given to lactating mothers compared to placebo or no treatment for term breastfed infants to prevent vitamin D deficiency and improve bone health

Patient or population: term breastfed infants to prevent vitamin D deficiency and improve bone health
Settings: community
Intervention: vitamin D given to lactating mothers compared to placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with vitaminD given to lactating mothers				
Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L Follow-up: 6 months	**679 per 1000**	**319 per 1000** (265 to 387)	**RR 0.47** (0.39 to 0.57)	512 (5 studies)	⊕⊕⊖⊖ **low** [1,2]	Infant risk of vitamin D insufficiency was related to maternal dosage.

Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L Follow-up: 6 months	**443 per 1000**	**66 per 1000** (40 to 106)	**RR 0.15** (0.09 to 0.24)	512 (5 studies)	⊕⊕⊖⊖ **low** [1,3]	Infant risk of vitamin D deficiency was related to maternal dosage.
Nutritional rickets - biochemical Alkaline phosphatase, calcium and phosphate levels. Follow-up: 3 to 6 months	**139 per 1000**	**8 per 1000** (1 to 61)	**RR 0.06** (0.01 to 0.44)	229 (2 studies)	⊕⊕⊖⊖ **low** [3, 4]	
Nutritional rickets - radiological Follow-up: 6 months	**15 per 1000**	**11 per 1000** (3 to 49)	**RR 0.76** (0.18 to 3.31)	536 (3 studies)	⊕⊖⊖⊖ **very low** [3,5]	All studies were in higher-risk populations.
Adverse effects (hypercalcaemia)	**27 per 1000**	**35 per 1000** (14 to 88)	**RR 1.31** (0.51 to 3.32)	557 (3 studies)	⊕⊕⊖⊖ **low** [5]	
Serum 25-OH vitamin D level at latest time reported nmol/L Follow-up: 6 months	The mean serum 25-OH vitamin D level ranged across control groups from **16.075 to 42.475 nmol/L**	The mean serum 25-OH vitamin D level at latest time reported to six months of age in the intervention groups was **24.60 higher** (21.59 to 27.60 higher)		597 (7 studies)	⊕⊕⊖⊖ **low** [1, 6, 7]	

*__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.

[1] Downgraded one level for moderate heterogeneity.
[2] Downgraded one level for serious indirectness as vitamin D insufficiency may not be predictive of bone health
[3] Downgraded one level for serious indirectness as all studies in higher-risk populations. No studies in lower-risk populations

[4] Downgraded one level for serious risk of bias. One study of good methodology reported no difference
[5] Downgraded two levels for very serious uncertainty. Few events and very wide confidence intervals which included the null
[6] Downgraded one level for serious indirectness as average vitamin D levels may not be predictive of bone health
[7] Heterogeneity may be explained by subgroup (dosage) and sensitivity analysis

Summary of findings 3. Vitamin D given to infants compared to vitamin D given to lactating mothers for term breastfed infants to prevent vitamin D deficiency and improve bone health

Vitamin D given to infants compared to vitamin D given to lactating mothers for term breastfed infants to prevent vitamin D deficiency and improve bone health

Patient or population: term breastfed infants to prevent vitamin D deficiency and improve bone health
Settings: community
Intervention: vitamin D given to infants compared to vitamin D given to lactating mothers

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with vitamin**D given to infants**	**Risk with** vitamin**D given lactating mothers**				
Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L Follow-up: 6 months	**213 per 1000**	**130 per 1000** (85 to 201)	**RR 0.61** (0.40 to 0.94)	334 (4 studies)	⊕⊖⊖⊖ **very low** [1,2,3]	
Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L Follow-up: 6 months	**128 per 1000**	**45 per 1000** (22 to 92)	**RR 0.35** (0.17 to 0.72)	334 (4 studies)	⊕⊖⊖⊖ **very low** [1,4,5]	
Nutritional rickets- biochemical Follow-up: 6 months	See comment	See comment	Not estimable	92 (1 study)	⊕⊖⊖⊖ **very low** [1,6]	No events
Adverse effect **(hypercalcaemia)** Follow-up: 6 months	**140 per 1000**	**171 per 1000** (67 to 433)	**RR 1.22** (0.48 to 3.09)	97 (1 study)	⊕⊕⊖⊖ **low** [1,7]	
Serum 25-OH vitamin D level at latest time reported **nmol/L** Follow-up: 6 months	The mean serum 25-OH vitamin D level ranged across control groups from **14.0 to 108.5 nmol/L**	The mean serum 25-OH vitamin D level at latest time reported to six months of age in the intervention groups was **14.35 higher** (9.64 to 19.06 higher)		269 (4 studies)	⊕⊕⊖⊖ **low** [1,8,9]	

*__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.

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[1] Downgraded one level for serious risk of bias as no study of good methodology.
[2] Downgraded one level for serious inconsistency as moderate level of heterogeneity between studies.
[3] Downgraded one level for serious indirectness as vitamin D insufficiency may not be predictive of bone health.
[4] Downgraded one level for serious inconsistency as high level of heterogeneity between studies.
[5] Downgraded one level for serious uncertainty as wide confidence intervals include null effect in random effects model.
[6] Downgraded two levels for serious uncertainty. No events.
[7] Downgraded one level for serious uncertainty. Very wide confidence intervals include null effect.
[8] Downgraded one level for serious indirectness as average vitamin D levels may not be predictive of bone health.
[9] Heterogeneity may be explained by subgroup (dosage) analysis.

BACKGROUND

Description of the condition

Breastfeeding is the optimal source of nutrition for infants under six months of age. The World Health Organization (WHO) recommends exclusive breastfeeding for the first six months of life, followed by continued breastfeeding with complementary food until two years of age and beyond (WHO 2003). Exclusive breastfeeding means that no other fluid or food is given to the infant. It is recommended that, for the duration of exclusive breastfeeding, a mother's breast milk alone is sufficient to meet the energy and nutrition requirements of her infant (Butte 2001). However, there are concerns that breastfed infants may not maintain adequate vitamin D status from sunshine or their mother's milk (Dawodu 2003; Lovell 2016). This is in part contributed to by low maternal vitamin D levels (Andiran 2002), and limited exposure of infants to sunlight (NHS 2017).

It is widely accepted that vitamin D levels are low in breast milk (Hollis 1981; ViÃÂ° Streym 2016). The reported prevalence of vitamin D insufficiency or deficiency in term breastfed infants without vitamin D supplementation ranges from 0.6% at seven months of age in Nepalese infants (Haugen 2016), to 40% at four months of age in infants in the USA (Merewood 2012), and even as high as 83% at one month of age in Qatari infants (Salameh 2016). The vast differences seen are likely to be caused by multiple factors, including geographical factors (latitude and season during measurement), skin pigmentation of the population studied, use of covered clothing and methodological differences (KasalovÃÂ¡ 2015; Matsuoka 1992; Munns 2016).

Total serum 25-OH vitamin D (calcidiol) is the generally accepted marker of vitamin D sufficiency (IOM 2011). Though there is no universal consensus, most guidelines report that 25-OH vitamin D of at least 50 nmol/L is adequate (EFSA 2016; IOM 2011; Munns 2016). A 25-OH vitamin D level of 30 to 50 nmol/L is considered insufficient, while a level lower than 30 nmol/L is considered deficient (Munns 2016) (Note: 1 nmol/L = 0.4 ng/mL; IOM 2011).

Vitamin D deficiency in an infant can result in a number of bone-related as well as 'non-bone'-related conditions (Wharton 2003). The bony condition resulting from vitamin D deficiency in children is nutritional rickets. Nutritional rickets is characterised by deficient mineralisation of cartilage and bone, growth failure and skeletal deformity (Shore 2013a). The 'non-bone' conditions resulting from vitamin D deficiency include seizure, myopathy (muscle weakness) and myelofibrosis (type of bone marrow cancer) (Wharton 2003). Nutritional rickets results from vitamin D deficiency, primary calcium deficiency, or both (Pettifor 2004). Two reviews on the epidemiology of nutritional rickets worldwide found that calcium deficiency may also be a major aetiology of nutritional rickets in some African, Middle Eastern and Asian countries (Creo 2017; Prentice 2013). For this Cochrane Review, the term 'nutritional rickets' refers to vitamin D-deficient nutritional rickets.

Infants with nutritional rickets often present at between three to 18 months of age, when exclusive or partial breastfeeding is predominant (Creo 2017). Prior to three months, the infant is relatively protected by placental transfer of vitamin D (Shore 2013b).

The progression of nutritional rickets can be described in three stages. Initially, low circulating calcium (hypocalcaemia) occurs as a result of reduced absorption from the gastrointestinal tract and reabsorption from bones. The hypocalcaemia is often transient, but in infants can be prolonged enough for the infant to become symptomatic, presenting with tetany (involuntary contraction of muscles) or seizures. Subsequently, direct feedback to the parathyroid gland producing secondary hyperparathyroidism results in normalisation of serum calcium, but this is also accompanied by hypophosphataemia and hyperphosphaturia. If vitamin D deficiency continues, the raised parathyroid hormone (PTH) can no longer maintain calcium levels and rickets becomes more severe (Fraser 1967).

Diagnosis of rickets is made from a combination of clinical features, radiological findings and biochemical abnormalities. The radiological (x-ray) findings that are most diagnostic of rickets are those that demonstrate disordered mineralisation and ossification (natural process of bone formation) of the physes, described as metaphyseal splaying. These are best seen in the metaphysis of fast-growing bones, such as the distal ulnar and radius, distal femur, proximal and distal tibia, proximal humerus and anterior ends of middle ribs. Other findings include osteopenia (mineral content of bone tissue is reduced) and deformities (Shore 2013b). Due to increased bone activity, raised alkaline phosphatase (ALP) and PTH are commonly found. Hypocalcaemia may not be present as this is dependant on the stage of rickets development (Fraser 1967). Specifically for vitamin D-deficient rickets, the 25-OH vitamin D levels are less than 30 nmol/L (Munns 2016).

Nutritional rickets can be treated by replacement of vitamin D and calcium (Misra 2008). However, in the case of nutritional rickets, much of the damage caused by the deficiency, such as the skeletal deformity, is not correctable. Therefore, it is important to prevent nutritional rickets in vulnerable groups, such as breastfed infants.

Other than bone health, vitamin D has also been implicated in other conditions, such as improving immunity, prevention of cardiovascular disease, prevention of certain types of malignancies and mental health protection (Pludowski 2013). However, it is beyond the scope of this Cochrane Review to consider these outcomes.

Description of the intervention

Vitamin D, also known as 'the sunshine vitamin', is a pro-hormone rather than a 'vitamin'. It has two physiologically active forms, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 (VD2) is formed from ultraviolet (UV) radiation in plants and yeast (thus the source is from food), while vitamin D3 (VD3) is synthesised in the skin from 7-dehydrocholesterol. The synthesis of VD3 is a two-step process, with the formation of pre-VD3 using UVB (spectral range 290 to 320 nm) and subsequent thermal isomerisation (change in structure or configuration) into VD3. Once formed, it is bound to vitamin D-binding protein for transport into the circulation (Holick 1980). Both VD2 and VD3 subsequently undergo similar metabolic pathways and are physiologically equivalent in function (Shore 2013a).

Vitamin D is considered a pro-hormone because it requires further metabolism in order to function. VD2 and VD3 undergo hydroxylation in the liver to form 25-OH vitamin D (calcidiol) and is further hydroxylated in the renal tubules to form of 1,25-OH_2 vitamin D (calcitriol), which is the active form of vitamin D (Shore 2013a). However, 25-OH vitamin D (calcidiol) is the most plentiful

and stable vitamin D metabolite in the human body and thus used for measurement of vitamin D level in the body (Adams 2010).

Vitamin D supplements come in two forms, either plant-based VD2 or animal-based VD3 (Wagner 2008). VD3 is frequently preferred over VD2 as it has greater efficacy in raising circulating levels of 25-OH vitamin D and is more sustained (Armas 2004; Oliveri 2015). VD3 is extensively used as part of milk formula or food fortification (Holick 1992).

For infants, supplements are available either in combination with other vitamins or alone (Wagner 2008). Sole vitamin D supplements are preferable over combination vitamin preparations to allow adequate vitamin D dosing without overdose of other vitamins (Wagner 2008). The recommended dose for vitamin D supplementation of infants is between 340 IU and 400 IU per day, starting from birth up until one year of age (Health Canada 2012; NICE 2014; Wagner 2008). At these amounts, the risk of vitamin D toxicity is low (IOM 2011). As vitamin D is found in breast milk, it is possible to supplement the breastfeeding mother with vitamin D, thus indirectly supplementing the infant (Haggerty 2010). However, doses of about 6400 IU/day are needed in the lactating mother to have adequate excretion into human milk (Haggerty 2010).

Vitamin D toxicity has been defined as hypercalcaemia, a 25-OH vitamin D level exceeding 250 nmol/L associated with hypercalcuria (excess calcium in the urine) and suppressed PTH (Munns 2016). Clinically, it may result in growth retardation and symptoms of hypercalcaemia (IOM 2011). Toxicity only occurs with dietary intake, not sun exposure (Holick 1981).

How the intervention might work

Human bone is first formed as cartilage and, later, bone tissue is laid down to replace the cartilage. This process is called bone mineralisation or ossification. As the infant grows, bones undergo longitudinal and radial growth and a process of modelling-remodelling takes place (Clarke 2008). Vitamin D plays an important role in these processes. The primary action of vitamin D is to increase the absorption of calcium from the gastrointestinal tract (Elder 2014). It also mobilises calcium from bone with the help of PTH by way of increasing osteoclastic bone resorption (bone cells that break down bone tissue) (Shore 2013a). In addition, vitamin D also increases the kidney's distal tubules reabsorption of calcium together with the action of PTH (IOM 2011). The net action of vitamin D is to increase serum calcium levels.

Good bone mineralisation during early childhood and adolescence is the foundation of stronger bones later in life preventing fractures and osteoporosis (Winzenberg 2013a). Aquisition of bone mineral content is greatest in the first year of life (Koo 2013). Therefore, it is hypothesised that prevention of vitamin D deficiency by supplementation of breastfed infants should lead to better bone health in future.

Why it is important to do this review

Vitamin D deficiency and nutritional rickets among breastfed infants are not uncommon. A review of the global incidence of nutritional rickets in the last 10 years found it is an important global health problem (Creo 2017). With increasing efforts to promote exclusive breastfeeding of infants from birth to six months old (WHO 2003), it is important the risk of vitamin D deficiency in these infants is addressed.

Vitamin D supplementation of term breastfed infants has been recommended by the American Academy of Pediatrics (AAP), Institute of Medicine, Canada Health and UK National Institute for Health and Care Excellence (NICE) Guidelines (Health Canada 2012; IOM 2011; NICE 2014; Wagner 2008). These guidelines state that breastfed infants should start supplements by one month of life. Adherence to these guidelines is influenced by the recommendations of individual physicians or other healthcare professionals (Crocker 2011; Taylor 2010; Umaretiya 2017). However, when surveyed, the most common reasons given for low adherence to guidelines by physicians or mothers included "breast milk has all the nutrients a baby needs" and "nutritional rickets is not an important disease" (Perrine 2010; Taylor 2010; Umaretiya 2017). Breastfeeding advocates have also expressed concerns that the suggestion that breast milk may be vitamin D-deficient and thus require additional supplementation may imply that artificial feeding is superior to breastfeeding (Heinig 2003).

There are three Cochrane Reviews and a Cochrane protocol on vitamin D supplementation for children and pregnant women (Palacios 2019a; Palacios 2019b; Winzenberg 2010; Winzenberg 2013b). A review on interventions to prevent nutritional rickets in term-born children reported few data specific to term breastfed infants (Lerch 2007). This review aims to focus on evidence from randomised controlled trials (RCTs), specifically for term breastfed infants for the role of vitamin D supplementation to prevent vitamin D deficiency and improve bone health.

OBJECTIVES

To determine the effect of vitamin D supplementation given to:

- infants compared to placebo or no intervention on vitamin D deficiency, bone density and growth in healthy term breastfed infants;
- lactating mothers compared to placebo or no intervention on vitamin D deficiency, bone density and growth in healthy term breastfed infants;
- infants compared to vitamin D supplementation given to lactating mothers on vitamin D deficiency, bone density and growth in healthy term breastfed infants;
- infants compared to periods of infant sun exposure on vitamin D deficiency, bone density and growth in healthy term breastfed infants.

For each of the above comparisons:

- to determine adverse effects from vitamin D supplementation compared to placebo, no intervention or other interventions in healthy term breastfed infants.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) or quasi-RCTs. We excluded cross-over studies. We considered unpublished studies or studies reported only as abstracts as eligible for inclusion, if the methods and data could be confirmed by the review author team.

Types of participants

We included term healthy infants who were breastfeeding (exclusive or partial), from birth to six months of age.

Types of interventions

Vitamin D supplement, either as a single preparation or combined with other vitamins, given directly to the infant or lactating mother. We did not apply a minimum duration of supplementation. We planned to perform the following separate comparisons:

- vitamin D given to infants versus placebo or no treatment;
- vitamin D given to lactating mothers versus placebo or no treatment;
- vitamin D given to infants versus vitamin D given to lactating mothers;
- vitamin D given to infants versus periods of infant sun exposure.

Types of outcome measures

Primary outcomes

- Bone mineral density measured by dual x-ray absorptiometry (DXA) or other validated technique (Pezzuti 2017). Where bone mineral density was not reported, we included bone mineral content as an alternative measure of bone mineralisation. Both bone mineral density and bone mineral content are accepted as measures of paediatric bone health (Crabtree 2014).
- Vitamin D deficiency based on serum 25-OH vitamin D levels (sufficiency > 50 nmol/L; insufficiency 30 to 50 nmol/L; deficiency < 30 nmol/L) (Munns 2016); (1 nmol/L = 0.4 ng/mL = 40 ng/dL = 400 ng/L = 0.4 µg/L)
- Nutritional rickets defined as clinical symptoms or signs; and/or radiological signs (including reduced mineralisation and ossification of the physes and metaphyseal splaying); and/or biochemical changes (raised PTH and alkaline phosphatase, hypophosphataemia and hyperphosphaturia with or without hypocalcaemia) (Munns 2016)
- Adverse effects including vitamin D toxicity (defined as hypercalcaemia and serum 25-OH vitamin D > 250 nmol/L, with hypercalciuria and suppressed PTH) (Munns 2016)

Secondary outcomes

- Lowest serum 25-OH vitamin D level (nmol/L) up to six months of age
- Serum 25-OH vitamin D level (nmol/L) at latest time reported during treatment to six months of age
- Fracture (radiologically confirmed)
- Osteomalacia - low bone mineral density reported on x-ray
- Infant growth at latest time measured:
  - weight gain (g/kg per day);
  - linear/height growth (cm/week);
  - head circumference (cm/week).
- Change of standardised growth at latest time measured:
  - change in weight z-score;
  - change in length z-score;
  - change in head circumference z-score.
- Size at latest time measured:
  - weight;
  - length/height;
  - head circumference.

Search methods for identification of studies

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialised register). We searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed), on 30 May 2020. We did not limit the search to any particular geographical region, language or timing of publication.

Electronic searches

We conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL Issue 5) in the Cochrane Library; MEDLINE via PubMed (1946 to 30 May 2020); Embase (1974 to 29 May 2020); and MIDIRS (1971 to April 2020) using the following search terms: ("Breast Feeding"[Mesh] OR breastfeed* OR breast feed* OR breastfed OR lactation) AND ("vitamin D"[Mesh] OR "vitamin D" OR ergocalciferol* OR cholecalciferol*), plus database-specific limiters for RCTs and neonates (see Appendix 1; Appendix 2; Appendix 3; Appendix 4 and Appendix 5 for the full search strategies for each database). We did not apply language restrictions.

We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; The World Health Organization's International Clinical Trials Registry Platform (ICTRP)); the ISRCTN Registry; and the Australian and New Zealand Trial Registry ANZCTR).

Searching other resources

We also searched the reference lists of any articles selected for inclusion in this review in order to identify additional relevant articles.

We searched abstracts and conference proceedings of the American Society for Bone and Mineral Research (2010 to 2018), the Perinatal Society of Australia and New Zealand (PSANZ) (2011 to 2018), the European Society for Pediatric Endocrinology (2014 to 2017), the Asia Pacific Pediatric Endocrine Society (APPES) (2010 to 2016), , the Sociedad Latino-Americana de Endo-crinologÃÂa PediÃÂ¡trica (SLEP) (2014), the Australasian Pediatric Endocrine Group (APEG) (2015), World Congress of Pediatric Gastroenterology Hepatology and Nutrition (2016), and the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) (2016 to 2018).

We contacted experts in the field for any unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (ML and DO) assessed titles and abstracts of all citations retrieved from the literature search to determine eligibility. Any difference in opinion was resolved through consensus or by consulting a third review author as arbiter (SA). We retrieved the full-text article versions of potentially eligible articles or when inadequate information was provided in the abstract. We listed excluded reports in the 'Characteristics of excluded studies'

tables. Included studies are listed in the 'Characteristics of included studies'. We recorded the study selection process in a PRISMA flow diagram (Figure 1).

Figure 1. Study flow diagram.

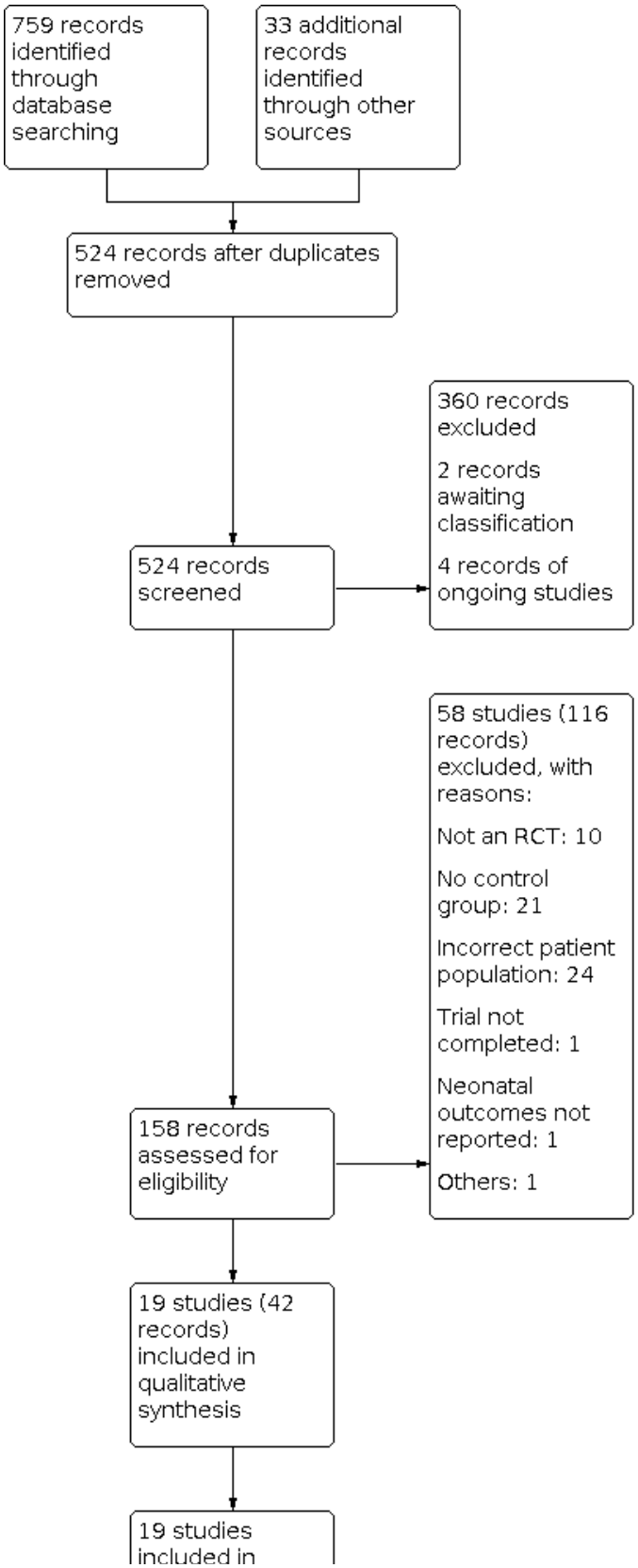
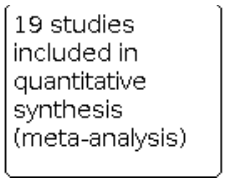


Figure 1. (Continued)



Data extraction and management

We independently extracted data from the included trials using specially designed data extraction forms. We requested additional unpublished information from the authors of original reports. We entered and cross-checked data using Review Manager 5 software (RevMan 2020), and compared extracted data for any differences. If noted, we resolved differences through discussion and consensus.

Assessment of risk of bias in included studies

Two review authors (ML and SA) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2017), for the following domains:

- sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias);
- any other bias.

We resolved any disagreements by discussion or by a third assessor. See Appendix 6 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We analysed study results using RevMan 5 (RevMan 2020). We reported continuous outcomes using mean difference (MD) and dichotomous outcomes as risk ratios (RRs) and risk difference (RD) with 95% confidence intervals (CI). For results that were statistically significant, we used the value of 1/RD to calculate the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH).

Unit of analysis issues

The unit of analysis was the participating infant in individual RCTs. Other unit of analyses issues were considered:

Cluster-randomised trials

We planned to make adjustments to the standard errors using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011, Section 16.3.6), using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial or from a study with a similar population. If we used ICC values from other sources, we reported this and conducted sensitivity analyses to investigate the effect of variation in the ICC. We considered it reasonable to combine the results from both cluster-RCTs and individual RCTs if there was little heterogeneity between the study designs and the interaction between the effect of the intervention and the choice of randomisation unit was considered to be unlikely. One cluster-randomised trial (Madar 2009), was found for which we estimated the ICC.

Trials with more than two treatment groups

For trials with more than two intervention groups, we only included the eligible groups. We combined intervention groups if we considered doses comparable, where appropriate. If the control group was shared by two or more study arms, we planned to divide the control group over the number of relevant subgroup categories to avoid double counting participants.

Dealing with missing data

We planned to obtain missing data from the trial authors when possible. Where we were unable to obtain missing data, we planned to examine the effect of excluding trials with substantial missing data (e.g. greater than 10% losses) in sensitivity analyses.

We planned to attempt to overcome potential bias from missing data (greater than 10% losses) using one or more of the following approaches:

- whenever possible, we planned to contact the original trial investigators to request missing data;
- we performed sensitivity analyses to assess how sensitive the results were to reasonable changes in the assumptions that were made (e.g. the effect of excluding trials with substantial missing data (greater than 10% losses);
- we addressed the potential impact of missing data (greater than 10% losses) upon the findings of the review in the Discussion section.

Assessment of heterogeneity

We used RevMan 5 to assess the heterogeneity of treatment effects between trials (RevMan 2020). We undertook this assessment using the following two formal statistical models:

- Chi^2 test, to assess whether observed variability in effect sizes between studies was greater than would be expected by chance. As this test has low power when few studies are included in the meta-analysis, we set the probability at the 10% level of significance;
- I^2 statistic, to ensure that pooling of data was valid. We graded the degree of heterogeneity as follows: none (< 25%); low (25% to 49%); moderate (50% to 74%); or high (≥ 75%). When we found evidence of heterogeneity, we assessed the source of heterogeneity by performing sensitivity and subgroup analyses, while looking for evidence of bias or methodological differences between trials.

Assessment of reporting biases

Where we identified 10 or more studies that included a specific intervention (comparison) and reported on the same outcome, we assessed reporting and publication biases by examining the degree of asymmetry of a funnel plot in RevMan 5 (RevMan 2020).

Data synthesis

Where we identified two or more studies that were homogenous, we performed a meta-analysis using RevMan 5 (RevMan 2020). We used a fixed-effect model for analysis as recommended by the Cochrane Neonatal Group (neonatal.cochrane.org/resources-review-authors). For studies that were clinically distinct, we did not combine the studies for meta-analysis and instead presented a narrative description of the study results. The narrative description included the general direction, size, consistency and strength of the evidence of effect of each individual study. We did not attempt to compare the effects of each study or draw an overall conclusion.

Certainty of evidence

We used the GRADE approach, as outlined in the GRADE Handbook (SchÃÂ¼nemann 2013), to assess the certainty of evidence for the following (clinically relevant) outcomes:

- vitamin D insufficiency/deficiency;
- serum 25-OH vitamin D level;
- number of infants diagnosed with nutritional rickets;
- bone mineral density;
- adverse effects.

Two review authors (MLT, DO) independently assessed the certainty of evidence for each of the outcomes above. We considered evidence from randomised controlled trials initially as high certainty but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We used the GRADEpro GDT Guideline Development Tool to create three 'Summary of findings' tables to report the certainty of evidence.

The GRADE approach results in an assessment of the certainty of a body of evidence as one of four grades.

1. High certainty: further research is very unlikely to change our confidence in the estimate of effect.
2. Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
3. low-certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4. Very low-certainty: we are very uncertain about the estimate.

Subgroup analysis and investigation of heterogeneity

Where sufficient data was available, we explored potential sources of heterogeneity by analysing whether results differed for infants at:

- high risk of vitamin D deficiency due to: pigmentation, covering or avoidance of sun exposure, and/or latitude (insufficient UV intensity most of the year), versus lower risk;
- seasonality of supplementation (winter versus non-winter);
- supplementation with plant-based VD2 versus animal-based VD3;
- dose of vitamin D to infant (200 to 400 IU/day; 400 to 800 IU/day; > 800 IU/day) or mother (400 to 2000 IU/day; 2000 to 4000 IU/day; > 4000 IU/day)
- duration of vitamin D supplementation (< one month; one to two months; two to four months; four to six months); and
- timing of commencement of vitamin D supplementation (from birth; one to two months; three to four months; five to six months).

Sensitivity analysis

We explored heterogeneity where sufficient data were available by performing sensitivity analyses. Where possible, we conducted sensitivity analyses to assess any change in the direction of effect caused by inclusion of studies of lower quality, based on assessment of: allocation concealment, adequate randomisation, blinding of treatment, less than 10% loss to follow-up, and intention-to-treat analyses.

RESULTS

Description of studies

Results of the search

Our search found 524 records (after deduplication) of potentially relevant studies from searching databases and following up on references of studies. Three hundred and sixty records were excluded after reading the titles and abstracts. After examining 158 records, we included 19 studies (with 42 records) and excluded 58 studies (with 116 records) in this review. We identified four ongoing studies and two studies awaiting classification.

For one study awaiting classification, we were are not able to determine if the participants were truly randomised and attempts to contact the authors have failed (Kim 2010). The other is published in abstract form with insufficient information for inclusion (Wagner 2018).

Four ongoing studies are pending conclusion (ACTRN12618001992291; ACTRN12614000334606), or current status could not be determined (ACTRN12615000642583; ChiCTR1800020179).

Included studies

We included 19 studies in this review out of which 17 were randomised controlled trials (RCT), with one quasi-RCT (Ala-Houhala 1986), and one cluster-RCT (Madar 2009). Eleven were two-arm studies (Alonso 2011; Greer 1981; Hollis 2015; Madar 2009; Moodley 2015; Naik 2017; Niramitmahapanya 2017; Rueter 2019; Thiele 2017; Trivedi 2020; Wagner 2006), seven were three-arm studies (Ala-Houhala 1985; Ala-Houhala 1986; Chandy 2016; Greer 1989; Ponnapakkam 2010; Rothberg 1982; Wheeler 2016), and one was a five-arm study (Roth 2016).

Participants (including total number)

A total of 2837 mother-infant pairs participated in the included studies. All the infants in the included studies were term, healthy, singleton infants, enrolled soon or up until six weeks after birth (birth: Ala-Houhala 1985; Ala-Houhala 1986; Greer 1989; Moodley 2015; Naik 2017; Niramitmahapanya 2017; Ponnapakkam 2010;

Roth 2016; Rothberg 1982; Thiele 2017; Trivedi 2020; two weeks until six weeks: Alonso 2011; Chandy 2016; Greer 1981; Hollis 2015; Madar 2009; Rueter 2019; Wagner 2006; Wheeler 2016). Hollis 2015 included late preterm infants but, in the final analysis, the average gestation of the infants included was 39 weeks.

The infants in the included studies were exclusively breastfed, or had mothers who intended to exclusively breastfeed at the start of the study. Two studies also included non-breastfeeding infants, but separate data were available for the exclusively breastfed infants (Alonso 2011; Madar 2009), At the end of the study, not all infants were still exclusively breastfed. Four studies had all infants enrolled in the studies exclusively breastfed from the start till end of the study (Greer 1981; Naik 2017; Thiele 2017; Trivedi 2020). Eight studies excluded the non-exclusively breastfed infants from analysis (Ala-Houhala 1985; Greer 1989; Hollis 2015; Niramitmahapanya 2017; Ponnapakkam 2010; Rothberg 1982; Wagner 2006; Wheeler 2016). Four studies included all exclusively and non-exclusively breastfed infants in their analyses (Chandy 2016; Moodley 2015; Rueter 2019; Roth 2016). Where reported, the exclusive breastfeeding rates at six months were 12% to 15% (Roth 2016), 24% (Moodley 2015), 64.7% at four months (Hollis 2015) and 70.5% (Rueter 2019). The proportion of infants with vitamin D insufficiency or deficiency at enrolment ranged from 13% to 96.4% (Madar 2009; Moodley 2015; Naik 2017; Wheeler 2016; Trivedi 2020).

The mothers in the studies were all healthy. While none of the studies specifically included women with known vitamin D insufficiency or deficiency, the proportion of mothers included who had vitamin D deficiency or insufficiency ranged from 10% to 90.4% in six studies (Ala-Houhala 1985; Moodley 2015; Naik 2017; Roth 2016; Trivedi 2020; Wheeler 2016). Rueter 2019 excluded infants of mothers with 25-hydroxyvitamin D (25-OH D) serum concentrations less than 50 nmol/L or greater than 100 nmol/L between 36 and 40 weeks' gestation, intended to reduce the risk of vitamin D deficiency or toxicity in the infant participants. The remaining studies either reported the mean 25-OH vitamin D levels at baseline (Chandy 2016; Hollis 2015; Niramitmahapanya 2017; Rothberg 1982; Wagner 2006), or did not report these levels at all (Ala-Houhala 1986; Alonso 2011; Greer 1981; Greer 1989; Madar 2009; Ponnapakkam 2010; Thiele 2017). In four studies, some or all of the women also took prenatal vitamin D (Ala-Houhala 1985; Ala-Houhala 1986; Greer 1989; Wagner 2006), while two studies excluded women who took prenatal vitamin D (Chandy 2016; Naik 2017).

Settings (latitude, season)

All studies were conducted in the community setting. All except two of the studies were from temperate countries (latitude between 23.5ÃÂ°N/S and 66.5ÃÂ°N/S): six from the USA (Greer 1981; Greer 1989; Hollis 2015; Ponnapakkam 2010; Thiele 2017; Wagner 2006), two from Finland (Ala-Houhala 1985; Ala-Houhala 1986), three from India (Chandy 2016; Naik 2017; Trivedi 2020), and one each from Australia (Rueter 2019), Mexico (Moodley 2015), New Zealand (Wheeler 2016), Norway (Madar 2009), South Africa (Rothberg 1982), and Spain (Alonso 2011). The two studies from the tropics (latitude between 23.5ÃÂ°N and 23.5ÃÂ°S), were from Bangladesh (Roth 2016), and Thailand (Niramitmahapanya 2017).

Among the studies conducted in temperate countries, 10 were non-seasonal (Alonso 2011; Chandy 2016; Greer 1989; Hollis 2015; Madar 2009; Moodley 2015; Naik 2017; Rueter 2019; Trivedi 2020; Wheeler 2016). Five studies were seasonal where two were conducted during winter (Ala-Houhala 1986; Rothberg 1982), and three were conducted during summer and winter (Ala-Houhala 1985; Greer 1981; Thiele 2017). The remaining studies did not specify the season (Ponnapakkam 2010; Wagner 2006).

Higher versus lower-risk populations

Prespecified criteria for studies of populations at high risk of vitamin D deficiency included pigmentation, covering or avoidance of sun exposure, or latitude, or both. In addition, studies with documented vitamin D insufficiency or deficiency at baseline were included as high risk. Ten studies were considered to be in high-risk populations: Ala-Houhala 1985 (latitude 61ÃÂ°N and 25% mothers vitamin D insufficient at baseline); Ala-Houhala 1986 (latitude 61ÃÂ°N and 63% mothers vitamin D insufficient at baseline); Chandy 2016 (pigmentation, covering and the average level of 25-OH vitamin D in mothers was considered vitamin D deficient at baseline); Madar 2009 (latitude 60ÃÂ°N and immigrants from Pakistan, Turkey and Somalia); Moodley 2015 (pigmentation and the the average level of 25-OH vitamin D in mothers was considered vitamin D deficient at baseline); Naik 2017 (pigmentation and the average level of 25-OH vitamin D in mothers was considered vitamin D deficient at baseline); Roth 2016 (pigmentation and the average level of 25-OH vitamin D in mothers was considered vitamin D deficient at baseline); Rothberg 1982 (winter, the average level of 25-OH vitamin D in mothers and infants was considered vitamin D deficient at baseline); Trivedi 2020 (pigmentation, the average level of 25-OH vitamin D in mothers and infants was considered vitamin D deficient at baseline); Wheeler 2016 (55% of mothers vitamin D insufficient at baseline).

Nine studies were considered to be in low-risk populations (Alonso 2011; Greer 1981; Greer 1989; Hollis 2015; Niramitmahapanya 2017; Ponnapakkam 2010; Rueter 2019; Thiele 2017; Wagner 2006).

Intervention

Vitamin D was given either to the infant (seven studies: Alonso 2011; Greer 1981; Greer 1989; Madar 2009; Moodley 2015; Ponnapakkam 2010; Rueter 2019), or lactating mother (six studies: Naik 2017; Niramitmahapanya 2017; Roth 2016; Thiele 2017; Trivedi 2020; Wheeler 2016), or both (six studies: Ala-Houhala 1985; Ala-Houhala 1986; Chandy 2016; Hollis 2015; Rothberg 1982; Wagner 2006).

In studies giving vitamin D to infants, vitamin D2 (ergocalciferol) drops were used in four studies (Ala-Houhala 1986; Greer 1981; Greer 1989; Madar 2009), at a dose of 400 IU/day. Vitamin D3 (cholecalciferol) drops were used in six studies (Alonso 2011; Greer 1989; Moodley 2015; Ponnapakkam 2010; Rueter 2019; Wagner 2006), at these doses: 200 IU/day, 400 IU/day, 402 IU/day or as 50,000 IU in a single dose. Three studies did not specify the type of vitamin D given (Ala-Houhala 1985; Chandy 2016; Rothberg 1982), but were given at a dose of 400 IU/day.

In studies giving vitamin D to lactating mothers, only oral vitamin D3 was used. The dose ranged from daily doses of 500 IU/day to 6400 IU/day, or monthly doses of 50 000 IU/dose to 120 000 IU/dose.

Co-interventions were given in seven studies: Chandy 2016 had the infants exposed to sunlight for one hour per day while Greer 1989, Thiele 2017 and Wagner 2006 gave all mothers 400 IU of vitamin D daily in the form of a prenatal vitamin. Naik 2017 gave all mothers a postnatal vitamin containing 125 IU vitamin D daily. All mothers

in Roth 2016 took high-dose prenatal vitamin D from the second trimester and pre and postnatal calcium 500 mg. All mothers in Trivedi 2020 took prenatal calcium 500 mg and a vitamin D3 250 IU supplement.

Comparators

Seven studies compared vitamin D given to infants versus placebo or no treatment (Alonso 2011; Greer 1981; Greer 1989; Madar 2009; Moodley 2015; Ponnapakkam 2010; Rueter 2019). Seven studies compared vitamin D given to lactating mothers versus placebo or no treatment (Naik 2017; Niramitmahapanya 2017; Roth 2016; Rothberg 1982; Thiele 2017; Trivedi 2020; Wheeler 2016). Another six studies compared vitamin D given to infants with vitamin D given to lactating mothers (Ala-Houhala 1985; Ala-Houhala 1986; Chandy 2016; Hollis 2015; Rothberg 1982; Wagner 2006). There were no studies comparing vitamin D given to infants with periods of infant sun exposure.

Duration of intervention

Duration of the intervention was very heterogenous. The shortest duration was a single dose at birth (Moodley 2015), and longest duration was 12 months (Alonso 2011). The majority of studies gave the intervention for less than eight weeks duration (Madar 2009; Naik 2017; Niramitmahapanya 2017; Rothberg 1982; Thiele 2017), or between 12 to 26 weeks duration (Ala-Houhala 1986; Ala-Houhala 1985; Greer 1981; Greer 1989; Hollis 2015; ;Ponnapakkam 2010; Rueter 2019; Roth 2016; Trivedi 2020; Wagner 2006; Wheeler 2016). One study gave the intervention for nine months (Chandy 2016), and another started the intervention prenatally from 24 to 28 weeks' gestation until 4 to 6 weeks' postnatally (Thiele 2017).

Duration of follow-up corresponded with the duration of the intervention in all but the following studies: Moodley 2015 and Naik 2017 had a follow-up duration of six months; Wheeler 2016 had a duration of follow-up of five months, Greer 1981 had a follow-up of one year; Rueter 2019 had a follow-up of two and a half years and Roth 2016 had a duration of follow-up of two years.

Funding sources

All but one study were funded by academic or research institutes or foundations without any industrial ties. One study was funded by a private research foundation which is food industry-based (Ponnapakkam 2010).

Seven studies had additional partial funding by industry - mainly providing the vitamin D and placebo (Ala-Houhala 1985; Ala-Houhala 1986; Greer 1981; Naik 2017; Rueter 2019; Trivedi 2020; Wheeler 2016).

Outcomes

Bone mineral content

Two studies reported this outcome (Greer 1981; Greer 1989), as bone mineral content (mg/cm). Bone mineral content was measured on the distal third of the left ulnar and radius using direct photon absorptiometry.

Vitamin D deficiency

Eleven studies reported the number of infants who had vitamin D insufficiency or deficiency at the end of intervention or follow-up (Ala-Houhala 1985; Chandy 2016; Greer 1989; Hollis 2015; Madar 2009; Moodley 2015; Naik 2017; Rueter 2019; Roth 2016; Trivedi 2020; Wheeler 2016). We categorised the studies to those reporting vitamin D insufficiency (defined as 25-OH vitamin D < 50 nmol/L), or vitamin D deficiency (defined as 25-OH vitamin D < 30 nmol/L), or both. All except two studies reported both deficiency and insufficiency. Madar 2009 and Rueter 2019 only reported the number of infants with 25-OH vitamin D levels of < 50 nmol/L.

Nutritional rickets

Five studies reported this outcome (Greer 1981; Naik 2017; Ponnapakkam 2010; Roth 2016; Trivedi 2020). Nutritional rickets were reported as biochemical rickets, radiological rickets or clinical rickets. Greer 1981 reported clinical rickets at one year follow-up (craniotabes, rachitic rosary or widened wrist) as well as biochemical rickets (serum alkaline phosphatase (ALP), serum calcium and serum phosphate); Naik 2017 reported radiological rickets (X-ray of both wrists) and biochemical rickets (serum ALP). Ponnapakkam 2010 reported rickets defined as a combination of raised ALP and hand radiographic changes and subclinical rickets as raised ALP alone. Roth 2016 reported both biochemical rickets (raised ALP > 450 mmol/L, with or without serum phosphate and calcium) and radiological rickets (based on X-rays of wrists and knees). Trivedi 2020 also reported both biochemical rickets (raised ALP) and radiological rickets (X-rays of both wrists).

Adverse effect in infants and mothers

The main adverse effects in infants reported was hypercalcaemia (serum calcium > 2.62 mmol/L in Chandy 2016; serum calcium > 2.8 mmol/L in Roth 2016 and Wheeler 2016; clinical features in Trivedi 2020). Urinary tract infection was reported by Ponnapakkam 2010. Two studies did not describe the adverse effects measured and only reported "no adverse effects" (Madar 2009; Moodley 2015).

The main adverse effects in mothers reported were hypercalcaemia (serum calcium > 2.6 in Chandy 2016 and Roth 2016; hypercalciuria (urine calcium:creatinine ratio > 0.2 mg/mg in Chandy 2016 and Naik 2017; urine calcium:creatinine ratio mmol/mmol in Roth 2016; urine calcium:creatinine ratio > 0.6 mol/100 mol in Wheeler 2016); and vitamin D toxicity (serum 25-OH) D > 125 nmol/L in Roth 2016). Maternal serum calcium levels were reported as continuous outcomes in Niramitmahapanya 2017, Rothberg 1982 and Thiele 2017. Maternal urine calcium:creatinine ratios were reported as continuous outcomes in Naik 2017 and Niramitmahapanya 2017.

Fractures and osteomalacia

No studies reported this outcome.

Serum 25-OH vitamin D levels

All 19 included studies reported serum vitamin D levels at the end of intervention. The vitamin D levels were reported as either ng/mL or nmol/L. In this review, all units were standardised to nmol/L (1 ng/mL = 2.5 nmol/L). All of the vitamin D levels were total vitamin D except one study which reported only vitamin D3 (25-OH D3) levels (Rothberg 1982). Three studies reported both the total vitamin D and vitamin D3 levels (Greer 1989; Madar 2009; Roth 2016).

Infant growth

Nine studies reported this outcome (Ala-Houhala 1985; Alonso 2011; Chandy 2016; Greer 1981; Greer 1989; Hollis 2015; Moodley 2015; Roth 2016; Wagner 2006). The measures of growth were reported as weight, length and head circumference at the end

of the intervention. In addition, Roth 2016 also reported the z-score for weight, length and head circumference at the end of the intervention.

Other outcomes not specified in the protocol

Several studies reported serum parathyroid hormone (PTH) levels (Ala-Houhala 1986; Alonso 2011; Greer 1981; Hollis 2015; Ponnapakkam 2010; Thiele 2017; Wheeler 2016), and breast milk vitamin D or antirachitic level (Niramitmahapanya 2017; Wagner 2006). These outcomes were not analysed in this review.

Excluded studies

We excluded 58 studies after examining the full text or abstract. Ten studies were excluded because they were not RCTs or had inadequate descriptions to determine whether they were RCTs (Bagnoli 2013; Challa 2005; Chan 1982; Kuryaninova 2017; Morris 2017; Onal 2010; Roberts 1981; Savino 2011; Terashita 2017; Zamora 1999). Ten studies were excluded as low birthweight or preterm infants were included (Abdel-Hady 2019; ACTRN12618001174279; Al-Beltagi 2020; Backstrom 1999; Delvin 2005; Francis 2018; Hibbs 2018; Kishore 2019; Kolodziejczyk 2017; Salas 2018). Four studies were excluded as the term infants were not breastfed (Grant 2014; Roberfroid 2012), or had a specific disorder (Lara-Corrales 2013; Norizoe 2014). Three studies compared interventions given to the mother but all the infants also received vitamin D (Bugrul 2013; Czech-Kowalska 2013; Saadi 2009). Twelve studies had the intervention only given to mothers antenatally and discontinued after delivery (Chawes 2016; Cooper 2016; Diogenes 2013; Baird 2016; Litonjua 2014; Mirghafourvand 2015; Nausheen 2018; NCT02713009; Perumal 2017; Rasmussen 2015; Rostami 2018; Wagner 2013). Sixteen studies were excluded because there was no control group - the intervention was compared to a different dose, regimen or preparation of vitamin D (Basile 2006; Dawudo 2019; Galdo 2018; Gallo 2013b; Gupta 2018; Hollis 2004; Huynh 2015; Ketha 2018; March 2015; O'Callaghan 2018; Oberhelman 2013; Rosendahl 2017; Shakiba 2010; Siafarikas 2011; Tomimoto 2018; Ziegler 2014). One study stopped early due to lack of recruits (ACTRN12613000732785). One study was excluded because the intervention was not vitamin D (Ho 1985). Details of all excluded studies are presented in Characteristics of excluded studies.

Risk of bias in included studies

Overall, risk of bias in the included studies was generally low except for blinding, incomplete outcome and selective reporting where there were some studies with high risk of biases. See Figure 2 and Figure 3 for the overall summary.

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

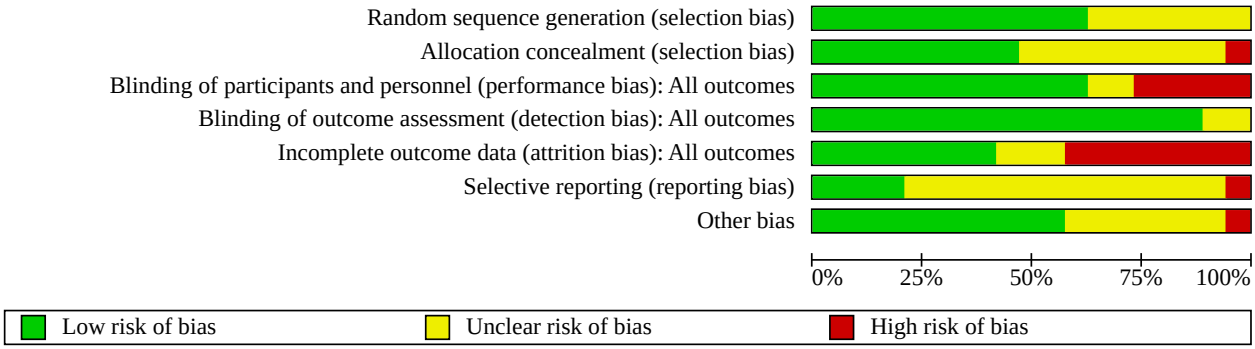
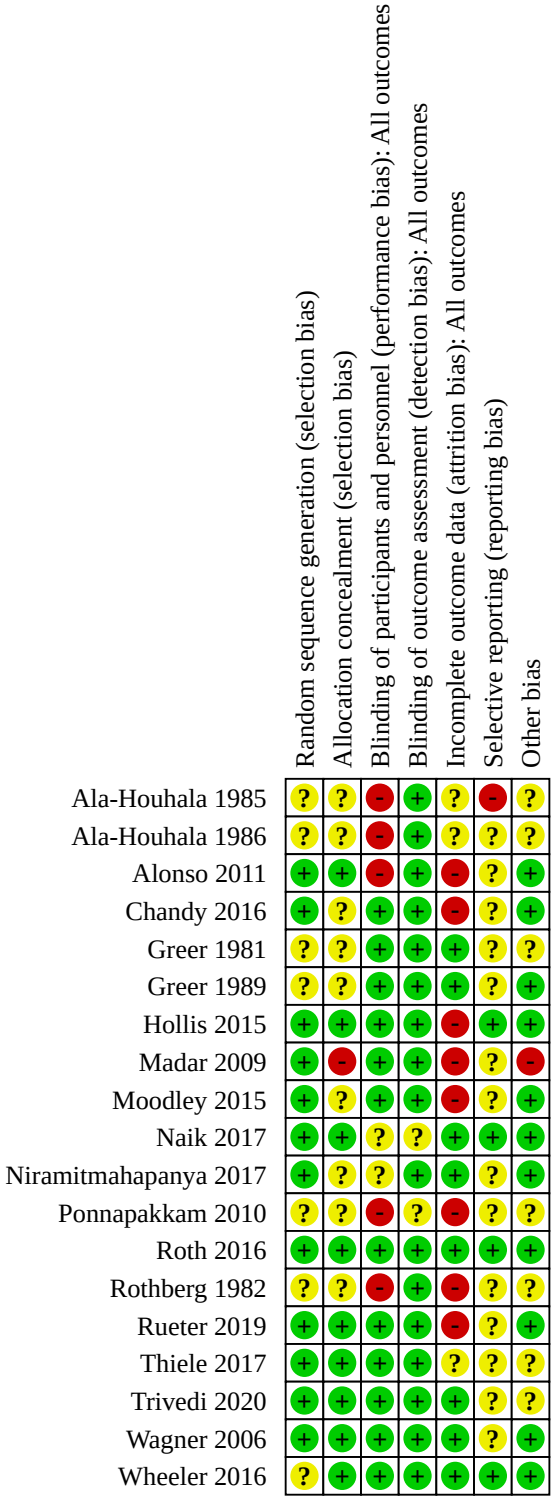


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation and allocation concealment was described in sufficient detail to be judged as having low risk of bias in eight studies (Alonso 2011; Hollis 2015; Naik 2017; Rueter 2019; Roth 2016; Thiele 2017; Trivedi 2020; Wagner 2006). Three studies had clear descriptions of random sequence generation to be judged as having low risk of bias but had no description of the allocation concealment (Chandy 2016; Moodley 2015; Niramitmahapanya 2017). One study did not describe method of randomisation but only the allocation concealment, which was judged to be low risk (Wheeler 2016). Six neither described random sequence generation nor allocation concealment, and thus were judged to be at unclear risk of both biases (Ala-Houhala 1985; Ala-Houhala 1986; Greer 1981; Greer 1989; Ponnapakkam 2010; Rothberg 1982). Madar 2009 was a cluster-RCT with clusters having random sequence generation but patient allocation was not concealed as cluster allocation was known.

Blinding

Twelve studies were judged to have low risk of bias for blinding as participants and outcome assessors were blinded (Chandy 2016; Greer 1981; Greer 1989; Hollis 2015; Madar 2009; Moodley 2015; Rueter 2019; Roth 2016; Thiele 2017; Trivedi 2020; Wagner 2006; Wheeler 2016). Participants were not blinded in five studies (Ala-Houhala 1985; Ala-Houhala 1986; Alonso 2011; Ponnapakkam 2010; Rothberg 1982). However, the detection bias in these studies were judged to be low risk as outcomes were unlikely to be affected by lack of blinding except one study (Ponnapakkam 2010), which was judged as unclear because it was not stated if the radiologist reading the X-rays was blinded. Two studies (Naik 2017; Niramitmahapanya 2017), did not describe the placebo used, however one of the studies (Niramitmahapanya 2017), had outcomes that were unlikely to be affected by lack of blinding and the other (Naik 2017), was judged as having unclear risk of detection bias because it was not stated if the radiologist reading the X-rays was blinded.

Incomplete outcome data

Eight studies were judged to have low risk of bias for incomplete outcome data (Greer 1981; Greer 1989; Naik 2017; Niramitmahapanya 2017; Roth 2016; Trivedi 2020; Wagner 2006; Wheeler 2016. Seven studies had high attrition rates (Alonso 2011; Chandy 2016; Madar 2009; Moodley 2015; Ponnapakkam 2010; Rueter 2019; Rothberg 1982), and one study stopped the intervention early in one arm (Hollis 2015). These studies were judged as having high risk of bias Three studies were judged as having unclear risk of bias because only the total number of participants with incomplete data was reported (Ala-Houhala 1985), it was unclear if all participants completed the study (Ala-Houhala 1986), and participants who did not receive the intervention were excluded even though an intention-to-treat analysis was reported (Thiele 2017).

Selective reporting

Four studies were judged to have low risk of bias for selective reporting as the study protocols were available and all prespecified outcomes were reported (Hollis 2015; Naik 2017; Roth 2016; Wheeler 2016). One study was judged as having high risk of selective reporting bias because the outcome of vitamin D deficiency was reported for only one group (Ala-Houhala 1985). The remaining 14 studies were judged as having unclear risk of bias as the study protocols were unavailable (Ala-Houhala 1986; Alonso 2011; Chandy 2016; Greer 1981; Greer 1989; Madar 2009; Moodley 2015; Niramitmahapanya 2017; Ponnapakkam 2010; Rueter 2019; Thiele 2017; Trivedi 2020; Wagner 2006), or details incompletely matched the published study (Rueter 2019).

Other potential sources of bias

Eleven studies were judged to have low risk of other potential bias as the baseline characteristics were reported and balanced (Alonso 2011; Chandy 2016; Greer 1989; Hollis 2015; Moodley 2015; Naik 2017; Niramitmahapanya 2017; Rueter 2019; Roth 2016; Wagner 2006; Wheeler 2016). One study was judged to have unclear risk of bias because the subgroup of breastfed infants in the study was not a predetermined subgroup (Madar 2009). Two studies were judged as having unclear risk of bias as there were some baseline differences between the groups but we were unsure about the reasons for this (Thiele 2017; Trivedi 2020). The remaining five studies did not report the baseline characteristics and thus were judged as having unclear risk of bias (Ala-Houhala 1985; Ala-Houhala 1986; Greer 1981; Ponnapakkam 2010; Rothberg 1982).

Effects of interventions

See: **Summary of findings 1** Vitamin D given to infants compared to placebo or no treatment for term breastfed infants to prevent vitamin D deficiency and improve bone health; **Summary of findings 2** Vitamin D given to lactating mothers compared to placebo or no treatment for term breastfed infants to prevent vitamin D deficiency and improve bone health; **Summary of findings 3** Vitamin D given to infants compared to vitamin D given to lactating mothers for term breastfed infants to prevent vitamin D deficiency and improve bone health

Comparison 1: vitamin D given to infants versus placebo or no treatment

Nine studies contributed to this comparison (Alonso 2011; Chandy 2016; Greer 1981; Greer 1989; Madar 2009; Moodley 2015; Ponnapakkam 2010; Rueter 2019; Rothberg 1982), with a total of 743 mother-infant pairs.

Bone mineral density/content at the end of intervention (mg/cm)

No study reported bone mineral density. There was no difference in the bone mineral content (Analysis 1.1), between the group of infants given vitamin D and the placebo group (MD 3.93 mg/cm, 95% CI -2.42 to 10.27; participants = 56; studies = 2; I^2 = 94%; very low-certainty evidence). We downgraded the certainty of evidence for risk of bias, inconsistency and imprecision. Studies reported effects in opposite directions.

Subgroup analyses (Analysis 4.1): both studies (Greer 1981; Greer 1989), compared oral D3 400 IU/day in low-risk infants from birth for three to six months. Greer 1981reported an increase in bone mineral content (MD 15.00 mg/cm, 95% CI 6.68 to 23.32; participants = 18), whereas Greer 1989 reported a decrease in bone mineral content (MD -11.50 mg/cm, 95% CI -21.32 to -1.68; participants = 38).

Sensitivity analysis (Analysis 4.2): neither study had good methodology.

Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L)

There was a reduction in the risk of vitamin D insufficiency (Analysis 1.2) in infants given vitamin D (RR 0.57, 95% CI 0.41 to 0.80; participants = 274; studies = 4; IÃÂ² = 42%; low-certainty evidence). We downgraded the certainty of evidence for bias and indirectness as vitamin D insufficiency may not be predictive of bone health.

Subgroup analyses:

- Infant risk (Analysis 4.3): there was a reduction in vitamin D insufficiency in high-risk infants (RR 0.65, 95% CI 0.46 to 0.94; participants = 134; studies = 3; IÃÂ² = 0%) and lower-risk infants (RR 0.19, 95% CI 0.07 to 0.53; participants = 140; studies = 1). The test for subgroup differences was significant (P = 0.03, IÃÂ² = 79.9%).
- Season of supplementation (Analysis 4.4): all studies had non-seasonal supplementation.
- D2 versus D3 supplementation (Analysis 4.5): a single study reported no difference in vitamin D insufficiency with D2 supplementation (RR 0.50, 95% CI 0.14 to 1.77; participants = 12), whereas there was reduction with D3 supplementation (RR 0.58, 95% CI 0.40 to 0.82; participants = 262; studies = 3; IÃÂ² = 61%). The test for subgroup differences was not significant (P = 0.83, IÃÂ² = 0%).
- Dosage (Analysis 4.6): a single study giving a single oral vitamin D dose of 50,000 IU at birth reported no difference in vitamin D insufficiency (RR 0.61, 95% CI 0.24 to 1.54; participants = 211), whereas there was a reduction in vitamin D insufficiency using 400 IU/day (RR 0.56, 95% CI 0.39 to 0.81; participants = 253; studies = 3; IÃÂ² = 61%). The test for subgroup differences was not significant (P = 0.89, IÃÂ² = 0%).
- Duration of supplementation (Analysis 4.7): test for subgroup differences was not significant (P = 0.97, IÃÂ² = 0%). Most data related to supplementation for ≥ six months.
- Timing of commencement (Analysis 4.8): all studies commenced vitamin D supplementation at birth.

Sensitivity analysis (Analysis 4.9): no study had good methodology.

Vitamin D deficiency (25-OH vitamin D < 30 nmol/L)

There was no difference in vitamin D deficiency (Analysis 1.3) in infants given vitamin D (RR 0.41, 95% CI 0.16 to 1.05; participants = 122; studies = 2; IÃÂ² = 0%; very low-certainty evidence). We downgraded the certainty of evidence for risk of bias and high level of imprecision. One study (Chandy 2016), in high-risk infants of D3 400 IU/day, reported no difference in vitamin D deficiency (RR 0.41, 95% CI 0.16 to 1.05; participants = 101), whereas the other small study (Moodley 2015), of vitamin D given as a single oral 50,000 IU dose at birth in high-risk infants, reported no events. Neither study had good methodology (Analysis 4.16). Subgroup analyses were not reported as there were insufficient studies.

Nutritional rickets

Two small studies (Greer 1981; Ponnapakkam 2010) in low-risk infants reported no infant with biochemical rickets (Analysis 1.4; Analysis 4.17; participants = 34; studies = 2; very low-certainty evidence). We downgraded the certainty of evidence as there were no events and the analysis was seriously underpowered. Neither study had good methodology (Analysis 4.18).

Another study (Rothberg 1982), reported "no infant had clinical or biochemical sequelae of low serum 25-OH D values during the immediate neonatal period". However, the duration of follow-up was only up to six weeks in this study which was too short for biochemical rickets to develop so the study was not included in this outcome. No study comparison reported radiological rickets.

Adverse effects

A single study (Chandy 2016) in high-risk infants having vitamin D3 400 IU/day reported hypercalcaemia (RR 1.45, 95% CI 0.54 to 3.86; participants = 98; low-certainty evidence). We downgraded the certainty of evidence for risk of bias and imprecision. The study did not have good methodology.

Lowest serum 25-OH vitamin D level up to six months of age

No study reported this outcome.

Serum 25-OH vitamin D level (nmol/L) at latest time reported during treatment to six months of age

The 25-OH vitamin D level was higher in infants receiving vitamin D compared to placebo (Analysis 1.7; MD 22.63 nmol/L, 95% CI 17.05 to 28.21; participants = 334; studies = 6; I^2 = 0%; low-certainty evidence). We downgraded the certainty of evidence due to risk of bias and indirectness as average 25-OH vitamin D levels may not predict deficiency or bone health.

Subgroup analyses:

- Infant risk (Analysis 4.20): 25-OH vitamin D levels were higher in infants receiving vitamin D compared to placebo in high-risk infants (MD 18.24 nmol/L, 95% CI 9.39 to 27.09; participants = 134; studies = 3; I^2 = 0%) and low-risk infants (MD 25.53 nmol/L, 95% CI 18.34 to 32.72; participants = 200; studies = 3; I^2 = 0%). The test for subgroup differences was not significant (P = 0.21, IÃÂ² = 36.2%).
- Season of supplementation (Analysis 4.21): all studies had non-seasonal supplementation.
- D2 versus D3 supplementation (Analysis 4.22): both D2 (MD 33.00 nmol/L, 95% CI 17.27 to 48.73; participants = 50; studies = 2; I^2 = 0%) and D3 (MD 21.14 nmol/L, 95% CI 15.17 to 27.11; participants = 284; studies = 4; I^2 = 0%) supplementation were associated with higher 25-OH vitamin D levels. The test for subgroup differences was not significant (P = 0.17, IÃÂ² = 47.6%).
- Dosage (Analysis 4.23): both a single study (Moodley 2015), giving a single oral vitamin D dose of 50,000 IU at birth (MD 22.75 nmol/L, 95% CI 3.43 to 42.07; participants = 21) and five studies giving 400 IU/day (MD 22.62 nmol/L, 95% CI 16.79 to 28.45; participants = 313; studies = 5; I^2 = 0%) reported increased 25-OH vitamin D levels. The test for subgroup differences was not significant (P = 0.99, IÃÂ² = 0%).
- Duration of supplementation (Analysis 4.24): analysis of increasing duration of supplementation found an increase in 25-OH levels from a single oral dose of vitamin D of 50,000 IU at birth (MD 22.75 nmol/L, 95% CI 3.43 to 42.07; participants = 21); no difference for 1 to 2 months supplementation (MD 30.30 nmol/L, 95% CI -6.51 to 67.11; participants = 12); and an increase for 4 to 6 months supplementation (MD 33.60 nmol/L, 95% CI 16.20 to 51.00; participants = 38); and > 6 months supplementation (MD 20.97 nmol/L, 95% CI 14.69 to 27.24; participants = 263; studies

= 3; I^2 = 0%). However, the test for subgroup differences was not significant (P = 0.58, IÃÂ² = 0%).

- Timing of commencement (Analysis 4.25): both supplementation from birth (MD 20.97 nmol/L, 95% CI 12.90 to 29.04; participants = 160; studies = 3; I^2 = 32%) and 1 month of age (MD 21.23 nmol/L, 95% CI 15.04 to 27.42; participants = 275; studies = 4; I^2 = 0%) increased vitamin 25-OH to a similar extent. The test for subgroup differences was not significant (P = 0.96, IÃÂ² = 0%).

Sensitivity analysis (Analysis 4.26): no study had good methodology.

Fracture (radiologically confirmed)

No study reported this outcome.

Osteomalacia - low bone mineral density reported on x-ray

No study reported this outcome.

Change of standardised growth at latest time measured (change in weight, length and head circumference z score)

No study reported this outcome.

Size at latest time measured

There was no difference in weight (Analysis 1.8; MD 123.63 g, 95% CI -170.02 to 417.28; participants = 143; studies = 2; IÃÂ² = 4%), length (Analysis 1.9; MD 0.73 cm, 95% CI -0.11 to 1.57; participants = 156; studies = 3; IÃÂ² = 55%), or head circumference (Analysis 1.10; MD 0.00 cm, 95% CI -0.60 to 0.60; participants = 105; studies = 1) of infants given vitamin D compared to a placebo group.

Comparison 2: vitamin D given to lactating mothers versus placebo or no treatment

Eight studies contributed to this comparison (Chandy 2016; Naik 2017; Niramitmahapanya 2017; Roth 2016; Rothberg 1982; Thiele 2017; Trivedi 2020; Wheeler 2016), with a total of 1907 mother-infant pairs.

Bone mineral density/content at the end of intervention

No study reported this outcome.

Vitamin D insufficiency (25-OH vitamin D < 50nmol/L)

There was a reduction in vitamin D insufficiency (Analysis 2.1), in infants of mothers given vitamin D (RR 0.47, 95% CI 0.39 to 0.57; participants = 512; studies = 5; IÃÂ² = 79%; low-certainty evidence). We downgraded the certainty of evidence for risk of bias and indirectness as vitamin D insufficiency may not be predictive of bone health, and all studies were in higher-risk populations.

Subgroup analysis

- Infant risk (Analysis 5.1): all studies were in higher-risk populations.
- Season of supplementation (Analysis 5.2): all studies were non-seasonal.
- D2 versus D3 supplementation (Analysis 5.3): all studies used oral D3.
- Dosage (Analysis 5.4): there was a significant effect of maternal dosage with a reduction in infant vitamin D insufficiency for dosages of 400 to 2000 IU/day (RR 0.71, 95% CI 0.49 to 1.03; participants = 186; studies = 2; IÃÂ² = 0%); > 2000 to 4000 IU/day (RR 0.43, 95% CI 0.34 to 0.56; participants = 216; studies = 2; IÃÂ² = 94%); and > 4000 IU/day (RR 0.33, 95% CI 0.20 to 0.53; participants = 110; studies = 1). The test for subgroup differences was significant (P = 0.02, IÃÂ² = 73.4%).
- Duration of supplementation (Analysis 5.5): the relationship between duration of maternal supplementation and infant vitamin D insufficiency is unclear. There was a reduction in infant vitamin D insufficiency with supplementation for < 1 month (RR 0.33, 95% CI 0.20 to 0.53; participants = 110; studies = 1); 1 to 3 months (RR 0.61, 95% CI 0.49 to 0.75; participants = 114; studies = 1); 4 to 6 months (RR 0.28, 95% CI 0.15 to 0.53; participants = 183; studies = 2; IÃÂ² = 91%); and > 6 months (RR 0.66, 95% CI 0.44 to 0.99; participants = 105; studies = 1). The test for subgroup differences was significant (P = 0.02, IÃÂ² = 70.8%), but the trend in effect was not clear from the data.
- Timing of commencement (Analysis 5.6): maternal supplementation from birth was associated with a reduction in infant vitamin D insufficiency (RR 0.45, 95% CI 0.37 to 0.55; participants = 431; studies = 4; IÃÂ² = 85%), but not with supplementation after 1 month age (RR 0.88, 95% CI 0.40 to 1.94; participants = 81; studies = 1). However, the test for subgroup differences was not significant (P = 0.11, IÃÂ² = 61.2%).

Sensitivity analysis (Analysis 5.7): there was a reduction in vitamin D insufficiency in studies of good methodology (RR 0.43, 95% CI 0.34 to 0.56; participants = 216; studies = 2; IÃÂ² = 94%).

Vitamin D deficiency (25-OH vitamin D < 30 nmol/L)

There was a reduction in vitamin D deficiency (Analysis 2.2), in infants of mothers given vitamin D (RR 0.15, 95% CI 0.09 to 0.24; participants = 512; studies = 5; I^2 = 66%; low-certainty evidence). We downgraded the certainty of evidence for risk of bias and indirectness as all studies were in higher-risk populations and none in lower-risk populations.

Subgroup analysis

- Infant risk (Analysis 5.8): all studies were in higher-risk populations.
- Season of supplementation (Analysis 5.9): all studies were non-seasonal.
- D2 versus D3 supplementation (Analysis 5.10): all studies used oral D3.
- Dosage (Analysis 5.11): there was a significant effect of maternal dosage with reductions in infant vitamin D deficiency for dosages of 400 to 2000 IU/day (RR 0.40, 95% CI 0.20 to 0.81; participants = 186; studies = 2; IÃÂ² = 0%); > 2000 to 4000 IU/day (RR 0.43, 95% CI 0.34 to 0.56; participants = 216; studies = 2; IÃÂ² = 94%); and > 4000 IU/day (RR 0.17, 95% CI 0.06 to 0.46; participants = 110; studies = 1). The test for subgroup differences was significant (P = 0.006, IÃÂ² = 80.4%).
- Duration of supplementation (Analysis 5.12): the relationship between duration of maternal supplementation and infant vitamin D deficiency is unclear. There was a reduction in infant vitamin D deficiency with supplementation for < 1 month (RR 0.17, 95% CI 0.06 to 0.46; participants = 110; studies = 1); 1 to 3 months (RR 0.06, 95% CI 0.0.2 to 0.17; participants = 114; studies = 1); and 4 to 6 months (RR 0.15, 95% CI 0.05 to 0.45; participants = 183; studies = 2; IÃÂ²= 59%); and no difference for > 6 months (RR 0.45, 95% CI 0.19 to 1.09; participants = 105; studies = 1).

The test for subgroup differences was significant (P = 0.04, IÃÂ² = 65.1%), but the trend in effect was not clear from the data.

- Timing of commencement (Analysis 5.13): maternal supplementation from birth was associated with a reduction in infant vitamin D deficiency (RR 0.45, 95% CI 0.37 to 0.55; participants = 431; studies = 4; IÃÂ² = 85%), but not supplementation after 1 month age (RR 0.32, 95% CI 0.10 to 1.02; participants = 81; studies = 1). However, the test for subgroup differences was not significant (P = 0.11, IÃÂ² = 61.2%).

Sensitivity analysis (Analysis 5.14): there was a reduction in vitamin D deficiency in studies of good methodology (RR 0.05, 95% CI 0.02 to 0.15; participants = 216; studies = 2; IÃÂ² = 0%).

Nutritional rickets

There was a reduction in biochemical rickets (Analysis 2.3), in infants of mothers given vitamin D (RR 0.06, 95% CI 0.01 to 0.44, 2 studies, 229 participants, IÃÂ² =0%, low-certainty evidence). We downgraded the certainty of evidence for risk of bias and indirectness as all studies were in higher-risk populations.

Subgroup analysis (Analysis 5.15): one study (Naik 2017), in higher-risk infants that supplemented mothers with oral D3 60,000 IU/day for 10 days, reported a reduction in biochemical rickets (RR 0.05, 95% CI 0.00 to 0.84; participants = 115). The other study (Trivedi 2020), in higher-risk infants supplemented mothers with oral D3 60,000 IU postpartum and at 6, 10, and 14 weeks and reported no difference in biochemical rickets (RR 0.16, 95% CI 0.02 to 1.29; participants = 114). However, the test for subgroup differences was not significant (P = 0.51, IÃÂ² = 0%).

Sensitivity analysis (Analysis 5.16): one study of good methodology (Trivedi 2020), reported no difference in biochemical rickets (RR 0.16, 95% CI 0.02 to 1.29; participants = 114).

There was no difference in radiological rickets (Analysis 2.4), in infants of mothers given vitamin D (RR 0.76, 95% CI 0.18 to 3.31; participants = 536; studies = 3; I^2 = 0%, low-certainty evidence). We downgraded the certainty of evidence for indirectness and very serious imprecision. All studies were in higher-risk populations.

Subgroup analyses

- Infant risk (Analysis 5.17): all studies were in high-risk populations.
- Season of supplementation (Analysis 5.18): all studies were non-seasonal.
- D2 versus D3 supplementation (Analysis 5.19): all studies used oral vitamin D3.
- Dosage (Analysis 5.20): there was no difference in radiological rickets in infants of mothers supplemented with > 2000 to 4000 IU/day (RR 0.48, 95% CI 0.05 to 5.18; participants = 421; studies = 2; IÃÂ² = 0%); or > 4000 IU/day (RR 1.05, 95% CI 0.15 to 7.23; participants = 115; studies = 1). The test for subgroup differences was not significant (P = 0.62, IÃÂ² = 0%).
- Duration of supplementation (Analysis 5.21): there was no difference in radiological rickets in infants of mothers supplemented for < 1 month (RR 1.05, 95% CI 0.15 to 7.23; participants = 115; studies = 1); or 4 to 6 months (RR 0.48, 95% CI 0.05 to 5.18; participants = 421; studies = 2; IÃÂ² = 0%). The test for subgroup differences was not significant (P = 0.62, IÃÂ² = 0%).
- Timing of commencement (Analysis 5.22): all studies supplemented mothers from birth.

Sensitivity analysis (Analysis 5.23): there was no difference in radiological rickets in studies of good methodology (RR 0.48, 95% CI 0.05 to 5.18; participants = 421; studies = 2; IÃÂ² = 0%).

Adverse effects

There was no difference in hypercalcaemia (Analysis 2.5) in infants of mothers given vitamin D (RR 1.31, 95% CI 0.51 to 3.32; participants = 557; studies = 3; IÃÂ² = 0%, low-certainty evidence). We downgraded the certainty of evidence for very serious imprecision.

Subgroup analysis (Analysis 5.24): no difference in hypercalcaemia was reported in one study (Chandy 2016), of maternal oral D3 120 000 IU within 7 days of delivery, then 1.5, 2.5 and 3.5 months, then monthly until 9 months (equivalent to D3 890 IU/day) (RR 1.19, 95% CI 0.43 to 3.29; participants = 101); or a study (Roth 2016), of oral D3 4000 IU/day till 26 weeks (RR 1.99, 95% CI 0.18 to 21.75; participants = 371). A study (Wheeler 2016), of oral D3 50 000 IU monthly from 4 weeks to 16 weeks (equivalent to D3 1670 IU/day) reported no infant with hypercalcaemia (n = 85).

Sensitivity analysis (Analysis 5.25): a single study of good methodology (Roth 2016), reported no difference in hypercalcaemia (RR 1.99, 95% CI 0.18 to 21.75; participants = 371).

Lowest serum 25-OH vitamin D level (nmol/L) up to six months of age

No study reported this outcome.

Serum 25-OH vitamin D level (nmol/L) at latest time reported during treatment to six months of age

The 25-OH vitamin D level was higher in infants of mothers receiving vitamin D compared to placebo (Analysis 2.7; (MD 24.60 nmol/L, 95% CI 21.59 to 27.60; participants = 597; studies = 7; I^2 = 64%; low-certainty evidence). We downgraded the certainty of evidence for indirectness as average 25-OH vitamin D levels may not be predictive of bone health and moderate heterogeneity. Inconsistency (heterogeneity) may be explained by differences in dosage (Analysis 5.29).

Subgroup analyses

- Infant risk (Analysis 5.26): 25-OH vitamin D levels were higher in infants receiving vitamin D compared to placebo in high-risk infants (MD 26.87 nmol/L, 95% CI 23.45 to 30.29; participants = 516; studies = 5; I^2 = 55%); and low-risk infants (MD 17.01 nmol/L, 95% CI 10.76 to 23.26; participants = 81; studies = 2; I^2 = 0%). The test for subgroup differences was significant (P = 0.007, IÃÂ² = 86.4%).
- Season of supplementation (Analysis 5.27): all studies were non-seasonal.
- D2 versus D3 supplementation (Analysis 5.28): all studies supplemented mothers with oral D3.
- Dosage (Analysis 5.29): the 25-OH vitamin D level was higher in infants of mothers receiving higher doses of vitamin D. Analysis of studies supplementing mothers with oral D3 400 to 2000 IU/day reported a MD 15.61 nmol/L, 95% CI 9.83 to 21.39; participants = 258; studies = 3; I^2 = 0%; studies with supplements

> 2000 to 4000 IU/day reported a MD 27.58 nmol/L, 95% CI 23.97 to 31.19; participants = 229; studies = 3; I^2 = 35%; and a study with supplements > 4000 IU/day reported a MD 33.65 nmol/L, 95% CI 18.49 to 48.81; participants = 110; studies = 1. The test for subgroup differences was significant (P = 0.001; IÃÂ² = 84.9%).

- Duration of supplementation (Analysis 5.30): the relationship between duration of maternal supplementation and infant 25-OH vitamin D levels is unclear. There was an increase in infant 25-OH vitamin D levels with supplementation for < 1 month (MD 33.65 nmol/L, 95% CI 18.49 to 48.81; participants = 110; studies = 1); 1 to 3 months (MD 17.01 nmol/L, 95% CI 10.76 to 23.26; participants = 81; studies = 2; I^2 = 0%); 4 to 6 months (MD 27.78 nmol/L, 95% CI 24.07 to 31.49; participants = 301; studies = 3; I^2 = 46%); and > 6 months (MD 15.50 nmol/L, 95% CI 4.62 to 26.38; participants = 105; studies = 1). The test for subgroup differences was significant (P = 0.006; IÃÂ² = 76.1%), but the trend in effect was not clear from the data.
- Timing of commencement (Analysis 5.31): analysis found that studies supplementing mothers from birth increased the infant 25-OH vitamin D level (MD 24.85 nmol/L, 95% CI 21.82 to 27.88; participants = 512; studies = 6; I^2 = 67%), whereas a single study supplementing mothers of infants after 1 month of age reported no difference (MD 11.42 nmol/L, 95% CI -10.27 to 33.11; participants = 85). However, the test for subgroup differences was not significant (P = 0.23; IÃÂ² = 30.8%).

Sensitivity analysis (Analysis 5.32): analysis of studies of good methodology found an increase in 25-OH vitamin D level (MD 28.28 nmol/L, 95% CI 24.51 to 32.04; participants = 216; studies = 2; I^2 = 32%).

Fracture (radiologically confirmed)

No study reported this outcome.

Osteomalacia - low bone mineral density reported on x-ray

No study reported this outcome.

Change of standardised growth at latest time measured (change in weight, length and head circumference z score)

A single study (Roth 2016), reported no difference in change of standardised growth at latest time measured for weight (Analysis 2.8; MD 0.07, 95% CI -0.12 to 0.26; participants = 461); length (Analysis 2.9; MD 0.12, 95% CI -0.07 to 0.31; participants = 461); and head circumference (Analysis 2.10; MD 0.00, 95% CI -0.17 to 0.17; participants = 461) in infants of mothers supplemented with vitamin D.

Size at latest time measured

There was no difference in the weight (Analysis 2.11, MD 30.16 g, 95% CI -134.51 to 194.84; participants = 567; studies = 2; IÃÂ² = 0%), length (Analysis 2.12; MD 0.43 cm, 95% CI -0.02 to 0.89; participants = 568; studies = 2; IÃÂ² = 58%) and head circumference (Analysis 2.13; MD -0.10 cm, 95% CI -0.33 to 0.14; participants = 567; studies = 2; IÃÂ²= 47%) in infants of mothers supplemented with vitamin D.

Comparison 3: vitamin D given to infants versus vitamin D given to lactating mothers

Six studies contributed to this comparison (Ala-Houhala 1985; Ala-Houhala 1986; Chandy 2016; Hollis 2015; Rothberg 1982; Wagner 2006), with a total of 801 mother-infant pairs.

Bone mineral density/content at the end of intervention

No study reported this outcome.

Vitamin D insufficiency (25-OH vitamin D < 50nmol/L)

There was a reduction in vitamin D insufficiency in infants receiving vitamin D supplements compared to infants of mothers receiving vitamin D supplements (Analysis 3.1; RR 0.61, 95% CI 0.40 to 0.94; participants = 334; studies = 4; IÃÂ² = 69%; very low-level certainty evidence). We downgraded the certainty of evidence for risk of bias, inconsistency and indirectness as vitamin D insufficiency may not predict infant bone health.

Subgroup analysis (Analysis 6.1): there was a significant effect of maternal dosage with a reduction in infant vitamin D insufficiency for infant 400 IU/day versus maternal 400 to 2000 IU/day (RR 0.06, 95% CI 0.01 to 0.37; participants = 141; studies = 2; IÃÂ² = 30%); but no difference for infant 400 IU/day versus maternal > 4000 IU/day (RR 1.02, 95% CI 0.15 to 6.95; participants = 95; studies = 1); and for infant 400 IU/day versus maternal D3 120 000 IU at delivery, 1.5, 2.5 and 3.5 months, then monthly till 9 months (RR 1.03, 95% CI 0.63 to 1.68; participants = 98; studies = 1). The test for subgroup differences was significant (P = 0.01, IÃÂ² = 77.5%).

Sensitivity analysis (Analysis 6.2): no study had good methodology.

Vitamin D deficiency (25-OH vitamin D < 30 nmol/L)

There was a reduction in vitamin D deficiency in infants receiving vitamin D supplements compared to infants of mothers receiving vitamin D supplements (Analysis 3.1; RR 0.61, 95% CI 0.40 to 0.94; participants = 334; studies = 4; IÃÂ² = 69%; very low-certainty evidence). We downgraded the certainty of evidence for risk of bias, inconsistency and imprecision.

Subgroup analysis (Analysis 6.3): there was a significant effect the comparison of infant dosage versus maternal dosage with a reduction in infant vitamin D insufficiency for infant dosage of 400 IU/day versus maternal dosage of 400 to 2000 IU/day (RR 0.06, 95% CI 0.01 to 0.37; participants = 141; studies = 2; IÃÂ² = 30%), but no difference for infant dosage of 400 IU/day versus maternal dosage > 4000 IU/day (RR 1.02, 95% CI 0.15 to 6.95; participants = 95; studies = 1), and for infant dosage of 400 IU/day versus maternal dosage of D3 120 000 IU at delivery, 1.5, 2.5 and 3.5 months, then monthly till 9 months (RR 1.03, 95% CI 0.63 to 1.68; participants = 98; studies = 1). The test for subgroup differences was significant (P = 0.03, IÃÂ² = 70.7%).

Sensitivity analysis (Analysis 6.4): no study had good methodology.

Nutritional rickets

A single study (Ala-Houhala 1985), in higher-risk infants reported no cases of biochemical rickets in either group (Analysis 3.3; Analysis 6.5; participants = 92; very low-certainty evidence).

Adverse effects

A single study (Chandy 2016), reported no difference in hypercalcaemia (Analysis 3.4; Analysis 6.6; RR 1.22, 95% CI 0.48 to 3.09; participants = 97; very low-certainty evidence).

Lowest serum 25-OH vitamin D level (nmol/L) up to six months of age

No study reported this outcome.

Serum 25-OH vitamin D level at latest time reported during treatment to six months of age (nmol/L)

The 25-OH- vitamin D level (Analysis 3.5), was higher in infants receiving vitamin D supplements compared to infants of mothers receiving vitamin D supplements (MD 14.35 nmol/L, 95% CI 9.64 to 19.06; participants = 269; studies = 4; IÃÂ² = 90%; very low-certainty evidence). We downgraded the certainty of evidence for risk of bias, inconsistency and indirectness. However, the inconsistency (heterogeneity) may be explained by differences in maternal vitamin D dosage.

Subgroup analysis (Analysis 6.7): there was a significant effect of maternal dosage on infant 25-OH vitamin D levels. All trials had an infant dose of 400 IU/day but maternal dosage varied. The 25-OH vitamin D levels were higher for the infant group for comparisons of infant 400 IU/day versus maternal 400 to 2000 IU/day (MD 36.80 nmol/L, 95% CI 26.78 to 46.82; participants = 47; studies = 1); infant 400 IU/day versus maternal > 2000 to 4000 IU/day (MD 13.50 nmol/L, 95% CI 6.45 to 20.55; participants = 30; studies = 1); but not for comparisons of infant 400 IU/day versus maternal > 4000 IU/day (MD 0.60 nmol/L, 95% CI -13.48 to 14.68; participants = 95; studies = 1); and infant 400 IU/day versus maternal D3 120 000 IU at delivery, 1.5, 2.5 and 3.5 months, then monthly till 9 months (MD 0.50 nmol/L, 95% CI -9.54 to 10.54; participants = 97; studies = 1). The test for subgroup differences was significant (P < 0.00001, IÃÂ² = 90.1%).

Sensitivity analysis (Analysis 6.8): no study had good methodology.

Fracture (radiologically confirmed)

No study reported this outcome.

Osteomalacia - low bone mineral density reported on x-ray

No study reported this outcome.

Change of standardised growth at latest time measured (change in weight, length and head circumference z score)

No study reported this outcome.

Size at latest time measured

There was no difference in weight (Analysis 3.6; MD 127.43 g, 95% CI -107.78 to 362.64; participants = 125; studies = 2; IÃÂ² = 79%); or length (Analysis 3.7; MD -0.67 cm, 95% CI -1.60 to 0.25; participants = 125; studies = 2; IÃÂ² = 89%). However, there was an increase in head circumference (MD 0.58 cm, 95% CI 0.07 to 1.08; participants = 125; studies = 2; IÃÂ² = 0%) in infants receiving vitamin D supplements compared to infants of mothers receiving vitamin D supplements.

Comparison 4: vitamin D given to infants versus periods of infant sun exposure

No study reported this comparison.

DISCUSSION

Summary of main results

Vitamin D supplementation given to infants compared with placebo/no intervention (9 studies, 743 mother-infant pairs)

Vitamin D supplementation of infants with 400 IU/day increased 25-OH vitamin D levels by an average of 22.63 nmol/L (95% CI 17.05 to 28.21), and reduced the incidence of vitamin D insufficiency (25-OH vitamin D < 50 nmol/L) by 23% (95% CI 33%, 14%). The effect was found in subgroup analysis of studies of infants at higher and lower risk of vitamin D deficiency. However, there was insufficient evidence to determine if infant vitamin D supplementation reduces the risk of vitamin D deficiency (25-OH vitamin D < 30 nmol/L) up till six months of age, affects bone mineral content, the incidence of biochemical or radiological rickets, or growth. We are very uncertain about adverse effects, including the risk of hypercalcaemia. The certainly of evidence for all outcomes was graded as low or very low. There were no studies of higher doses (> 400 IU/day) of infant vitamin D compared to placebo.

Vitamin D supplementation given to lactating mothers compared with placebo/no intervention (8 studies, 1907 mother-infant pairs)

Vitamin D supplementation of lactating mothers increased infant 25-OH vitamin D levels by an average of 24.60 nmol/L (95% CI 21.59 to 27.60), reduced the incidence of vitamin D insufficiency (25-OH vitamin D < 50 nmol/L) by 35% (95% CI 42%, 28%), and vitamin D deficiency (25-OH vitamin D < 30 nmol/L) by 38% (95% CI 44%, 32%). There was low-certainty evidence that vitamin D supplementation of lactating mothers reduced the incidence of biochemical rickets by 14% (95% CI 0.21%, 7%). The two studies that reported biochemical rickets used maternal dosages of oral D3 60,000 IU/day for 10 days (Naik 2017), and oral D3 60,000 IU postpartum and at 6, 10, and 14 weeks (Trivedi 2020). However, infant bone mineral content was not reported and there was insufficient evidence to determine if maternal vitamin D supplementation has an effect on radiological rickets. All studies enrolled patient populations at high risk of vitamin D deficiency. In subgroup analyses, there were significant associations between maternal dose of vitamin D and infant vitamin D insufficiency, vitamin D deficiency and 25-OH vitamin D level. We are uncertain of the effects of vitamin D supplementation of lactating mothers on infant growth and adverse effects including hypercalcaemia.

Vitamin D supplementation given to infants compared with vitamin D supplementation given to lactating mothers (6 studies, 801 mother-infant pairs)

Vitamin D supplementation of infants compared to vitamin D supplementation of lactating mothers increased the infant 25-OH vitamin D level by an average difference of 14.35 nmol/L (95% CI 9.64 to 19.06), reduced the incidence of vitamin D insufficiency (25-OH vitamin D < 50 nmol/L) by 9% (95% CI 17%, 1%), and vitamin D deficiency (25-OH vitamin D < 30 nmol/L) by 10% (95% CI 16%, 3%). However, infant bone mineral content and radiological rickets were not reported. There was insufficient evidence to determine if maternal vitamin D supplementation has an effect on infant biochemical rickets. All studies enrolled patient populations at high risk of vitamin D deficiency. All studies compared an infant dose of vitamin D 400 IU/day with maternal vitamin D doses ranging from 400 IU/day to > 4000 IU/day. In subgroup analysis, there was

a significant association between maternal dose of vitamin D and infant 25-OH vitamin D level with trials supplementing mothers with < 4000 IU/day reporting a lower infant 25-OH vitamin level. We are also very uncertain about adverse effects, including the risk of hypercalcaemia.

Overall completeness and applicability of evidence

Our search was comprehensive, using Cochrane methods. However, a number of studies that compared different doses of vitamin D given either to infants or lactating mothers were ineligible. Studies limited to vitamin D supplementation of pregnant women were also excluded.

Although most of the studies had only exclusively breastfed infants, we included studies where a majority of infants were breastfed. This is reflective of the real-world situation as globally the exclusive breastfeeding rate of infants under six months is only 40% (https://www.who.int/features/factfiles/breastfeeding/en/ updated August 2017).

We prespecified criteria for studies of populations at high risk of vitamin D deficiency which included pigmentation, covering or avoidance of sun exposure, and/or latitude (above 52ÃÂ°N or below 52ÃÂ°S is associated with insufficient UV intensity most of the year), and included studies with documented vitamin D insufficiency or deficiency at baseline as high risk. Ten studies were considered to be in high-risk populations. All studies comparing maternal vitamin D supplementation to placebo were in high-risk populations. Subgroup analysis for population risk was possible for infant vitamin D supplementation of infants compared to placebo, which found a significant a reduction in incidence of vitamin D insufficiency for studies enrolling both higher and lower-risk infants, and significantly increased 25-OH vitamin D levels in both subgroups. However, only studies enrolling higher-risk populations reported vitamin D deficiency.

The majority of studies used an infant dose of 400 IU/day of vitamin D3. A single small study (Ponnapakkam 2010), reported a lower dose of vitamin D of 200 IU/day. A single high vitamin D oral dose of 50,000 IU at birth was assessed by a single small study (Moodley 2015), which reported increased 25-OH vitamin D levels, but was insufficiently powered to assess vitamin D insufficiency, deficiency or adverse effects. Maternal vitamin D doses ranged from 400 IU/day to 6000 IU/day. Maternal doses < 4000 IU/day were associated with lower infant 25-OH vitamin D levels than infant doses of 400 IU/day. Maternal dosages of 6000 IU/day (Hollis 2015), and maternal intermittent high doses (120 000 IU at delivery, 1.5, 2.5 and 3.5 months, then monthly till 9 months (Chandy 2016), were associated with similar infant 25-OH vitamin D levels, and a similar incidence of vitamin D insufficiency and vitamin D deficiency compared to infant doses of 400 IU/day.

A minority of studies have reported bone health outcomes including bone mineral content, and biochemical and/or radiological rickets. The evidence is insufficient to determine if infant vitamin D supplementation improves bone mineral content or reduces the incidence of nutritional rickets. All studies of maternal supplementation compared to placebo were in high-risk populations. A reduction of biochemical but not radiological rickets was found in analysis of two studies of high-dose maternal D3 supplementation (Naik 2017; Trivedi 2020). Despite the analysis of infant oral D3 400 IU/day finding higher infant 25-OH vitamin D levels compared to infants of mothers supplemented with vitamin D, there was insufficient evidence to determine if infant supplementation improves bone health compared to maternal supplementation.

There were few studies reporting vitamin D deficiency (25-OH vitamin D < 30 nmol/L). Most studies reported vitamin D insufficiency (25-OH vitamin D < 50 nmol/L) so we were not able to report vitamin D deficiency consistently. This problem has also resulted in inconsistent reporting of effects of interventions in the different comparison groups.

Quality of the evidence

The primary focus of this review is whether vitamin D supplementation for term breastfed infants prevents vitamin D deficiency and improves bone health. Evidence that relates to surrogate measures has accordingly been downgraded as being indirect. The certainty of evidence for use of infant or maternal vitamin D supplementation for prevention of vitamin D deficiency (25-OH vitamin D < 30 nmol/L) or improving bone health was graded as low to very low. There was a lack of studies reporting vitamin D deficiency (25-OH vitamin D < 30 nmol/L) and measures of bone health, including bone mineral content, nutritional rickets (biochemical or radiological, or both) or fractures, which means that analyses lacked precision or data were not available. The certainty of evidence for infant vitamin D insufficiency and 25-OH vitamin D level was downgraded for indirectness as these measures may not be adequately predictive of vitamin D deficiency and bone health (Roth 2018). low-certainty evidence suggests infant and maternal vitamin D supplementation increase infant 25-OH vitamin D levels and reduce the incidence of vitamin D insufficiency in high-risk infants. Very low-certainty evidence suggests infant supplementation when compared to maternal supplementation may be more effective at preventing vitamin D insufficiency and vitamin D deficiency, although there was a significant effect of maternal dosage in subgroup analysis. There was very low-certainty of evidence for the incidence of adverse effects, including hypercalcaemia and hypercalciuria from either infant or maternal supplementation.

Potential biases in the review process

The influence of selective reporting and publication bias on this review are difficult to assess due to the limited number of studies in each analysis, and the majority of outcomes were only reported by a limited number of studies. The extensive search including trial registries and expert informants reduced the risk of publication bias. This review followed the methods of the Cochrane Collaboration and its Neonatal Review Group. All three authors contributed and cross-checked the review independently. There are no conflicts of interest to declare.

Agreements and disagreements with other studies or reviews

Two Cochrane Reviews assessed the effect of vitamin D supplementation for women during pregnancy (Palacios 2019a), and dosage regimens of vitamin D supplementation for women during pregnancy (Palacios 2019b). Maternal vitamin D supplementation with or without calcium supplementation increased maternal vitamin D concentration at term. No trial reported any case of hypercalcaemia. However, given the scarcity of data in general for maternal adverse events, no firm conclusions

could be drawn (Palacios 2019a). Comparing maternal doses during pregnancy of vitamin D 601 IU/d or higher versus 600 IU/d or lower, as well as maternal doses of vitamin D 4000 IU/d or more versus 3999 IU/d or less, both maternal and cord blood 25-OH D concentration at term was higher for each of the higher-dose comparisons (Palacios 2019b). However, adverse effects on infants including hyper- or hypocalcaemia and hypercalciuria were not reported.

A Cochrane protocol assessing the effects of vitamin D supplementation for prevention of vitamin D deficiency in preterm and low birth weight infants has been published (Pharange 2015).

The Global Consensus Recommendations on Prevention and Management of Nutritional Rickets recommend 400 IU/day is adequate to prevent rickets and is recommended for all infants from birth to 12 months of age, independent of their mode of feeding (Munns 2016). The US Dietary Guidelines Advisory Committee 2020 Advisory Report also recommends a similar dose during infancy (US Dietary Guidelines Advisory Committee 2020). This review does not provide strong support to routine supplementation of infants or their mothers in lower-risk populations.

AUTHORS' CONCLUSIONS

Implications for practice

For breastfed infants, low to very low-certainty evidence found vitamin D supplementation 400 IU/day for up to 6 months increases 25-OH vitamin D levels and reduces the incidence of vitamin D insufficiency, but there was insufficient evidence to assess its effect on vitamin D deficiency and bone health (biochemical or radiological rickets, or bone mineral density). There were no studies of higher doses of infant vitamin D compared to placebo.

For infants at higher risk of vitamin D deficiency who are breastfeeding, low to very low-certainty evidence suggests maternal vitamin D supplementation reduced the incidence of vitamin D insufficiency and vitamin D deficiency. There is very low-certainty evidence that maternal supplementation reduces biochemical rickets. There is insufficient evidence to determine if maternal vitamin D supplementation has an effect on radiological rickets.

Low to very low-certainty evidence in populations at higher risk of vitamin D deficiency found vitamin D supplementation of infants leads to greater increases in infant 25-OH vitamin D levels, reductions in the incidence of vitamin D insufficiency and vitamin D deficiency compared to vitamin D supplementation of lactating mothers. However, there is currently no evidence of an effect on markers of bone health. Higher maternal doses (vitamin D3 > 4000 IU/day) resulted in similar infant 25-OH vitamin D levels as for infants given 400 IU/day.

There is currently insufficient evidence to recommend routine supplementation of vitamin D for breastfeeding mothers or their infants in populations at lower risk of vitamin D deficiency. In populations at high risk of vitamin D deficiency, vitamin D 400 IU per day given to the infant, or higher doses given to the breastfeeding mother, may prevent vitamin D deficiency, although effects on bone health are unclear.

Implications for research

There is a need for adequately powered clinical trials of vitamin D supplementation in breastfeeding infants or lactating mothers that report the incidence of vitamin D deficiency and longer-term markers of bone health. The ongoing studies identified in this review do not appear to address these outcomes as they do not propose to evaluate the effects of vitamin D supplementation on bone health. Adverse effects, including vitamin D excess, vitamin D toxicity, hypercalcaemia and hypercalciuria, should be reported.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ala-Houhala 1985

Study characteristics	
Methods	3-arm, randomised controlled study Setting: Finland (61ÃÂ°N) during winter and summer months
Participants	92 infant-mother pairs Infant: healthy term breastfed infants Mother: half of the mothers had vitamin D supplementation (500 IU per day) during pregnancy (varying duration from full pregnancy and from mid trimester). Mother-infant pairs that failed to exclusively breastfeed were excluded.
Interventions	Group 1: mothers given oral vitamin D 1000 IU per day from birth till 20 weeks, infants not supplemented (n = 32) Group 2: infants given oral vitamin D 400 IU per day from birth till 20 weeks (n = 31)

Ala-Houhala 1985 *(Continued)*

	Group 3: infants given oral vitamin D 1000 IU per day from birth till 20 weeks (n = 29)
Outcomes	• Serum 25-OH vitamin D (mother and infant) at 0, 8 and 20 weeks • Serum calcium (mother and infant) at 0, 8 and 20 weeks • Serum magnesium (mother and infant) at 0, 8 and 20 weeks • Alkaline phosphatase (mother and infant) at 0, 8 and 20 weeks
Notes	Data from a pilot study reported in the same report not included. Data for winter groups at 8 weeks only extractable from report Correspondence to Dr M Ala-Houhala, Department of Clinical Sciences, University of Tampere, Teiskontic 35, SF-33520 Tampere, Finland Dr Ala-Houhala is no longer at University of Tampere (email correspondence). Trial registration not found.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Reported as (quote:) "randomly allocated" without further description
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded as no placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. However, all outcomes were unlikely to affected by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 mother-infant pairs were excluded from analysis because of failure to completely breastfeed. It was not known which group they belonged to.
Selective reporting (reporting bias)	High risk	No protocol available. Unclear primary outcome. Number of infants with vitamin D deficiency was reported only for Group 1.
Other bias	Unclear risk	Baseline characteristics not reported

Ala-Houhala 1986

Study characteristics

Methods	3-arm quasi-randomised controlled study Setting: Finland (61ÃÂ°N) during winter months
Participants	49 infant-mother pairs Infant: term, healthy, breastfeeding

Ala-Houhala 1986 *(Continued)*

	Mother: healthy women; some mothers received vitamin D during pregnancy 500 IU either throughout pregnancy (n = 8) or during 2nd trimester (n = 8).
Interventions	Group 1: mothers given oral vitamin D3 2000 IU per day for 15 weeks; infants not supplemented (n = 17) Group 2: mothers given oral vitamin D3 1000 IU per day for 15 weeks; infants not supplemented (n = 16) Group 3: mothers not supplemented, infants given oral vitamin D2 400 IU per day for 15 weeks (n = 16)
Outcomes	• Maternal and infant serum concentrations of vitamin D metabolites including 25-OH vitamin D, 24.25-OH_2 D and 1alpha, 25-OH_2 D at birth, 8 weeks and 15 weeks • Maternal and infant serum minerals (calcium, ionised calcium, and inorganic phosphorus), albumin, parathyroid hormone, and alkaline phosphatase at birth, 8 weeks and 15 weeks
Notes	Correspondence to Dr M Ala-Houhala, Department of Clinical Sciences, University of Tampere, Teiskontic 35, SF-33520 Tampere, Finland Dr Ala-Houhala is no longer at University of Tampere (email correspondence). Trial registration not found.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects divided in succession into three groups". However, the method was not described.
Allocation concealment (selection bias)	Unclear risk	Method of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded as no placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. However all outcomes were unlikely to affected by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether all participants completed study
Selective reporting (reporting bias)	Unclear risk	Protocol not available. Primary outcomes unclear
Other bias	Unclear risk	Baseline characteristics not reported

Alonso 2011

Study characteristics

Methods	Parallel-group, randomised controlled trial Setting: Spain (43ÃÂ°N), all year
Participants	23 exclusively breastfed infants

Alonso 2011 *(Continued)*

	Inclusion criteria: term healthy infants in the first 15 days of life **Exclusion criteria**: chronic disease, use of medications known to affect vitamin D metabolism, refusal to participate, prematurity, dark skin pigmentation, sunlight exclusion for cultural or religious reasons, breastfeeding by vegetarian mothers
Interventions	Intervention: infant oral vitamin D 402 IU per day (67 IU cholecalciferol per drop) from 1 to 12 months of age (n = 10) Control: no intervention (n = 13)
Outcomes	• Serum 25-OH vitamin D level at 3, 6 and 12 months (ng/mL) • Serum PTH level at 3, 6 and 12 months • Number of participants with vitamin D deficiency (defined as 25-OH vitamin D < 11 ng/mL)
Notes	The study had a total of 88 mother-infant pairs. Only the data for the 23 exclusively breastfed infants were used. Trial registration not found.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used computer-generated sequence (Epi Dat 3.1)
Allocation concealment (selection bias)	Low risk	Phone call assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded as no control group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No control group. However all outcomes were unlikely to affected by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	The intervention group had more dropouts by 12 months than control group (37.5% compared to 20%). Reasons for dropouts included non-compliance and biochemical alteration.
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable
Other bias	Low risk	Groups similar at baseline

Chandy 2016

Study characteristics

Methods	3-arm randomised controlled trial Setting: India (26ÃÂ°N), all year
Participants	230 mother-infant pairs

Chandy 2016 *(Continued)*

	Inclusion criteria: mothers with healthy infants who intend to exclusively breastfeed for the first 6 months **Exclusion criteria**: infant birth weight less than 2 kg, sick neonate admitted to the intensive care unit, mother or infant on treatment with anticonvulsants or antitubercular drugs and mothers who had received any vitamin D other than the 10 µg present in Ca tablets
Interventions	Group 1: mothers given single oral vitamin D3 3000 µg (120,000 IU) within 7 days of delivery, and then 3000 µg at 1.5, 2.5 andÃÂ 3.5 months, and then oral vitamin D3 3000 µg monthly up until 9 months ÃÂ Infants were given placebo syrup (n = 74). Group 2: infants given oral vitamin D3 10 µg (400 IU) daily for 9 months. Mothers received placebo sachets (n = 78). Group 3: mothers and infants given placebo (n = 78) Co–intervention for all 3 groups: daily sun exposure with 15-minute traditional massage daily. All mothers were given 500 mg of elemental Ca daily and instructions about dietary sources of calcium.
Outcomes	• Infant serum 25-OH vitamin D at 3ÃÂ·5 months • Infant serum Ca, P, alkaline phosphatase and plasma PTH at 3.5 months of age • Infant anthropometry including weight, length, head circumference and maximum diameter of the anterior fontanelle measured at 3.5, 6 and 9 months • Number of days the baby suffered diarrhoeal or respiratory morbidity within 9 months of life • Mother’s serum 25-OH vitamin D and calciuria at 3.5 months • Infant's number of teeth at 9 months
Notes	Clinical trial registration: CTRI/2012/09/002958 Mothers had vitamin D 25-OH levels that averaged in the deficiency range (30 nmol/L) at baseline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation used
Allocation concealment (selection bias)	Unclear risk	Not described. Quote: “Allocation was done by one research staff who supervised medication distribution”.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo used for infants and mothers were in the similar form as the intervention (syrup and sachet respectively).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo used for infants and mothers were in the similar form as the intervention (syrup and sachet respectively).
Incomplete outcome data (attrition bias) All outcomes	High risk	High number of attrition in all groups but they were balanced (approximately 30% to 40% dropouts per group). Dropouts were excluded from analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available. Duration of intervention was 9 months, but the primary outcomes were measured at 3.5 months only.
Other bias	Low risk	Groups similar at baseline

Greer 1981

Study characteristics	
Methods	Parallel-group, randomised controlled trial Setting: USA (39ÃÂ°N) during summer and winter months
Participants	18 breast-fed infants **Inclusion criteria**: term, healthy exclusively breast-fed infants between 2 to 3 weeks of life **Exclusion criteria**: major congenital anomalies, bone disorders, and gastrointestinal disease
Interventions	Intervention: oral vitamin D2 (ergocalciferol) (suspended in propylene glycol) 400 IU per day until 12 weeks of life (n = 9) Placebo:Ã Â placebo (propylene glycol) once a day until 12 weeks of life (n = 9)
Outcomes	• Bone mineral analysis – one-third distal radius and ulna, left hand at 3, 6 and 12 weeks • Serum calcium, magnesium, phosphate, ALP, PTH, calcitonin at 3, 6 and 12 weeks • Serum 25-OH vitamin D at 3, 6 and 12 weeks • Breastmilk for Ca, Mg and PO4 at 3, 6 and 12 weeks • Length, weight and head circumference at 3, 6 and 12, 26 and 52 weeks
Notes	Trial registration not found.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported (quote:) "divided randomly into two groups"'. However, the method was not described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	(Quote:) “Double blind” fashion. The intervention was prepared in the same solution as the placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	(Quote:) “Double blind” fashion. The intervention was prepared in the same solution as the placebo. Blinding revealed at 26 weeks
Incomplete outcome data (attrition bias) All outcomes	Low risk	None reported
Selective reporting (reporting bias)	Unclear risk	Protocol not available. Length was reported completely but weight and head circumference were not reported other than (quote:) “normal”.
Other bias	Unclear risk	Baseline characteristics not reported

Greer 1989

Study characteristics	
Methods	Parallel-group, randomised controlled trial Setting: USA (43ÃÂ°N), all year
Participants	46 breast-fed infants **Inclusion criteria**: term, healthy,ÃÂ breast-fed **Exclusion criteria**: major congenital anomalies, neurologic disorders, and gastrointestinal disease
Interventions	Intervention: oral vitamin D2 (ergocalciferol) (suspended in propylene glycol) 400 IU per day for 6 months (n = 22) Control: placebo (oral propylene glycol) once a day for 6 monthsÃ Â (n = 24)ÃÂ
Outcomes	• Serum calcium, phosphorus, PTH, 25-OH vitamin D2, 25-OH vitamin D3, and 1,25-OH_2 D concentrations at birth (cord blood) and at 1.5, 3, and 6 months of age • Weight and length at 1.5, 3, and 6 months of age • Bone mineral content and bone width at 1.5, 3, and 6 months of age
Notes	An additional 12 full-term, healthy, exclusively formula-fed infants recruited as a comparison group was not included. Trial registration not found.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described. The comparison group separate from the randomisation was not included.
Allocation concealment (selection bias)	Unclear risk	Method of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The intervention was prepared in the same solution as the placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The intervention was prepared in the same solution as the placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Both groups had an equal number of dropouts because they did not exclusively breastfeed. These were excluded from analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	Groups similar at baseline

Hollis 2015

Study characteristics	
Methods	Parallel-group, randomised controlled trial Setting: 2 cities in USA (33ÃÂºN and 43ÃÂºN), all year
Participants	334 infant-mother pairs **Inclusion criteria**: exclusively breastfeeding mothers and their singleton infants receiving no other form of nutrition than human milk at the time of study entry within 4 to 6 weeks postpartum, if they planned to continue exclusive/full breastfeeding for the next 6 months. Infants must be > 35 weeks' gestation and healthy. **Exclusion criteria**: mothers with pre-existing type I or II diabetes, hypertension, parathyroid disease, and uncontrolled thyroid disease; infants below 35 weeks' gestation, with a history of > 72 hours in the NICU; any inborn error of metabolism; history of congenital anomalies; those who chose to combination feed after enrolment and before the 4-month study visit were excluded from the study.
Interventions	Intervention: oral vitamin D3 400 IU per day given to infants for 6 months. Placebo to mothers (n = 169) Control: oral vitamin D3 6000 IU per day given to mothers for 6 months. Placebo to infants (n = 165) Co-intervention: mothers in both groups received a prenatal vitamin containing 400 IU vitamin D3 per day.
Outcomes	• Maternal and infant total circulating 25-OH vitamin D (ng/mL) at 4 and 7 months postpartum • Number of women and infants with a concentration of 25-OH vitamin D of at least 50 nmol/L (20 ng/mL) at 7 months' postpartum • Maternal and Infant intact parathyroid hormone (pg/mL), total serum calcium (mg/dL), total serum phosphorus (mg/dL), and total serum creatinine (mg/dL). • Infant current weight, length, head circumference, and fontanelle area • Maternal and infant urinary calcium to creatinine ratio Definition of vitamin D deficiency: 25-OH vitaminD < 50 nmol/L or < 20 ng/mL
Notes	It was initially a 3-arm trial (the 3rd arm: Mother: 2400 IU (2000 vitamin D3 per day and 1 prenatal dose containing 400 IU vitamin D3) Infant: placebo for 6 months) but this arm was stopped early by the Data and Safety Monitoring Committee due to safety concerns for the infants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence used. Quote: "Mothers were randomized to 1 of the 3 treatment groups using Proc Plan in SAS".
Allocation concealment (selection bias)	Low risk	Centralised computer allocation used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Investigators, study team,and subject remained blinded to treatment assignment." Placebo used was identical in appearance and taste to the vitamin D3 supplements used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Investigators, study team,and subject remained blinded to treatment assignment." Placebo used was identical in appearance and taste to the vitamin D3 supplements used.

Hollis 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	One arm with 55 participants was stopped early due to safety concerns in infants and was excluded from analysis.
Selective reporting (reporting bias)	Low risk	Protocol available. All outcomes specified in the protocol were reported.
Other bias	Low risk	Groups similar at baseline

Madar 2009

Study characteristics	
Methods	Cluster-randomised controlled trial Setting: Norway (60ÃÂ°N), all year
Participants	66 infants (24 exclusively breastfed) **Inclusion criteria**: 6-week-old infants with immigrant background from Pakistan, Turkey and Somalia
Interventions	Intervention: 5 drops orally 10 microgram (400 IU) vitamin D2 per day + brochure on vitamin D and method of administration for 7 weeks (n = 11) Control: usual care i.e. oral information about vitamin D and recommendation of vitamin D supplementation to the infants for 7 weeks (n = 13)
Outcomes	1. Serum 25-OH vitamin D (total) concentrations at baseline and at 7 weeks' post-intervention 2. Serum 25-OH vitamin D < 50 nmol/L at baseline and at 7 weeks' post-intervention 3. Serum 25-OH vitamin D2 at baseline and at 7 weeks post-intervention 4. Serum 25-OH vitamin D3 at baseline and at 7 weeks post-intervention
Notes	Breastfeeding was not an inclusion criterion. However, a subgroup analysis for exclusively breastfed infants was conducted. Trial registration not found. Intraclass correlation coefficient for vitamin D level reported as 0.72 (Major 2013): Design effect = 1+(3-1)*0.72 = 2.26

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Clinics with similar number of children were randomly paired. Within each pair, the names of both child health clinics were placed in a box and one was drawn by an independent person. The clinic drawn was allocated to the intervention group.
Allocation concealment (selection bias)	High risk	After clinic assignment, individual consent obtained from potential participants at each clinic (44% declined to participate)
Blinding of participants and personnel (performance bias)	Low risk	No placebo used. However, all outcomes were not likely influenced by knowledge of the intervention.

Madar 2009 *(Continued)*

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Preparation of the blood samples and laboratory analysis were conducted at the clinic, so unlikely they were blinded.Ã Â However,Ã Â the statistician conducting the analysis was blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Excluded 4/26 from the intervention group and 11/40 from the control group who didn't complete the study from analysis (23% excluded)
Selective reporting (reporting bias)	Unclear risk	Protocol not available. Outcomes were not completely reported for the subgroup of exclusively breastfed infants.
Other bias	High risk	Subgroup analysis was not planned. More infants taking supplements at baseline in the control group and fewer infants exclusively breastfed

Moodley 2015

Study characteristics	
Methods	Parallel-group randomised controlled trial Setting: Mexico (33ÃÂ°N), all year
Participants	51 infants **Inclusion criteria**: healthy infants born to women ≥ 18 years of age at Tijuana General Hospital, Mexico were enrolled within 24 hours after birth and prior to routine BCG vaccine administration. Intention to breast feed was recorded. **Exclusion criteria**: preterm (< 37 weeks' gestation), had low birth weight (< 2500 g) or had received vitamin D supplementation, mothers had active or recent (within 1 year) tuberculosis disease, HIV infection, maternal fever, or maternal use of vitamin D supplements, steroids or immune-regulatory medications All infants were breast-fed at birth.
Interventions	Intervention: single dose of oral vitamin D3 50,000 IU, given as 0.7 mL of liquid at birth (n = 27) Control: single dose ofÃÂ placebo, given as 0.7 mL of medium chain triglycerides at birth (n = 22)
Outcomes	• Infant serum 25-OH vitamin D level at baseline, 2 months and 6 months • Number of infants with vitamin D deficiency (i.e. 25-OH vitamin D < 15 ng/mL) at baseline, 2 months and 6 months • Number of infants with vitamin D insufficiency (i.e. 25-OH vitamin D between15 to 32 ng/mL) at baseline, 2 months and 6 months
Notes	Trial registration not found.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated sequence was used (http://www.randomizer.org).

Moodley 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The intervention and placebo were (quote:) "administered in pre-filled and pre-coded syringes that were indistinguishable".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	High risk	Very high attrition rate with 76% of participants stopped breastfeeding by 2 months
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	Groups similar at baseline

Naik 2017

Study characteristics	
Methods	Parallel-group, randomised controlled trial Setting: India (29ÃÂ°N), all year
Participants	130 infant-mother pairs **Inclusion criteria (infant)**:ÃÂ healthy, term (37 to 41 completed weeks) infants. Appropriate for gestation age **Exclusion criteria (infant)**: congenital malformations, suspicion of chromosomal anomalies and endocrine disorders, perinatal asphyxia, hypocalcaemia, hypoglycaemia, respiratory distress, or sepsis in the neonatal period **Inclusion criteria (mother)**: had a spontaneous term (37 to 41 completed weeks) healthy pregnancy and single live fetus, admitted in the labour, willing for exclusive breastfeeding and regular follow-up **Exclusion criteria (mother)**: received vitamin D within last 3 months
Interventions	Intervention: mothers given oral vitamin D3 (cholecalciferol) 60,000 IU per day within 24 to 48 hours after delivery for 10 days (n = 65) Control: mothers given oral placebo containing inert sugar within 24 to 48 hours after delivery for 10 days (n = 65) Co-intervention: mothers in both groups received routine supplementation of tablet calcium (elemental calcium 500 mg; vitamin D3 125 IU) as per local postnatal protocol.
Outcomes	• Serum 25-OH vitamin D of mothers and infants at baseline and at 6 months • Urinary calcium: creatinine ratio of mothers and infants at 14 weeks and 6 months • Serum calcium, phosphorus and ALP of infants at 6 months • Radiological rickets in infants at 6 months (with X-ray of both wrists)

Naik 2017 *(Continued)*

Notes	Indian Council of Medical Research registry trial number: CTRI-REF/2014/02/006436

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation by computer-generated randomisation table
Allocation concealment (selection bias)	Low risk	Allocation by opaque envelope concealment technique
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo was (quote:) "inert sugar" – it was ÃÂ unclear if it was possible for participants to taste the difference.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	All outcomes except X-rays were unlikely to be affected by knowledge of the intervention.Ã Â Not stated if the radiologist interpreting the X-ray was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was balanced in both groups. Those who didn't complete the study were excluded from analysis (15/130; 11%).
Selective reporting (reporting bias)	Low risk	Protocol available. All prespecified outcomes reported
Other bias	Low risk	Groups similar at baseline

Niramitmahapanya 2017

Study characteristics

Methods	Parallel-group randomised controlled trial Setting: Thailand (14ÃÂ°N), all year
Participants	72 mother-infant pairs **Inclusion criteria (infant)**: term (> 37 weeks), healthy, breast-fed **Inclusion criteria (mother)**: healthy, not vitamin D deficient (defined as 25-OH vitamin D level < 25 nmol/L) **Exclusion criteria (mother)**: 25-OH vitamin D level < 25 nmol/L or > 75 nmol/L
Interventions	Intervention: mothers given oral vitamin D3 1800 IU per day for 6 weeks (n = 37) Control: mothers given oral placebo (not described) for 6 weeks (n = 35)
Outcomes	• Maternal 25-OH vitamin D levels at 6 weeks • Infant 25-OH vitamin D levels at 6 weeks • Breastmilk 25-OH vitamin D levels at 6 weeks
Notes	Trial registration not found.

Niramitmahapanya 2017 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo not described. However, attending physician and enrolling personnel were reported to be blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Attending physician and enrolling personnel were reported to be blinded. All outcomes were unlikely to be affected by knowledge of the intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was balanced in both groups. Those who didn't complete study were excluded from analysis (2/68; 3%).
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	Groups similar at baseline

Ponnapakkam 2010

Study characteristics	
Methods	3-arm, randomised controlled trial. Setting: USA (30ÃÂ°N), unknown season
Participants	80 infants; only 25 infants completed the study. **Inclusion criteria**: term babies with no known bone disorders and those whose parents indicated that they intended to breastfeed (> 50% of total intake) for at least the 1st 3 months of life **Exclusion criteria:** > 50% supplementation with formula in the first 3 months of life, radiographic evidence of rickets, hypocalcaemic seizure, hypocalcaemia, hypercalcaemia, or hypervitaminosis D (elevated 25-OH vitamin D levels)
Interventions	Group 1: infant oral vitamin D drops (0.5 mL) 200 IU per day from birth until 6 months old (n = 8) Group 2: infant oral vitamin D drops (0.5 mL) 200 IU day from 2 months until 6 months old (n = 9) Group 3 (Control): no vitamin D from birth until 6 months old (n = 8)
Outcomes	• Height and weight at 0, 2, 4, and 6 months • Serum calcium, phosphorus, parathyroid hormone (PTH) and alkaline phosphatase (ALP) at 0, 2, 4, and 6 months • Serum 25-OH vitamin D at 0, 2, 4, and 6 months • Rickets: diagnosed based on elevation of ALP, evidence of rachitic changes on hand X-ray

Ponnapakkam 2010 *(Continued)*

	• Subclinical rickets defined as raised ALP
Notes	Trial registration not found Only data from group 1 (vitamin D, birth to 6 months) and Group 3 (placebo) used in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not reported whether the control group (group 3) received any placebo. There was a time difference of 2 months in starting the intervention in groups 1 and 2.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	All outcomes except X-rays were unlikely to be affected by knowledge of the intervention. Not stated if the radiologist interpreting the X-ray was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	High number of loss to attrition (70%) – these participants were excluded because they did not breastfeed. The number excluded in each group was not reported.
Selective reporting (reporting bias)	Unclear risk	Protocol not available. Height and weight not reported
Other bias	Unclear risk	Baseline characteristics not reported

Roth 2016

Study characteristics	
Methods	5-arm, randomised controlled trial Setting: Dhaka, Bangladesh (24ÃÂºN), all year
Participants	1164 mother-infant pairs **Inclusion criteria**: mothers at 17 to 24 weeks' gestation based on last menstrual period and or second trimester ultrasound. Infants: as the enrolment was during pregnancy, the gestation of the infant was not included as a criterion. **Exclusion criteria**: history of medical conditions that may predispose the participant to vitamin D sensitivity, altered vitamin D metabolism or hypercalcaemia, or both, or history of renal calculi; current high-risk pregnancy based on severe anaemia, proteinuria, or hypertension; multiple gestation, major congenital anomaly, or severe oligohydramnios based on maternal history or ultrasound, or both; unwillingness to stop taking non-study vitamin D or calcium supplements or a multivitamin with calcium or vitamin D, or both; currently prescribed vitamin D supplements as part of a physician's treatment plan for vitamin D deficiency; previous participation in the same study

Roth 2016 *(Continued)*

Interventions	Group 1: prenatal oral vitamin D3 600 IU per day until delivery, followed by maternal and infant placebo until 26 weeks' postpartum (n = 260 mothers, 254 infants) Group 2: prenatal oral vitamin D3 2400 IU per day until delivery, followed by maternal and infant placebo until 26 weeks' postpartum (n = 260 mothers, 252 infants) Group 3: prenatal oral vitamin D3 4000 IU per day until delivery, followed by maternal and infant placebo until 26 weeks' postpartum (n = 260 mothers, 252 infants) Group 4: prenatal oral vitamin D3 4000 IU per day until delivery, followed by maternal postnatal oral vitamin D3 4000 IU per day and infant placebo until 26 weeks' postpartum (n = 260 mothers, 249 infants) Group 5 (control) prenatal placebo until delivery, followed by maternal and infant placebo until 26 weeks' postpartum (n = 260 mothers, 247 infants) Co-intervention: calcium 500 mg/day as calcium carbonate (Calbo; Square Pharmaceuticals, Dhaka, Bangladesh) and iron and folic acid (66 mg elemental iron per day, and 350 µg folic acid per day included in the standard formulation available in Bangladesh) were provided to all mothers throughout the intervention phase (prenatal period and up to 6 months' postpartum.
Outcomes	• Infant linear growth (length for age z score) at 1 and 2 years • Infant weight, length, limb length, mid arm circumference and head circumference at 3 months, 1 year and 2 years • Infant linear growth velocity at 1, 3, 6, 12, 18 and 24 months • Gestation at birth and birth weight • Infant and maternal serum 25-OH vitamin D at delivery, 3 and 6 months • Maternal serum calcium • Adverse effects: maternal urolithiasis, death, stillbirth, infant morbidity, maternal morbidity • Maternal and infant serum calcium up until 6 months • Maternal and infant urine calcium to creatinine ratio • Maternal intact parathyroid hormone (PTH) • Infant rickets (biochemical and X-ray confirmed) • Other pregnancy outcomes e.g. placental weight, gestational hypertension, stillbirth • Other maternal and infant outcomes e.g. hospitalisation, death
Notes	Only data from groups 3 and 4 were used in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence used. Quote: "A computer-generated, simple randomization scheme was created independently by the trial statistician".
Allocation concealment (selection bias)	Low risk	Quote: "Concealment of trial-group assignments was ensured with the use of pre-labelled and sequentially numbered but otherwise identical supplement vials."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Tablets containing the different doses of vitamin D3 and placebo were identical in appearance and taste.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Tablets containing the different doses of vitamin D3 and placebo were identical in appearance and taste.

Roth 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for and attrition balanced between groups (approximately 11% attrition per group). Analysis was a complete-case, intention-to-treat analysis.
Selective reporting (reporting bias)	Low risk	Proctocol available. All outcomes specified in the protocol were reported.
Other bias	Low risk	Groups were similar at baseline.

Rothberg 1982

Study characteristics	
Methods	4-arm, randomised controlled trial Setting: South Africa (26ÃÂ°S), during mid-winter to spring
Participants	77 mother-infant pairs **Inclusion criteria (mother)**: white, well-nourished, nursing mothers who did not take any additional vitamin D from other vitamin preparations or milk. Mothers received only iron and folate supplements during pregnancy. **Inclusion criteria (infant)**: breastfeeding infants, not on vitamin D supplementation
Interventions	Group 1: Mothers given oral vitamin D 500 IU per day starting from delivery until 6 weeks, infants not supplemented (n = 20) Group 2: Mothers given oral vitamin D 1000 IU per day starting from delivery until 6 weeks, infants not supplemented (n = 20) Group 3: Infants given oral vitamin D 400 IU per day starting from birth until 6 weeks, mothers not supplemented (n = 17) Group 4: Mothers given placebo (not described) starting from delivery until 6 weeks, infants not supplemented (n = 20)
Outcomes	• Serum 25-OH vitamin D3 in mothers and infants on 4th postnatal day and 6 weeks later • Serum calcium, phosphorus and ALP in mothers and infants on 4th postnatal day and 6 weeks later
Notes	Trial registration not found.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported (quote:) 'randomised' but method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Reported as (quote:) 'double-blinded', but no description of the placebo. In some groups, the infants were given the intervention and in others it was the mothers. Likely not able to blind

Rothberg 1982 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	All outcomes unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Mothers who stopped breastfeeding were excluded from analysis. The number from each group that were excluded was not balanced. Overall high attrition rate (37/77; 40%)
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Baseline characteristics not reported

Rueter 2019

Study characteristics	
Methods	Parallel-group, randomised controlled trial Setting: Perth, Australia,(32ÃÂ°S) all seasons
Participants	195 infants, 89% exclusively or partially breastfed to 6 months **Inclusion criteria**: healthy term (> 37 weeks' gestation) singleton infants before 28 days of age. All the infants had a 1st-degree relative (mother, father, or sibling) with a history of allergic disease (asthma, eczema, and allergic rhinitis). **Exclusion criteria**: mothers had smoked during pregnancy or had an underlying immunodeficiency/autoimmune disease or those with maternal 25-hydroxyvitamin D (25-OH D) serum concentrations less than 50 nmol/L or greater than 100 nmol/L between 36 and 40 weeks' gestation, intended to reduce the risk of vitamin D deficiency or toxicity in the infant participants
Interventions	Intervention: 400 IU/day vitamin D3 (Ddrops (Woodbridge, Ontario, Canada) (n = 97)) Control: placebo group received an identical product of coconut and palm kernel oil containing no vitamin D (n = 98). Given to the infants orally as 1 drop of liquid (0.03 mL) per day. Supplementation occurred within 28 days after birth and was stopped at 6 months of age. Caregivers were advised to cease administration of the trial product if the infant was consuming 1000 mL/day or more vitamin D–fortified infant formula.
Outcomes	• Developing immune phenotype: infant allergic disease and infection at 3 and 6 months • Response to toll-like receptor ligands, polyclonal mitogen, and allergens • UV dosimetry • 25-OH D levels at 3 and 6 months
Notes	Reported trial registration ACTRN12606000281594 did not document vitamin D groups of published trial.

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

Rueter 2019 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "The pharmacy created a randomization plan from an online source (www.randomization.com), for each of the 4 stratification groups."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was conducted by the Princess Margaret Hospital for Children Clinical Trials Pharmacy and stratified according to a history of maternal allergic disease and the participant's sex."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both the intervention (vitamin D) and control (placebo) oils were packaged to appear identical and to maintain the blind."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Pharmacy staff had no contact with participants, and all research staff remained blind to the allocations until analyses were completed."
Incomplete outcome data (attrition bias) All outcomes	High risk	Excess losses: blood samples were collected from 140 of 195 infants (72%) (n = 68 from the vitamin D group) at 3 months of age and 141 of 195 infants (72%) (n = 73 from the vitamin D group) at 6 months of age
Selective reporting (reporting bias)	Unclear risk	Cited trial registration did not match trial intervention.
Other bias	Low risk	Groups similar at baseline.

Thiele 2017

Study characteristics	
Methods	Parallel-group randomised controlled trial Setting: USA (47ÃÂ°N) during summer and winter
Participants	16 mother-infant pairs **Inclusion criteria (mother)**: pregnant women between 24 to 28 weeks' gestation, history of breastfeeding with a prior infant and intention to breastfeed for 4 to 6 weeks **Exclusion criteria (mother)**: pre-existing diabetes, hypertension, parathyroid disease, uncontrolled thyroid disease and use of vitamin D supplements beyond a prenatal supplement for the last 6 months **Inclusion criteria (infant)**: none but all of the mothers delivered term infants during the study
Interventions	Intervention: mothers given oral vitamin D3 3400 IU daily from 24 to 28 weeks' gestation until 4 to 6 weeks' postpartum (n = 8) Control: mothers given placebo daily from 24 to 28 weeks' gestation until 4 to 6 weeks' postpartum (n = 8) Co-intervention: both groups received prenatal vitamin containing 400 IU vitamin D3 per day.
Outcomes	• Maternal serum 25-OH vitamin D at birth and 4 to 6 weeks • Maternal serum Ca, PTH at birth and 4 to 6 weeks • Infant capillary heel prick 25-OH vitamin D at 24 to 72 hours and 4 to 6 weeks
Notes	Trial registration not found.

Thiele 2017 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used random sequence generator.
Allocation concealment (selection bias)	Low risk	Allocation concealment by sealed numbered packets containing intervention or placebo.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was visually identical to the intervention and packed in identical pill bottles.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis stated but 3/16 (19%) participants who did not receive the intended intervention were excluded.
Selective reporting (reporting bias)	Unclear risk	Protocol not available.
Other bias	Unclear risk	Significant baseline difference in maternal calorie intake.

Trivedi 2020

Study characteristics	
Methods	Parallel-group randomised controlled trial. Setting: India, (29ÃÂ°N), all year.
Participants	132 mother-infant pairs. Consecutive mothers in labour with term gestation (37 to 41 completed weeks), appropriate for gestational age babies were included. Infants exclusively breastfed **Exclusion criteria (mother)**: those with chronic illnesses like tuberculosis, diabetes mellitus, chronic liver disease, chronic kidney disease, severe anaemia, HIV, hepatitis B, gestational diabetes mellitus, pregnancy-induced hypertension, hypothyroidism, or who had received vitamin D in the last 3 months (apart from Tab ostocalcium (elemental calcium 500 mg, vitamin D3 250 IU), given during antenatal period under national antenatal programme) **Exclusion criteria (infant)**: infants born with low birth weight, had congenital, chromosomal or endocrinological disorders, suffered perinatal asphyxia, hypocalcaemia, hypoglycaemia, respiratory distress, intracranial infection, or had undergone exchange blood transfusion
Interventions	Intervention: mothers received oral vitamin D3 60,000 IU (one sachet diluted with water) between 24 and 48 hours' postpartum and at 6, 10, and 14 weeks amounting to total 240,000 IU of vitamin D3 (equivalent to 2450 IU/day) Control: mothers received placebo ('inert' sugar).
Outcomes	• Maternal serum and cord blood concentrations of 25-OH D at recruitment; and infants at 6 months • Hypovitaminosis D (25-OH D < 11 ng/mL)

Trivedi 2020 *(Continued)*

- Rdiological rickets at 6 months of age (X-ray of both wrists)
- Biochemical rickets (serum alkaline phosphatase ≥ 420 IU/L)
- Hypovitaminosis D: vitamin D deficiency: < 11 ng/mL; vitamin D insufficiency: < 20 ng/mL; vitamin D sufficiency: ≥ 20 ng/mL
- Clinical evidence of hypercalcaemia: poor feeding, polyuria, vomiting, constipation, seizures, and lethargy and hypotonia

Notes	Trial registration not found At recruitment the serum 25-OH D was < 20 ng/mL (vitamin D insufficiency) in all the mothers and 99.1% infants. A large number of mothers (90.4%) and their infants (88.6%) had vitamin D deficiency (25-OH D < 11 ng/mL).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation table
Allocation concealment (selection bias)	Low risk	Randomisation by a 3rd person who was not directly involved in the study. The allocation of the mother–infant pair to intervention or control group was carried out by a serially numbered opaque sealed envelope concealment technique.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The drug and placebo were similar in texture and appearance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The randomisation key was decoded in 2 steps. 1st, the serial numbers were converted to either A or B and data were analysed. After the statistical results were available, the 2nd decoding was carried out; ‘‘A’’ stood for vitamin D3 and ‘‘B’’ for placebo. Thus, subjects, investigators and the data analyser were not aware of the characteristics of the 2 groups until the results were revealed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	18 of 132 infants lost (14%); 114 followed up to 6 months. Similar losses in each group. 1 infant excluded who did not exclusively breastfeed.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Infants in the control group had higher median vitamin 25-OH D levels at recruitment.

Wagner 2006

Study characteristics

Methods	Parallel-group randomised controlled trial. Setting: USA (34ÃÂ°N), unknown season.
Participants	19 mother-infant pairs

Wagner 2006 *(Continued)*

	Inclusion criteria (mother): fully lactating mothers who planned to continue full breastfeeding for the next 6 months within 1 month postpartum **Exclusion criteria (mother)**: pre-existing type I or II diabetes, hypertension, parathyroid disease, and uncontrolled thyroid disease **Inclusion criteria (infant)**: none but all of the infants were term
Interventions	Group 1: mothers given oral vitamin D3 6400 IU per day; infants given oral placebo 0.5 mL per day for 6 months (n = 9) Group 2: mothers given oral vitamin D3 400 IU per day; infants given oral vitamin D3 300 IU per day for 6 months (n = 10) Co-intervention to mothers: prenatal vitamin containing vitamin D3 400 IU per day
Outcomes	• Weight, length, head circumference and BMI of infants at each monthly visit • Serum total calcium, phosphorus, vitamin D3 and 25-OH D in infants and mothers at baseline, 3rd and 6th month of intervention • Milk vitamin D antirachitic activity by measuring vitamin D3 and 25-OH D at each monthly visit • Urinary calcium:creatinine ratio in infants and mothers at each monthly visit
Notes	Trial registration not found

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Central allocation done via the General Clinical Research Center website.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mother's placebo was identical in appearance to the vitamin D3 tablets and the infant placebo was identical in appearance, taste and smell to the vitamin D3 drops.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis was used.
Selective reporting (reporting bias)	Unclear risk	Protocol not available.
Other bias	Low risk	Groups similar at baseline.

Wheeler 2016

Study characteristics

Methods	3-arm randomised controlled trial

Wheeler 2016 *(Continued)*

	Setting: New Zealand (45ÃÂºS), all year
Participants	90 mother-infant pairs (women were enrolled at 20 weeks' gestation but intervention started at 4 weeks' postpartum) **Inclusion criteria (mother)**: healthy pregnant women planning to exclusively breastfeed for more than 5 months **Exclusion criteria**: intent to use vitamin D supplements (either mother or infant) during postpartum period, history of disorders known to affect calcium or vitamin D metabolism, plan to travel outside of NZ and living outside Dunedin **Inclusion criteria (infant)**: term (> 37 weeks)
Interventions	Group 1: mothers given oral vitamin D3 50 000 IU 1x per month from 4 weeks' postpartum until 16 weeks' postpartum (n = 30) Group 2: mothers given oral vitamin D3 100 000 IU 1x per month from 4 weeks' postpartum until 16 weeks' postpartum (n = 30) Group 3: mothers given placebo 1x per month from 4 weeks' postpartum until 16 weeks' postpartum (n = 30)
Outcomes	• Infant length and weight at birth, 4 and 20 weeks of age (BMI and z-scores) • Infant cord blood and blood at birth and 20 weeks for calcium, phosphate, albumin, ALP, 25-OH vitamin D, PTH • Maternal blood for calcium, phosphate, albumin, ALP, 25-OH vitamin D, PTH • Maternal urine calcium to creatinine ratio
Notes	Australian New Zealand Clinical Trials Registry at www.anzctr.org.au as ACTRN12611000108910

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Low risk	Allocation by coded supplement container. Randomisation list kept in a sealed envelope until completion of trial.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was identical in appearance to the intervention. All study personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was balanced in both groups. Those who didn't complete study were excluded from analysis.
Selective reporting (reporting bias)	Low risk	Proctocol available. All outcomes specified in the protocol were reported.
Other bias	Low risk	Groups similar at baseline.

ALP: alkaline phosphatase;
BCG vaccine: Bacillus Calmette-GuÃÂ©rin vaccine
BMI: Body mass index
Ca: calcium
ITT: intention-to-treat
Mg: magnesium
NICU: neonatal intensive care unit
P: phosphorous
PO4: phosphate
PTH: parathyroid hormone
UV: ultraviolet

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

Study	Reason for exclusion
Abdel-Hady 2019	Enrolled preterm infants gestational age 28 weeks to < 37 weeks. No control group. Study comparing different doses of vitamin D given to infants
ACTRN12613000732785	Randomised trial of vitamin D3 400 iU/day versus placebo in term breastfed infants. Unable to recruit so stopped (author communication)
ACTRN12618001174279	Trial registration. Enrolled preterm infants < 36 weeks' gestation
Al-Beltagi 2020	Enrolled preterm infants with respiratory distress syndrome comparing 3 different doses of vitamin D (control, 400 iU/day and 800 iU/day)
Backstrom 1999	Not term infants - enrolled 70 preterm infants with birth weight less than 2000 g and gestational age less than 37 weeks
Bagnoli 2013	Not an RCT. 73 infants from a larger cohort of 205 infants were divided according to their feeding type and vitamin D supplementation.
Baird 2016	Ongoing study: intervention given to pregnant women. No postpartum intervention
Basile 2006	No control group. Study comparing different doses of vitamin D given to mothers
Bugrul 2013	Intervention given to mothers. All infants received vitamin D drops of 400 IU/day.
Challa 2005	Not an interventional study
Chan 1982	Observational study
Chawes 2016	Women were randomised to a daily dose of 2400 IU vitamin D3 supplementation or matching placebo tablets from pregnancy week 24 to 1 week postpartum. Primary outcome was age of development of persistent wheeze in the infant in the first 3 years of life.
Cooper 2016	Intervention given to pregnant women. No postpartum intervention
Czech-Kowalska 2013	Intervention given to mothers. All infants received vitamin D drops of 400 IU/day.
Dawudo 2019	RCT of 6000 IU vitamin D to mother compared with 600 IU vitamin D to mother and 400 IU vitamin D to infants. The 2 groups did not fit the comparisons of this review.
Delvin 2005	Enrolled preterm infants. Multiple vitamin intervention
Diogenes 2013	Intervention given to pregnant women. No postpartum intervention. Trial of calcium plus vitamin D versus placebo

Study	Reason for exclusion
Francis 2018	Enrolled very low birthweight infants < 1500 g
Galdo 2018	Study comparing different doses of vitamin D given to infants
Gallo 2013a	No control group. Study comparing different doses of vitamin D given to infants
Gallo 2013b	No control group. Study comparing vitamin D2 and vitamin D3 given to infants
Grant 2014	Intervention started antenatally. Intention to breastfeed was not an inclusion criterion. Despite high breastfeeding initiation (95%), exclusive breastfeeding at 6 months was only 12%.
Gupta 2018	No control group. Study comparing different doses of vitamin D given to mothers
Hibbs 2018	Enrolled preterm infants 28 to 36 weeks' gestation
Ho 1985	No vitamin D used. Compared sun exposure to no sun exposure
Hollis 2004	No control group. Study comparing different doses of vitamin D given to mothers
Huynh 2015	No control group. Study comparing different dose regimen of vitamin D given to mothers
Ketha 2018	Compared daily versus bolus dose maternal vitamin D3 supplementation in lactating women
Kishore 2019	Enrolled preterm infants 28 to 36 weeks' gestation
Kolodziejczyk 2017	Ongoing study: Enrolling only preterm infants (24 to 32 weeks' gestation)
Kuryaninova 2017	Not an RCT. Vitamin D doses were selected based on the initial level of calcidiol. Most infants > 6 months age
Lara-Corrales 2013	Enrolled infants with atopic dermatitis, mean age 15 +/- 24 months. Excluded as not "healthy term infants from birth to 6 months age"
Litonjua 2014	Intervention given to pregnant women. No postpartum intervention
March 2015	No control group. Study comparing different doses of vitamin D given to mothers
Mirghafourvand 2015	Intervention given to pregnant women. No postpartum intervention
Morris 2017	Prospective cohort study nested within an RCT (Roth 2016)
Nausheen 2018	Intervention given to pregnant women. No postpartum intervention
NCT02713009	Ongoing study: intervention given to pregnant women. No postpartum intervention
Norizoe 2014	Enrolled breastfed infants with eczema at 1 month of age. Excluded as not "healthy term infants from birth to 6 months age"
O'Callaghan 2018	No control group. Study comparing different doses of vitamin D given to mothers
Oberhelman 2013	No control group. Study comparing different dose regimen of vitamin D given to mothers
Onal 2010	Method of allocation to intervention not reported. Study reported to be a cross-sectional study
Perumal 2017	Intervention given to pregnant women. No postnatal intervention

Study	Reason for exclusion
Rasmussen 2015	RCT on effect of vitamin D on bone mineral density on pregnant women. No neonatal outcome
Roberfroid 2012	Follow-up of a cohort of infants born to women randomly assigned to UNICEF/WHO/United Nations University multiple micronutrient supplement for pregnant and lactating women (UNIMMAP) compared with the usual iron and folic acid supplement (IFA) during pregnancy. Intervention given to pregnant women. No postpartum intervention
Roberts 1981	Allocation to intervention was not random.
Rosendahl 2017	No control group. Study comparing different doses of vitamin D given to infants
Rostami 2018	Intervention given to pregnant women. No postpartum intervention
Saadi 2009	Intervention given to mothers. All infants received vitamin D drops of 400 IU/day
Salas 2018	Enrolled extremely preterm infants with gestational ages between 23 and 27 weeks
Savino 2011	Not randomly allocated to intervention
Shakiba 2010	No control group. Study comparing different doses and dose regimens of vitamin D given to infants
Siafarikas 2011	No control group. Study comparing different doses of vitamin D given to infants
Terashita 2017	Not a randomised controlled study
Tomimoto 2018	No control group. Study comparing different doses of vitamin D given to Vitamin D deficient breastfed infants
Wagner 2013	Intervention given to pregnant women. No postnatal intervention
Zamora 1999	Retrospective cohort study
Ziegler 2014	No control group. Study comparing different doses of vitamin D given to infants

IFA: iron and folic acid
PTH: parathyroid hormone
RCT: randomised controlled trial
UNICEF: United Nations Children's Fund
UNIMMAP: UNICEF/WHO/UNU international multiple micronutrient preparation
WHO: World Health Organization

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

Kim 2010

Methods	3-arm study. Method of randomisation and allocation not reported
Participants	Term healthy infants
Interventions	Group 1: formula-fed infants (n = 25) Group 2: breastfed infants without vitamin D supplementation (n = 28) Group 3: breastfed infants + vitamin D 200 IU/day given as 0.5 mL of multivitamin drops, daily from 2 months up till 1 year of age (n = 21)

Kim 2010 *(Continued)*

Outcomes	• Serum 25-OH vitamin D levels at birth, 6 months and 12 months • Bone mineral density and bone mineral content at birth, 6 months and 12 months • Serum parathyroid hormone (PTH) level at birth, 6 months and 12 months • Serum inorganic phosphate at birth, 6 months and 12 months
Notes	Contact email on article invalid

Wagner 2018

Methods	Factorial designed randomised controlled trial
Participants	Lactating mothers
Interventions	Mothers randomised to receive either 400 vs. 6400 IU vitamin D3/day and infants 400 IU/day or placebo (if mother was in 6400 IU group)
Outcomes	• 25-OH D concentration and infant anti-HBV IgG titers at 4 and 7 months of age
Notes	Published as abstract only. Reported subset of larger study

HBV: hepatitis B
IgG: immunoglobulin G
PTH: parathyroid hormone

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

ACTRN12614000334606

Study name	VITALITY trial: randomised controlled trial to establish the role of postnatal vitamin D supplementation in infant immune health
Methods	Blinded randomised controlled trial
Participants	Healthy, term, breastfeeding 6 to 8 week-old infants. Mothers must intend to breastfeed until 6 months old.
Interventions	400 IU vitamin D3-cholecalciferol (1 drop, 0.03 mL) (Baby D drops) or an identical placebo (1 drop vegetable oil) daily until 12 months of age
Outcomes	• Challenge-proven food allergy at 12 months of age • Number of lower respiratory tract infections by 12 months of age • Food sensitisation (positive skin prick test) at 12 months of age • Moderately-severe and persistent eczema at 12 months of age • Vitamin D deficiency at 12 months of age
Starting date	December 2014.
Contact information	michael.field@mcri.edu.au
Notes	Estimated date of completion December 2020

ACTRN12615000642583

Study name	Infants of vitamin D deficient mothers - trial comparing Pentavite and vitamin D3 supplement - effect on vitamin D level at 6 weeks
Methods	Randomised controlled trial
Participants	Infants of vitamin D deficient mothers aged 3 to 42 days
Interventions	Oral pentavite 0.45 mL daily for 6 weeks or single dose of vitamin D3 50,000 units orally on day 3 once low level established
Outcomes	• Blood level of vitamin D at 6 weeks • Need for further treatment - if vitamin D level still low on blood levels may need further treatment period
Starting date	1 October 2012
Contact information	Dr Simon Costello. Email: costellosimon@bigpond.com
Notes	Author communication sent

ACTRN12618001992291

Study name	The Vaccination Infant Supplementation (VISS) Study - assessing the effect of vitamin D and probiotic supplementation around vaccination on infant's temperature and sleep pattern
Methods	Randomised placebo controlled trial
Participants	Infants who have not yet been immunised (age range: 4 to 24 months). Infants currently breastfed (e.g. exclusively or breast and formula-fed)
Interventions	1000 IU vitamin D3 liquid supplied with a 0.25 mL dropper and 2.3 g probiotic powder mixed in milk (breast milk or formula) daily for 2 months
Outcomes	• Tympanic ear temperature • Carer's mood/stress: composite measure • Indirect measure of infant's health by validated Bond-Lader Questionnaire (0, 4, 8 weeks) • Carer's sleep • Infant growth: sleep/cry pattern • Other symptoms to be recorded, including colds, mouth ulcers, rashes • Weight (0, 4, 8 weeks)
Starting date	4 February 2019
Contact information	A/Prof Karin Ried. Email: karinried@niim.com.au
Notes	Anticipated completion 12/12/2020

ChiCTR1800020179

Study name	Study for vitamins and fatty acids status of breast milk and effects of related supplementation during lactation on the health of mothers and infants: a randomized clinical trial

ChiCTR1800020179 *(Continued)*

Methods	Randomised parallel-group controlled trial
Participants	Full-term, single birth, healthy and disease-free infants; breastfeeding
Interventions	Vitamin A, vitamin D and DHA; control group: placebo
Outcomes	• Levels of vitamins in breast milk • Fatty acids in breast milk • The levels of vitamins in serum of lactating mothers • The levels of fatty acids in serum of lactating mothers • Length of infants • Weight of infants • Head circumference of infants
Starting date	1 January 2019
Contact information	Ye Ding. Email: dy03120319@163.com; Z Wang: email: zhixu.wang@126.com
Notes	

DHA: DocosahexaenoicAcid

DATA AND ANALYSES

Comparison 1. Vitamin D given to infants compared to placebo or no treatment

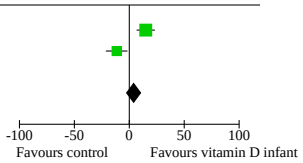
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Bone mineral content at the end of intervention	2	56	Mean Difference (IV, Fixed, 95% CI)	3.93 [-2.42, 10.27]
1.2 Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L	4	274	Risk Ratio (IV, Fixed, 95% CI)	0.57 [0.41, 0.80]
1.3 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L	2	122	Risk Ratio (IV, Fixed, 95% CI)	0.41 [0.16, 1.05]
1.4 Nutritional rickets: biochemical	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.5 Adverse effects (hypercalcaemia)	1	98	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.54, 3.86]
1.6 Adverse effects (others)	3	49	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.14, 64.26]
1.7 Serum 25-OH vitamin D level at latest time reported to six months of age	6	334	Mean Difference (IV, Fixed, 95% CI)	22.63 [17.05, 28.21]
1.8 Size at latest time measured: weight	2	143	Mean Difference (IV, Fixed, 95% CI)	123.63 [-170.02, 417.28]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9 Size at latest time measured: length	3	156	Mean Difference (IV, Fixed, 95% CI)	0.73 [-0.11, 1.57]
1.10 Size at latest time measured: head circumference	1	105	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.60, 0.60]

Analysis 1.1. Comparison 1: Vitamin D given to infants compared to placebo or no treatment, Outcome 1: Bone mineral content at the end of intervention

Study or Subgroup	Vitamin D infant Mean [mg/cm]	SD [mg/cm]	Total	Control Mean [mg/cm]	SD [mg/cm]	Total	Weight	Mean Difference IV, Fixed, 95% CI [mg/cm]
Greer 1981	79	9	9	64	9	9	58.2%	15.00 [6.68 , 23.32]
Greer 1989	89.5	12.5	19	101	17.9	19	41.8%	-11.50 [-21.32 , -1.68]
Total (95% CI)			**28**			**28**	**100.0%**	**3.93 [-2.42 , 10.27]**

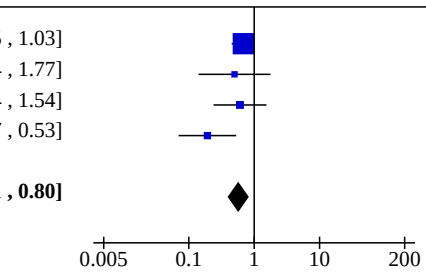
Heterogeneity: Chi² = 16.30, df = 1 (P < 0.0001); I² = 94%
Test for overall effect: Z = 1.21 (P = 0.22)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Vitamin D given to infants compared to placebo or no treatment, Outcome 2: Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Chandy 2016	19	47	32	54	68.2%	0.68 [0.45 , 1.03]
Madar 2009 (1)	2	6	4	6	7.2%	0.50 [0.14 , 1.77]
Moodley 2015 (2)	4	11	6	10	13.3%	0.61 [0.24 , 1.54]
Rueter 2019	4	68	22	72	11.3%	0.19 [0.07 , 0.53]
Total (95% CI)		**132**		**142**	**100.0%**	**0.57 [0.41 , 0.80]**
Total events:	29		64			

Heterogeneity: Chi² = 5.21, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 3.25 (P = 0.001)
Test for subgroup differences: Not applicable



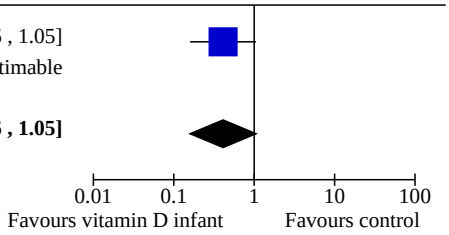
Footnotes

(1) Used design factor and ICC
(2) Reported at 3 months. Insufficient infants supplemented after 3 months.

Analysis 1.3. Comparison 1: Vitamin D given to infants compared to placebo or no treatment, Outcome 3: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Chandy 2016 (1)	5	47	14	54	100.0%	0.41 [0.16 , 1.05]
Moodley 2015 (2)	0	11	0	10		Not estimable
Total (95% CI)		**58**		**64**	**100.0%**	**0.41 [0.16 , 1.05]**
Total events:	5		14			

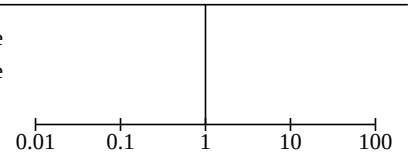
Heterogeneity: Not applicable
Test for overall effect: Z = 1.85 (P = 0.06)
Test for subgroup differences: Not applicable



Footnotes
(1) < 25 nmol/L
(2) < 37.5 nmol/L

Analysis 1.4. Comparison 1: Vitamin D given to infants compared to placebo or no treatment, Outcome 4: Nutritional rickets: biochemical

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Risk Ratio M-H, Fixed, 95% CI
Greer 1981 (1)	0	9	0	9	Not estimable
Ponnapakkam 2010 (2)	0	8	0	8	Not estimable

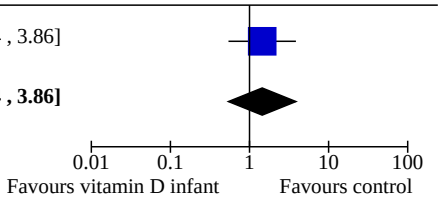


Footnotes
(1) Reported normal alkaline phosphatase, calcium and phosphate levels. None with clinical rickets
(2) Reported plasma alkaline phosphatase, calcium, phosphate and PTH

Analysis 1.5. Comparison 1: Vitamin D given to infants compared to placebo or no treatment, Outcome 5: Adverse effects (hypercalcaemia)

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chandy 2016 (1)	8	47	6	51	100.0%	1.45 [0.54 , 3.86]
Total (95% CI)		**47**		**51**	**100.0%**	**1.45 [0.54 , 3.86]**
Total events:	8		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable

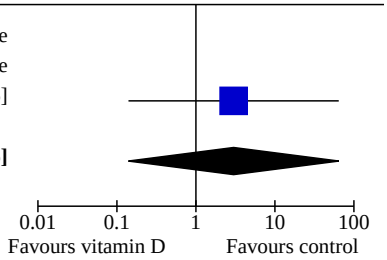


Footnotes
(1) Ca > 2.62 mmol/L

Analysis 1.6. Comparison 1: Vitamin D given to infants compared to placebo or no treatment, Outcome 6: Adverse effects (others)

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Madar 2009 (1)	0	6	0	6		Not estimable
Moodley 2015 (2)	0	11	0	10		Not estimable
Ponnapakkam 2010 (3)	1	8	0	8	100.0%	3.00 [0.14 , 64.26]
Total (95% CI)		**25**		**24**	**100.0%**	**3.00 [0.14 , 64.26]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable

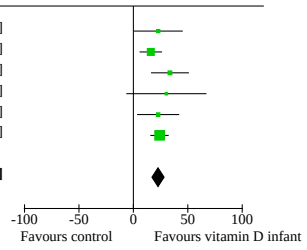


Footnotes
(1) Reported as "no adverse events", data adjusted for clustering effect
(2) Reported as "no adverse events"
(3) Urinary tract infection

Analysis 1.7. Comparison 1: Vitamin D given to infants compared to placebo or no treatment, Outcome 7: Serum 25-OH vitamin D level at latest time reported to six months of age

Study or Subgroup	Vitamin D infant Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
Alonso 2011	95	25.5	8	72.1	26.5	14	6.2%	22.90 [0.43 , 45.37]
Chandy 2016	61.3	25.2	47	45.3	27.8	54	29.1%	16.00 [5.66 , 26.34]
Greer 1989	92.4	29.7	19	58.8	24.8	19	10.3%	33.60 [16.20 , 51.00]
Madar 2009	82.5	35.3	6	52.2	29.5	6	2.3%	30.30 [-6.51 , 67.11]
Moodley 2015	91.25	26	11	68.5	18.9	10	8.3%	22.75 [3.43 , 42.07]
Rueter 2019 (1)	83.2	27.8	68	59.2	22.7	72	43.8%	24.00 [15.56 , 32.44]
Total (95% CI)			**159**			**175**	**100.0%**	**22.63 [17.05 , 28.21]**

Heterogeneity: Chi² = 3.38, df = 5 (P = 0.64); I² = 0%
Test for overall effect: Z = 7.95 (P < 0.00001)
Test for subgroup differences: Not applicable

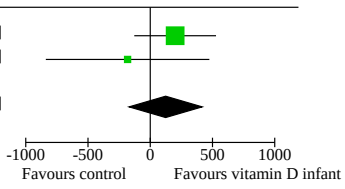


Footnotes
(1) Reported at 3 months. Insufficient infants supplemented after 3 months.

Analysis 1.8. Comparison 1: Vitamin D given to infants compared to placebo or no treatment, Outcome 8: Size at latest time measured: weight

Study or Subgroup	Vitamin D infant Mean [g]	SD [g]	Total	Control Mean [g]	SD [g]	Total	Weight	Mean Difference IV, Fixed, 95% CI [g]
Chandy 2016	6000	741	52	5800	963	53	80.0%	200.00 [-128.30 , 528.30]
Greer 1989	7570	858	19	7752	1182	19	20.0%	-182.00 [-838.74 , 474.74]
Total (95% CI)			**71**			**72**	**100.0%**	**123.63 [-170.02 , 417.28]**

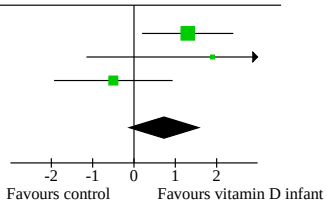
Heterogeneity: Chi² = 1.04, df = 1 (P = 0.31); I² = 4%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Vitamin D given to infants compared to placebo or no treatment, Outcome 9: Size at latest time measured: length

Study or Subgroup	Vitamin D infant Mean [cm]	SD [cm]	Total	Control Mean [cm]	SD [cm]	Total	Weight	Mean Difference IV, Fixed, 95% CI [cm]
Chandy 2016	61.6	2.37	52	60.3	3.33	53	58.0%	1.30 [0.20 , 2.40]
Greer 1981	67.1	2.4	6	65.2	3.2	7	7.6%	1.90 [-1.15 , 4.95]
Greer 1989	65.8	2.1	19	66.3	2.4	19	34.4%	-0.50 [-1.93 , 0.93]
Total (95% CI)			**77**			**79**	**100.0%**	**0.73 [-0.11 , 1.57]**

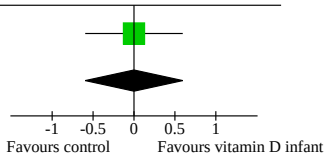
Heterogeneity: Chi² = 4.42, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 1.69 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Vitamin D given to infants compared to placebo or no treatment, Outcome 10: Size at latest time measured: head circumference

Study or Subgroup	Vitamin D infant Mean [cm]	SD [cm]	Total	Control Mean [cm]	SD [cm]	Total	Weight	Mean Difference IV, Fixed, 95% CI [cm]
Chandy 2016	40	1.63	52	40	1.48	53	100.0%	0.00 [-0.60 , 0.60]
Total (95% CI)			**52**			**53**	**100.0%**	**0.00 [-0.60 , 0.60]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



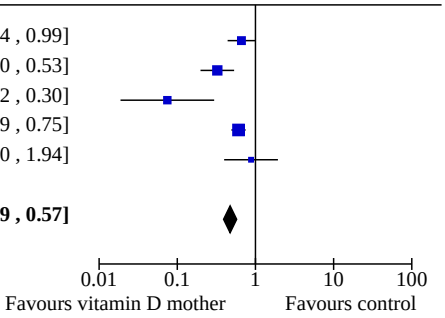
Comparison 2. Vitamin D given to lactating mothers compared to placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L	5	512	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.39, 0.57]
2.2 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L	5	512	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.09, 0.24]
2.3 Nutritional rickets: biochemical	2	229	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.44]
2.4 Nutritional rickets: radiological	3	536	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.18, 3.31]
2.5 Adverse effects (hypercalcaemia)	3	557	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.51, 3.32]
2.6 Adverse effects (all)	3	314	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.7 Serum 25-OH vitamin D level at latest time reported to six months of age	7	597	Mean Difference (IV, Fixed, 95% CI)	24.60 [21.59, 27.60]
2.8 Change of standardised growth at latest time measured (weight) [z score]	1	461	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.12, 0.26]
2.9 Change of standardised growth at latest time measured (length) [z score]	1	461	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.07, 0.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.10 Change of standardised growth at latest time measured (head circumference) [z score]	1	461	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.17, 0.17]
2.11 Size at latest time measured: weight	2	567	Mean Difference (IV, Fixed, 95% CI)	30.16 [-134.51, 194.84]
2.12 Size at latest time measured: length	2	568	Mean Difference (IV, Fixed, 95% CI)	0.43 [-0.02, 0.89]
2.13 Size at latest time measured: head circumference	2	567	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.33, 0.14]

Analysis 2.1. Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 1: Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L

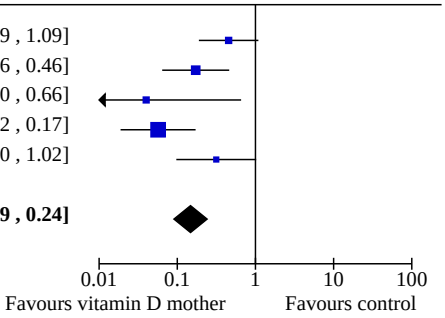
	Vitamin D mother		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Chandy 2016	20	51	32	54	18.6%	0.66 [0.44 , 0.99]	
Naik 2017	13	53	43	57	24.8%	0.33 [0.20 , 0.53]	
Roth 2016	2	49	29	53	16.6%	0.07 [0.02 , 0.30]	
Trivedi 2020	35	58	56	56	34.3%	0.61 [0.49 , 0.75]	
Wheeler 2016	13	55	7	26	5.7%	0.88 [0.40 , 1.94]	
Total (95% CI)		**266**		**246**	**100.0%**	**0.47 [0.39 , 0.57]**	
Total events:	83		167				
Heterogeneity: Chi² = 19.41, df = 4 (P = 0.0007); I² = 79%							
Test for overall effect: Z = 7.61 (P < 0.00001)							
Test for subgroup differences: Not applicable							



Analysis 2.2. Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 2: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chandy 2016	6	51	14	54	12.3%	0.45 [0.19 , 1.09]
Naik 2017 (1)	4	53	25	57	21.8%	0.17 [0.06 , 0.46]
Roth 2016	0	49	13	53	11.7%	0.04 [0.00 , 0.66]
Trivedi 2020	3	58	51	56	46.9%	0.06 [0.02 , 0.17]
Wheeler 2016	4	55	6	26	7.4%	0.32 [0.10 , 1.02]
Total (95% CI)		**266**		**246**	**100.0%**	**0.15 [0.09 , 0.24]**
Total events:	17		109			

Heterogeneity: Chi² = 11.70, df = 4 (P = 0.02); I² = 66%
Test for overall effect: Z = 7.69 (P < 0.00001)
Test for subgroup differences: Not applicable

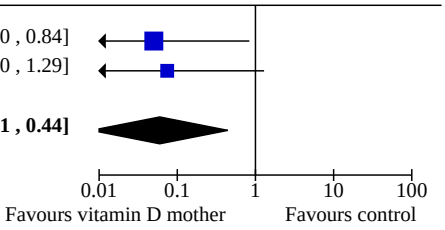


Footnotes
(1) < 27.5 nmol/L

Analysis 2.3. Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 3: Nutritional rickets: biochemical

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Naik 2017	0	56	10	59	60.7%	0.05 [0.00 , 0.84]
Trivedi 2020	0	58	6	56	39.3%	0.07 [0.00 , 1.29]
Total (95% CI)		**114**		**115**	**100.0%**	**0.06 [0.01 , 0.44]**
Total events:	0		16			

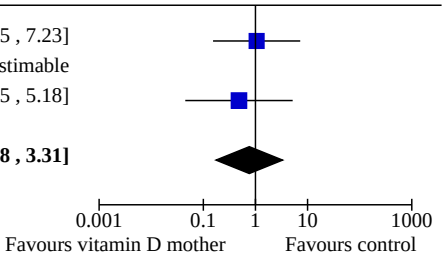
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 2.76 (P = 0.006)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 4: Nutritional rickets: radiological

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Naik 2017	2	56	2	59	48.9%	1.05 [0.15 , 7.23]
Roth 2016	0	152	0	155		Not estimable
Trivedi 2020	1	58	2	56	51.1%	0.48 [0.05 , 5.18]
Total (95% CI)		**266**		**270**	**100.0%**	**0.76 [0.18 , 3.31]**
Total events:	3		4			

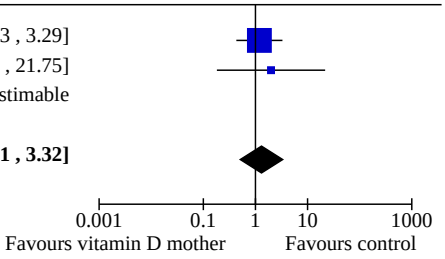
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.36 (P = 0.72)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 5: Adverse effects (hypercalcaemia)

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chandy 2016 (1)	7	50	6	51	85.6%	1.19 [0.43 , 3.29]
Roth 2016 (2)	2	186	1	185	14.4%	1.99 [0.18 , 21.75]
Wheeler 2016	0	57	0	28		Not estimable
Total (95% CI)		**293**		**264**	**100.0%**	**1.31 [0.51 , 3.32]**
Total events:	9		7			

Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)
Test for subgroup differences: Not applicable

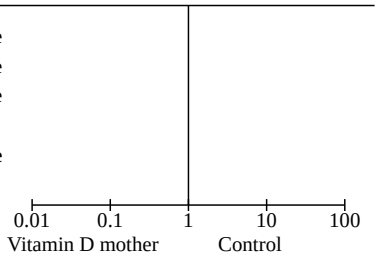


Footnotes
(1) Ca > 2.62 mmol/L
(2) Single reading of Ca > 2.8 mmol/L or 2 readings of Ca > 2.6 mmol/L

Analysis 2.6. Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 6: Adverse effects (all)

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Naik 2017	0	56	0	59		Not estimable
Trivedi 2020	0	58	0	56		Not estimable
Wheeler 2016	0	57	0	28		Not estimable
Total (95% CI)		**171**		**143**		**Not estimable**
Total events:	0		0			

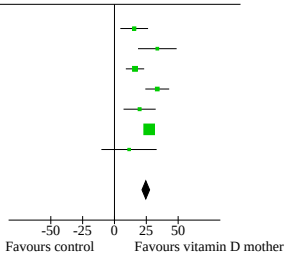
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 7: Serum 25-OH vitamin D level at latest time reported to six months of age

Study or Subgroup	Vitamin D mother Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
Chandy 2016 (1)	60.8	29.037	51	45.3	27.777	54	7.6%	15.50 [4.62 , 26.38]
Naik 2017	72.975	36.675	53	39.325	44.325	57	3.9%	33.65 [18.49 , 48.81]
Niramitmahapanya 2017	40.4	12.56	35	24.28	17.2	33	17.4%	16.12 [8.93 , 23.31]
Roth 2016	80.4	21.8	49	46.8	26.4	53	10.3%	33.60 [24.23 , 42.97]
Thiele 2017	62.225	11.075	7	42.475	11.975	6	5.7%	19.75 [7.14 , 32.36]
Trivedi 2020	43.327	12.8	58	16.075	9.4	56	53.2%	27.25 [23.14 , 31.36]
Wheeler 2016	48.8211	38.7	57	37.4	51.9	28	1.9%	11.42 [-10.27 , 33.11]
Total (95% CI)			**310**			**287**	**100.0%**	**24.60 [21.59 , 27.60]**

Heterogeneity: Chi² = 16.52, df = 6 (P = 0.01); I² = 64%
Test for overall effect: Z = 16.06 (P < 0.00001)
Test for subgroup differences: Not applicable

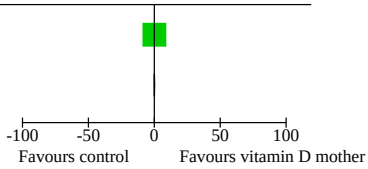


Footnotes
(1) Converted from median and IQR

Analysis 2.8. Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 8: Change of standardised growth at latest time measured (weight) [z score]

Study or Subgroup	Vitamin D mother Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Roth 2016	-0.87	1.03	231	-0.94	1.06	230	100.0%	0.07 [-0.12 , 0.26]
Total (95% CI)			**231**			**230**	**100.0%**	**0.07 [-0.12 , 0.26]**

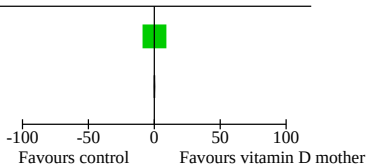
Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable



Analysis 2.9. Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 9: Change of standardised growth at latest time measured (length) [z score]

Study or Subgroup	Vitamin D mother Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Roth 2016	-0.9	0.98	231	-1.02	1.07	230	100.0%	0.12 [-0.07 , 0.31]
Total (95% CI)			**231**			**230**	**100.0%**	**0.12 [-0.07 , 0.31]**

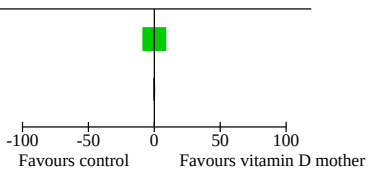
Heterogeneity: Not applicable
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Not applicable



Analysis 2.10. Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 10: Change of standardised growth at latest time measured (head circumference) [z score]

Study or Subgroup	Vitamin D mother Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Roth 2016	-1.2	0.89	231	-1.2	0.92	230	100.0%	0.00 [-0.17 , 0.17]
Total (95% CI)			**231**			**230**	**100.0%**	**0.00 [-0.17 , 0.17]**

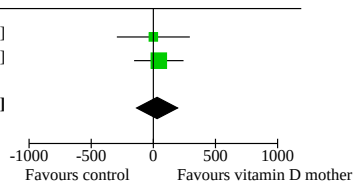
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 2.11. Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 11: Size at latest time measured: weight

Study or Subgroup	Vitamin D mother Mean [g]	SD [g]	Total	Control Mean [g]	SD [g]	Total	Weight	Mean Difference IV, Fixed, 95% CI [g]
Chandy 2016	5800	519	54	5800	962	53	31.4%	0.00 [-293.66 , 293.66]
Roth 2016	8469	1031	231	8425	1142	229	68.6%	44.00 [-154.88 , 242.88]
Total (95% CI)			**285**			**282**	**100.0%**	**30.16 [-134.51 , 194.84]**

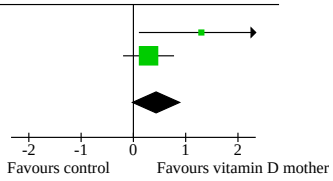
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.36 (P = 0.72)
Test for subgroup differences: Not applicable



Analysis 2.12. Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 12: Size at latest time measured: length

Study or Subgroup	Vitamin D mother Mean [cm]	SD [cm]	Total	Control Mean [cm]	SD [cm]	Total	Weight	Mean Difference IV, Fixed, 95% CI [cm]
Chandy 2016	61.6	2.96	54	60.3	3.33	53	14.3%	1.30 [0.11 , 2.49]
Roth 2016	72.68	2.53	231	72.39	2.8	230	85.7%	0.29 [-0.20 , 0.78]
Total (95% CI)			**285**			**283**	**100.0%**	**0.43 [-0.02 , 0.89]**

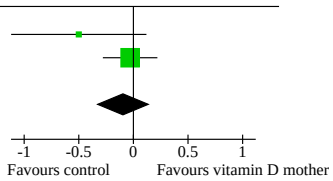
Heterogeneity: Chi² = 2.35, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 1.89 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 2.13. Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 13: Size at latest time measured: head circumference

Study or Subgroup	Vitamin D mother Mean [cm]	SD [cm]	Total	Control Mean [cm]	SD [cm]	Total	Weight	Mean Difference IV, Fixed, 95% CI [cm]
Chandy 2016	39.5	1.777	54	40	1.48	53	14.0%	-0.50 [-1.12 , 0.12]
Roth 2016	43.89	1.34	231	43.92	1.39	229	86.0%	-0.03 [-0.28 , 0.22]
Total (95% CI)			**285**			**282**	**100.0%**	**-0.10 [-0.33 , 0.14]**

Heterogeneity: Chi² = 1.90, df = 1 (P = 0.17); I² = 47%
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable



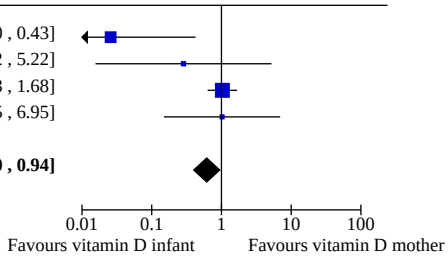
Comparison 3. Vitamin D given to infants compared to vitamin D given to lactating mothers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L	4	334	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.40, 0.94]
3.2 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L	4	334	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.17, 0.72]
3.3 Nutritional rickets	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.3.1 Biochemical	1	92	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.4 Adverse effects (hypercalcaemia)	1	97	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.48, 3.09]
3.5 Serum 25-OH vitamin D level at latest time reported to six months of age	4	269	Mean Difference (IV, Fixed, 95% CI)	14.35 [9.64, 19.06]
3.6 Size at latest time measured: weight	2	125	Mean Difference (IV, Fixed, 95% CI)	127.43 [-107.78, 362.64]
3.7 Size at latest time measured: length	2	125	Mean Difference (IV, Fixed, 95% CI)	-0.67 [-1.60, 0.25]
3.8 Size at latest time measured: head circumference	2	125	Mean Difference (IV, Fixed, 95% CI)	0.58 [0.07, 1.08]

Analysis 3.1. Comparison 3: Vitamin D given to infants compared to vitamin D given to lactating mothers, Outcome 1: Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L

Study or Subgroup	Vitamin D to infant Events	Total	Vitamin D to mother Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ala-Houhala 1985	0	60	10	32	36.7%	0.03 [0.00 , 0.43]
Ala-Houhala 1986	0	16	3	33	6.3%	0.29 [0.02 , 5.22]
Chandy 2016	19	47	20	51	51.7%	1.03 [0.63 , 1.68]
Hollis 2015	2	47	2	48	5.3%	1.02 [0.15 , 6.95]
Total (95% CI)		**170**		**164**	**100.0%**	**0.61 [0.40 , 0.94]**
Total events:	21		35			

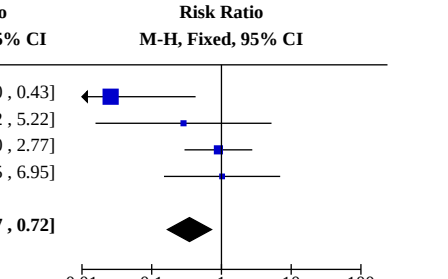
Heterogeneity: Chi² = 9.78, df = 3 (P = 0.02); I² = 69%
Test for overall effect: Z = 2.23 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Vitamin D given to infants compared to vitamin D given to lactating mothers, Outcome 2: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L

Study or Subgroup	Vitamin D to infant Events	Total	Vitamin D to mother Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ala-Houhala 1985	0	60	10	32	57.5%	0.03 [0.00 , 0.43]
Ala-Houhala 1986	0	16	3	33	9.8%	0.29 [0.02 , 5.22]
Chandy 2016	5	47	6	51	24.3%	0.90 [0.30 , 2.77]
Hollis 2015	2	47	2	48	8.4%	1.02 [0.15 , 6.95]
Total (95% CI)		**170**		**164**	**100.0%**	**0.35 [0.17 , 0.72]**
Total events:	7		21			

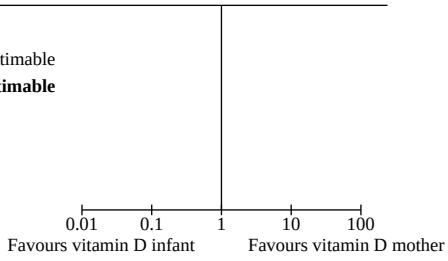
Heterogeneity: Chi² = 7.34, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 2.85 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Vitamin D given to infants compared to vitamin D given to lactating mothers, Outcome 3: Nutritional rickets

Study or Subgroup	Vitamin D to infant Events	Total	Vitamin D to mother Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 Biochemical						
Ala-Houhala 1985	0	60	0	32		Not estimable
Subtotal (95% CI)		**60**		**32**		**Not estimable**
Total events:	0		0			

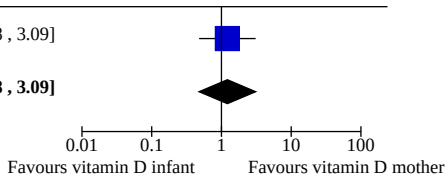
Heterogeneity: Not applicable
Test for overall effect: Not applicable



Analysis 3.4. Comparison 3: Vitamin D given to infants compared to vitamin D given to lactating mothers, Outcome 4: Adverse effects (hypercalcaemia)

Study or Subgroup	Vitamin D to infant Events	Total	Vitamin D to mother Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chandy 2016 (1)	8	47	7	50	100.0%	1.22 [0.48 , 3.09]
Total (95% CI)		**47**		**50**	**100.0%**	**1.22 [0.48 , 3.09]**
Total events:	8		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable

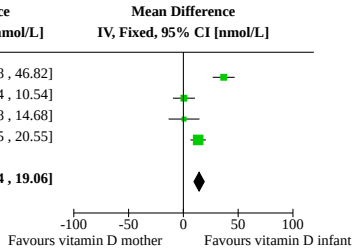


Footnotes
(1) > 2.62 mmol/l

Analysis 3.5. Comparison 3: Vitamin D given to infants compared to vitamin D given to lactating mothers, Outcome 5: Serum 25-OH vitamin D level at latest time reported to six months of age

Study or Subgroup	Vitamin D to infant Mean [nmol/L]	SD [nmol/L]	Total	Vitamin D to mother Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
Ala-Houhala 1985	50.8	25.157	30	14	9.25	17	22.1%	36.80 [26.78 , 46.82]
Chandy 2016	61.3	25.185	47	60.8	25.259	50	22.0%	0.50 [-9.54 , 10.54]
Hollis 2015	109.1	31.8	47	108.5	38	48	11.2%	0.60 [-13.48 , 14.68]
Rothberg 1982	38	9.25	12	24.5	10.211	18	44.7%	13.50 [6.45 , 20.55]
Total (95% CI)			**136**			**133**	**100.0%**	**14.35 [9.64 , 19.06]**

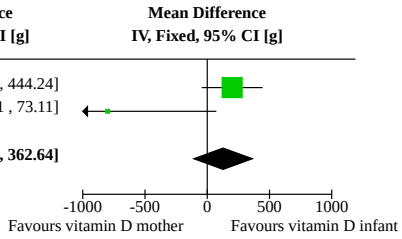
Heterogeneity: Chi² = 30.31, df = 3 (P < 0.00001); I² = 90%
Test for overall effect: Z = 5.97 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Vitamin D given to infants compared to vitamin D given to lactating mothers, Outcome 6: Size at latest time measured: weight

Study or Subgroup	Vitamin D to infant Mean [g]	SD [g]	Total	Vitamin D to mother Mean [g]	SD [g]	Total	Weight	Mean Difference IV, Fixed, 95% CI [g]
Chandy 2016	6000	741	52	5800	518	54	92.7%	200.00 [-44.24 , 444.24]
Wagner 2006	7600	800	10	8400	1100	9	7.3%	-800.00 [-1673.11 , 73.11]
Total (95% CI)			**62**			**63**	**100.0%**	**127.43 [-107.78 , 362.64]**

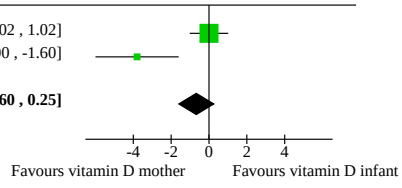
Heterogeneity: Chi² = 4.67, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable



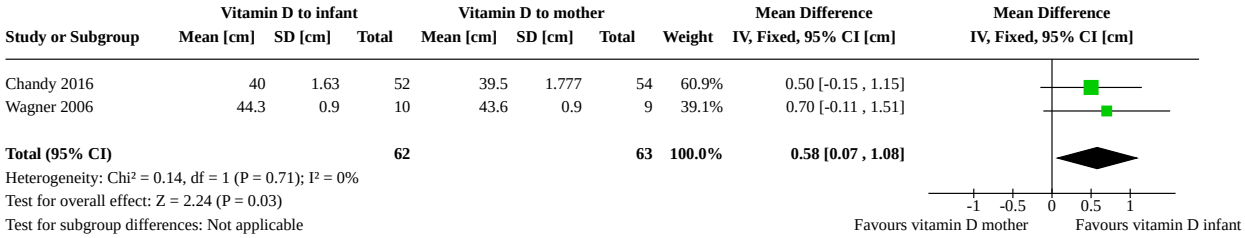
Analysis 3.7. Comparison 3: Vitamin D given to infants compared to vitamin D given to lactating mothers, Outcome 7: Size at latest time measured: length

Study or Subgroup	Vitamin D to infant Mean [cm]	SD [cm]	Total	Vitamin D to mother Mean [cm]	SD [cm]	Total	Weight	Mean Difference IV, Fixed, 95% CI [cm]
Chandy 2016	61.6	2.37	52	61.6	2.96	54	82.3%	0.00 [-1.02 , 1.02]
Wagner 2006	65.5	1.8	10	69.3	2.9	9	17.7%	-3.80 [-6.00 , -1.60]
Total (95% CI)			**62**			**63**	**100.0%**	**-0.67 [-1.60 , 0.25]**

Heterogeneity: Chi² = 9.45, df = 1 (P = 0.002); I² = 89%
Test for overall effect: Z = 1.42 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: Vitamin D given to infants compared to vitamin D given to lactating mothers, Outcome 8: Size at latest time measured: head circumference



Comparison 4. Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Bone mineral content at the end of intervention: subgroup analysis	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1.1 Lower-risk infants; D2 400 IU/day birth to 3 months	1	18	Mean Difference (IV, Fixed, 95% CI)	15.00 [6.68, 23.32]
4.1.2 Lower-risk infants; D2 400 IU/day birth to 6 months	1	38	Mean Difference (IV, Fixed, 95% CI)	-11.50 [-21.32, -1.68]
4.2 Bone mineral content at the end of intervention: sensitivity analysis	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.2.1 Other studies	2	56	Mean Difference (IV, Fixed, 95% CI)	3.93 [-2.42, 10.27]
4.3 Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): infant risk	4	274	Risk Ratio (IV, Fixed, 95% CI)	0.57 [0.41, 0.80]
4.3.1 Higher-risk infants	3	134	Risk Ratio (IV, Fixed, 95% CI)	0.65 [0.46, 0.94]
4.3.2 Lower-risk infants	1	140	Risk Ratio (IV, Fixed, 95% CI)	0.19 [0.07, 0.53]
4.4 Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): season of supplementation	4		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
4.4.1 Supplementation not seasonal	4	274	Risk Ratio (IV, Fixed, 95% CI)	0.57 [0.41, 0.80]
4.5 Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): D2 versus D3	4	274	Risk Ratio (IV, Fixed, 95% CI)	0.57 [0.41, 0.80]
4.5.1 Vitamin D2	1	12	Risk Ratio (IV, Fixed, 95% CI)	0.50 [0.14, 1.77]
4.5.2 Vitamin D3	3	262	Risk Ratio (IV, Fixed, 95% CI)	0.58 [0.40, 0.82]
4.6 Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L: dosage	4	274	Risk Ratio (IV, Fixed, 95% CI)	0.57 [0.41, 0.80]
4.6.1 Vitamin D single oral 50,000 IU at birth	1	21	Risk Ratio (IV, Fixed, 95% CI)	0.61 [0.24, 1.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.6.2 Vitamin D dose 400 IU/day	3	253	Risk Ratio (IV, Fixed, 95% CI)	0.56 [0.39, 0.81]
4.7 Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): duration of supplementation	4	274	Risk Ratio (IV, Fixed, 95% CI)	0.57 [0.41, 0.80]
4.7.1 Vitamin D single oral 50,000 IU at birth	1	21	Risk Ratio (IV, Fixed, 95% CI)	0.61 [0.24, 1.54]
4.7.2 1 to 2 months	1	12	Risk Ratio (IV, Fixed, 95% CI)	0.50 [0.14, 1.77]
4.7.3 > 6 months	2	241	Risk Ratio (IV, Fixed, 95% CI)	0.57 [0.39, 0.83]
4.8 Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): timing of commencement	4	274	Risk Ratio (IV, Fixed, 95% CI)	0.57 [0.41, 0.80]
4.8.1 From birth	3	134	Risk Ratio (IV, Fixed, 95% CI)	0.65 [0.46, 0.94]
4.8.2 From 1 month age	1	140	Risk Ratio (IV, Fixed, 95% CI)	0.19 [0.07, 0.53]
4.9 Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): sensitivity analysis	4	274	Risk Ratio (IV, Fixed, 95% CI)	0.57 [0.41, 0.80]
4.9.1 Other studies	4	274	Risk Ratio (IV, Fixed, 95% CI)	0.57 [0.41, 0.80]
4.10 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: infant risk	2		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
4.10.1 Higher-risk infants	2	122	Risk Ratio (IV, Fixed, 95% CI)	0.41 [0.16, 1.05]
4.11 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: season of supplementation	2		Risk Difference (IV, Fixed, 95% CI)	Subtotals only
4.11.1 Supplementation not seasonal	2	122	Risk Difference (IV, Fixed, 95% CI)	-0.09 [-0.20, 0.02]
4.12 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: D2 versus D3	2		Risk Difference (IV, Fixed, 95% CI)	Subtotals only
4.12.1 Vitamin D3	2	122	Risk Difference (IV, Fixed, 95% CI)	-0.09 [-0.20, 0.02]
4.13 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: dosage	2		Risk Difference (IV, Fixed, 95% CI)	Subtotals only
4.13.1 Vitamin D single oral 50,000 IU at birth	1	21	Risk Difference (IV, Fixed, 95% CI)	0.00 [-0.17, 0.17]
4.13.2 Vitamin D dose 400 IU/day	1	101	Risk Difference (IV, Fixed, 95% CI)	-0.15 [-0.30, -0.01]

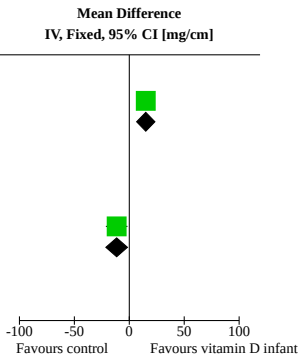
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.14 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: duration of supplementation	2		Risk Difference (IV, Fixed, 95% CI)	Subtotals only
4.14.1 Vitamin D single oral 50,000 IU at birth	1	21	Risk Difference (IV, Fixed, 95% CI)	0.00 [-0.17, 0.17]
4.14.2 > 6 months	1	101	Risk Difference (IV, Fixed, 95% CI)	-0.15 [-0.30, -0.01]
4.15 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: timing of commencement	2		Risk Difference (IV, Fixed, 95% CI)	Subtotals only
4.15.1 From birth	2	122	Risk Difference (IV, Fixed, 95% CI)	-0.09 [-0.20, 0.02]
4.16 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: sensitivity analysis	2		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
4.16.1 Other studies	2	122	Risk Ratio (IV, Fixed, 95% CI)	0.41 [0.16, 1.05]
4.17 Nutritional rickets: biochemical: subgroup analysis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.17.1 Low-risk infants: D 200 IU/day birth to 6 months	1	16	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.17.2 Low-risk infants: D2 400 IU/day birth to 6 months; all seasons	1	18	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.18 Nutritional rickets: biochemical: sensitivity analysis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.18.1 Other studies	2	34	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.19 Adverse effects (hypercalcaemia): subgroup and sensitivity analyses	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.19.1 Other studies: Vitamin D dose 400 IU/day birth to 9 months	1	98	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.54, 3.86]
4.20 Serum 25-OH vitamin D level at latest time reported to six months of age: infant risk	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.20.1 Higher-risk infants	3	134	Mean Difference (IV, Fixed, 95% CI)	18.24 [9.39, 27.09]
4.20.2 Lower-risk infants	3	200	Mean Difference (IV, Fixed, 95% CI)	25.53 [18.34, 32.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.21 Serum 25-OH vitamin D level at latest time reported to six months of age: season of supplementation	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.21.1 All year	6	334	Mean Difference (IV, Fixed, 95% CI)	22.63 [17.05, 28.21]
4.22 Serum 25-OH vitamin D level at latest time reported to six months of age: D2 versus D3	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.22.1 Vitamin D2 preparation	2	50	Mean Difference (IV, Fixed, 95% CI)	33.00 [17.27, 48.73]
4.22.2 Vitamin D3 preparation	4	284	Mean Difference (IV, Fixed, 95% CI)	21.14 [15.17, 27.11]
4.23 Serum 25-OH vitamin D level at latest time reported to six months of age: dosage	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.23.1 Vitamin D single oral 50,000 IU at birth	1	21	Mean Difference (IV, Fixed, 95% CI)	22.75 [3.43, 42.07]
4.23.2 Vitamin D 400 IU/day	5	313	Mean Difference (IV, Fixed, 95% CI)	22.62 [16.79, 28.45]
4.24 Serum 25-OH vitamin D level at latest time reported to six months of age: duration of supplementation	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.24.1 Vitamin D single oral 50,000 IU at birth	1	21	Mean Difference (IV, Fixed, 95% CI)	22.75 [3.43, 42.07]
4.24.2 1 to 2 months	1	12	Mean Difference (IV, Fixed, 95% CI)	30.30 [-6.51, 67.11]
4.24.3 4 to 6 months	1	38	Mean Difference (IV, Fixed, 95% CI)	33.60 [16.20, 51.00]
4.24.4 > 6 months	3	263	Mean Difference (IV, Fixed, 95% CI)	20.97 [14.69, 27.24]
4.25 Serum 25-OH vitamin D level at latest time reported to six months of age: timing of commencement	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.25.1 From birth	3	160	Mean Difference (IV, Fixed, 95% CI)	20.97 [12.90, 29.04]
4.25.2 From 1 month age	4	275	Mean Difference (IV, Fixed, 95% CI)	21.23 [15.04, 27.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.26 Serum 25-OH vitamin D level at latest time reported to six months of age: sensitivity analysis	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.26.1 Other studies	6	334	Mean Difference (IV, Fixed, 95% CI)	22.63 [17.05, 28.21]

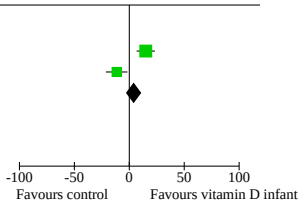
Analysis 4.1. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 1: Bone mineral content at the end of intervention: subgroup analysis

Study or Subgroup	Vitamin D infant Mean [mg/cm]	SD [mg/cm]	Total	Control Mean [mg/cm]	SD [mg/cm]	Total	Weight	Mean Difference IV, Fixed, 95% CI [mg/cm]
4.1.1 Lower-risk infants; D2 400 IU/day birth to 3 months								
Greer 1981	79	9	9	64	9	9	100.0%	15.00 [6.68 , 23.32]
Subtotal (95% CI)			**9**			**9**	**100.0%**	**15.00 [6.68 , 23.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.54 (P = 0.0004)								
4.1.2 Lower-risk infants; D2 400 IU/day birth to 6 months								
Greer 1989	89.5	12.5	19	101	17.9	19	100.0%	-11.50 [-21.32 , -1.68]
Subtotal (95% CI)			**19**			**19**	**100.0%**	**-11.50 [-21.32 , -1.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.30 (P = 0.02)								
Test for subgroup differences: Chi² = 16.30, df = 1 (P < 0.0001), I² = 93.9%								



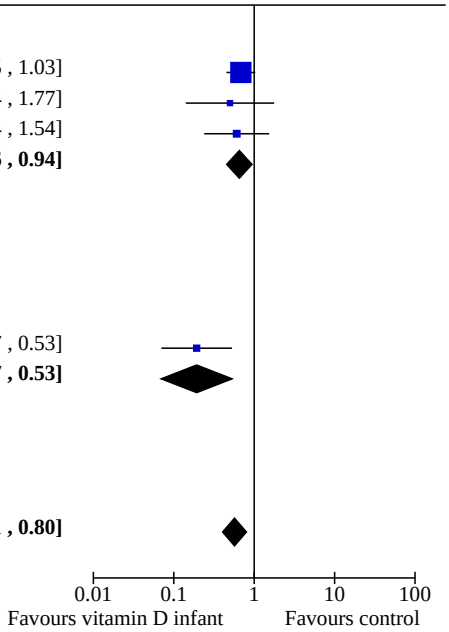
Analysis 4.2. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 2: Bone mineral content at the end of intervention: sensitivity analysis

Study or Subgroup	Vitamin D infant Mean [mg/cm]	SD [mg/cm]	Total	Control Mean [mg/cm]	SD [mg/cm]	Total	Weight	Mean Difference IV, Fixed, 95% CI [mg/cm]
4.2.1 Other studies								
Greer 1981	79	9	9	64	9	9	58.2%	15.00 [6.68 , 23.32]
Greer 1989	89.5	12.5	19	101	17.9	19	41.8%	-11.50 [-21.32 , -1.68]
Subtotal (95% CI)			**28**			**28**	**100.0%**	**3.93 [-2.42 , 10.27]**
Heterogeneity: Chi² = 16.30, df = 1 (P < 0.0001); I² = 94%								
Test for overall effect: Z = 1.21 (P = 0.22)								



Analysis 4.3. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 3: Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): infant risk

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
4.3.1 Higher-risk infants						
Chandy 2016	19	47	32	54	68.2%	0.68 [0.45 , 1.03]
Madar 2009 (1)	2	6	4	6	7.2%	0.50 [0.14 , 1.77]
Moodley 2015	4	11	6	10	13.3%	0.61 [0.24 , 1.54]
Subtotal (95% CI)		**64**		**70**	**88.7%**	**0.65 [0.46 , 0.94]**
Total events:	25		42			
Heterogeneity: Chi² = 0.24, df = 2 (P = 0.89); I² = 0%						
Test for overall effect: Z = 2.31 (P = 0.02)						
4.3.2 Lower-risk infants						
Rueter 2019	4	68	22	72	11.3%	0.19 [0.07 , 0.53]
Subtotal (95% CI)		**68**		**72**	**11.3%**	**0.19 [0.07 , 0.53]**
Total events:	4		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.19 (P = 0.001)						
Total (95% CI)		**132**		**142**	**100.0%**	**0.57 [0.41 , 0.80]**
Total events:	29		64			
Heterogeneity: Chi² = 5.21, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 3.25 (P = 0.001)						
Test for subgroup differences: Chi² = 4.97, df = 1 (P = 0.03), I² = 79.9%						

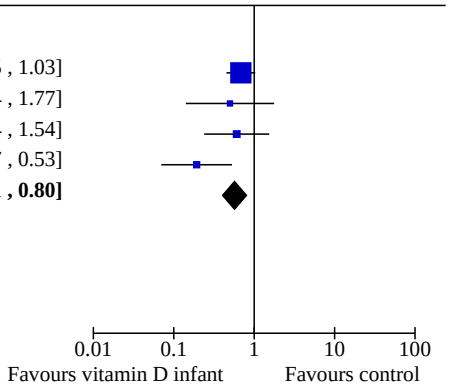


Footnotes

(1) Used design factor and ICC

Analysis 4.4. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 4: Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): season of supplementation

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
4.4.1 Supplementation not seasonal						
Chandy 2016	19	47	32	54	68.2%	0.68 [0.45 , 1.03]
Madar 2009 (1)	2	6	4	6	7.2%	0.50 [0.14 , 1.77]
Moodley 2015	4	11	6	10	13.3%	0.61 [0.24 , 1.54]
Rueter 2019	4	68	22	72	11.3%	0.19 [0.07 , 0.53]
Subtotal (95% CI)		**132**		**142**	**100.0%**	**0.57 [0.41 , 0.80]**
Total events:	29		64			
Heterogeneity: Chi² = 5.21, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 3.25 (P = 0.001)						

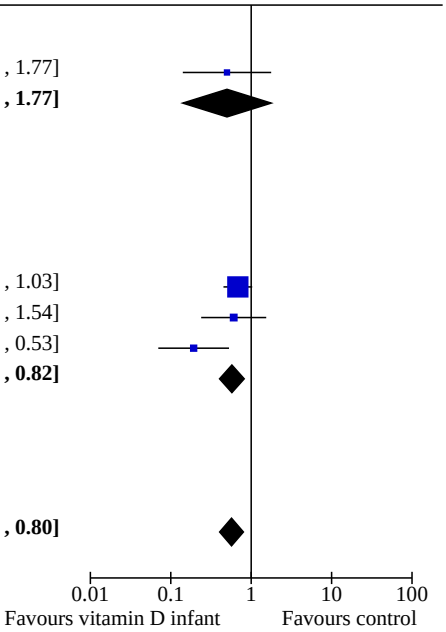


Footnotes

(1) Used design factor and ICC

Analysis 4.5. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 5: Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): D2 versus D3

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
4.5.1 Vitamin D2						
Madar 2009 (1)	2	6	4	6	7.2%	0.50 [0.14 , 1.77]
Subtotal (95% CI)		**6**		**6**	**7.2%**	**0.50 [0.14 , 1.77]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
4.5.2 Vitamin D3						
Chandy 2016	19	47	32	54	68.2%	0.68 [0.45 , 1.03]
Moodley 2015	4	11	6	10	13.3%	0.61 [0.24 , 1.54]
Rueter 2019	4	68	22	72	11.3%	0.19 [0.07 , 0.53]
Subtotal (95% CI)		**126**		**136**	**92.8%**	**0.58 [0.40 , 0.82]**
Total events:	27		60			
Heterogeneity: Chi² = 5.16, df = 2 (P = 0.08); I² = 61%						
Test for overall effect: Z = 3.07 (P = 0.002)						
Total (95% CI)		**132**		**142**	**100.0%**	**0.57 [0.41 , 0.80]**
Total events:	29		64			
Heterogeneity: Chi² = 5.21, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 3.25 (P = 0.001)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.83), I² = 0%						

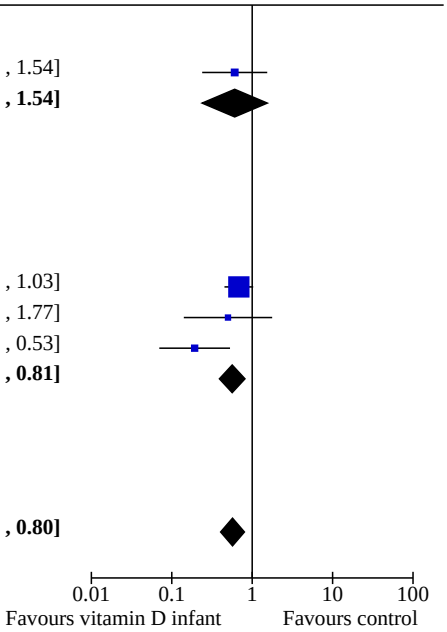


Footnotes

(1) Used design factor and ICC

Analysis 4.6. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 6: Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L: dosage

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
4.6.1 Vitamin D single oral 50,000 IU at birth						
Moodley 2015	4	11	6	10	13.3%	0.61 [0.24 , 1.54]
Subtotal (95% CI)		**11**		**10**	**13.3%**	**0.61 [0.24 , 1.54]**
Total events:	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
4.6.2 Vitamin D dose 400 IU/day						
Chandy 2016	19	47	32	54	68.2%	0.68 [0.45 , 1.03]
Madar 2009 (1)	2	6	4	6	7.2%	0.50 [0.14 , 1.77]
Rueter 2019	4	68	22	72	11.3%	0.19 [0.07 , 0.53]
Subtotal (95% CI)		**121**		**132**	**86.7%**	**0.56 [0.39 , 0.81]**
Total events:	25		58			
Heterogeneity: Chi² = 5.19, df = 2 (P = 0.07); I² = 61%						
Test for overall effect: Z = 3.08 (P = 0.002)						
Total (95% CI)		**132**		**142**	**100.0%**	**0.57 [0.41 , 0.80]**
Total events:	29		64			
Heterogeneity: Chi² = 5.21, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 3.25 (P = 0.001)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%						

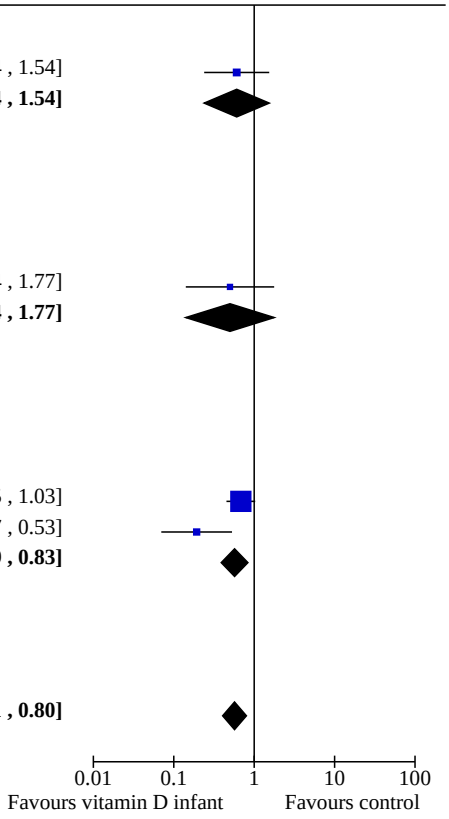


Footnotes

(1) Used design factor and ICC

Analysis 4.7. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 7: Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): duration of supplementation

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
4.7.1 Vitamin D single oral 50,000 IU at birth						
Moodley 2015	4	11	6	10	13.3%	0.61 [0.24 , 1.54]
Subtotal (95% CI)		**11**		**10**	**13.3%**	**0.61 [0.24 , 1.54]**
Total events:	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
4.7.2 1 to 2 months						
Madar 2009 (1)	2	6	4	6	7.2%	0.50 [0.14 , 1.77]
Subtotal (95% CI)		**6**		**6**	**7.2%**	**0.50 [0.14 , 1.77]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
4.7.3 > 6 months						
Chandy 2016	19	47	32	54	68.2%	0.68 [0.45 , 1.03]
Rueter 2019	4	68	22	72	11.3%	0.19 [0.07 , 0.53]
Subtotal (95% CI)		**115**		**126**	**79.5%**	**0.57 [0.39 , 0.83]**
Total events:	23		54			
Heterogeneity: Chi² = 5.15, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 2.89 (P = 0.004)						
Total (95% CI)		**132**		**142**	**100.0%**	**0.57 [0.41 , 0.80]**
Total events:	29		64			
Heterogeneity: Chi² = 5.21, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 3.25 (P = 0.001)						
Test for subgroup differences: Chi² = 0.06, df = 2 (P = 0.97), I² = 0%						

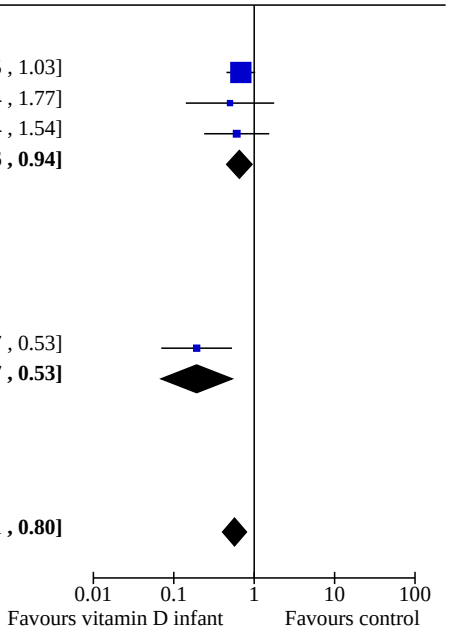


Footnotes

(1) Used design factor and ICC

Analysis 4.8. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 8: Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): timing of commencement

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
4.8.1 From birth						
Chandy 2016	19	47	32	54	68.2%	0.68 [0.45 , 1.03]
Madar 2009 (1)	2	6	4	6	7.2%	0.50 [0.14 , 1.77]
Moodley 2015	4	11	6	10	13.3%	0.61 [0.24 , 1.54]
Subtotal (95% CI)		**64**		**70**	**88.7%**	**0.65 [0.46 , 0.94]**
Total events:	25		42			
Heterogeneity: Chi² = 0.24, df = 2 (P = 0.89); I² = 0%						
Test for overall effect: Z = 2.31 (P = 0.02)						
4.8.2 From 1 month age						
Rueter 2019	4	68	22	72	11.3%	0.19 [0.07 , 0.53]
Subtotal (95% CI)		**68**		**72**	**11.3%**	**0.19 [0.07 , 0.53]**
Total events:	4		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.19 (P = 0.001)						
Total (95% CI)		**132**		**142**	**100.0%**	**0.57 [0.41 , 0.80]**
Total events:	29		64			
Heterogeneity: Chi² = 5.21, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 3.25 (P = 0.001)						
Test for subgroup differences: Chi² = 4.97, df = 1 (P = 0.03), I² = 79.9%						

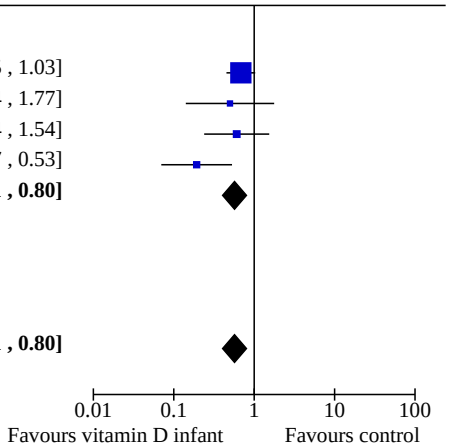


Footnotes

(1) < 50 nmol/l, used design factor and ICC

Analysis 4.9. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 9: Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): sensitivity analysis

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
4.9.1 Other studies						
Chandy 2016	19	47	32	54	68.2%	0.68 [0.45 , 1.03]
Madar 2009 (1)	2	6	4	6	7.2%	0.50 [0.14 , 1.77]
Moodley 2015	4	11	6	10	13.3%	0.61 [0.24 , 1.54]
Rueter 2019	4	68	22	72	11.3%	0.19 [0.07 , 0.53]
Subtotal (95% CI)		**132**		**142**	**100.0%**	**0.57 [0.41 , 0.80]**
Total events:	29		64			
Heterogeneity: Chi² = 5.21, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 3.25 (P = 0.001)						
Total (95% CI)		**132**		**142**	**100.0%**	**0.57 [0.41 , 0.80]**
Total events:	29		64			
Heterogeneity: Chi² = 5.21, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 3.25 (P = 0.001)						
Test for subgroup differences: Not applicable						

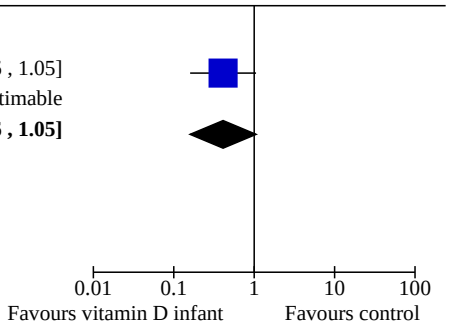


Footnotes

(1) Used design factor and ICC

Analysis 4.10. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 10: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: infant risk

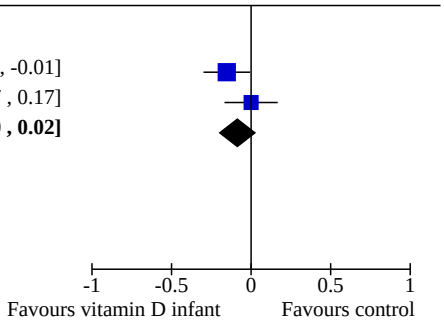
Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
4.10.1 Higher-risk infants						
Chandy 2016 (1)	5	47	14	54	100.0%	0.41 [0.16 , 1.05]
Moodley 2015 (2)	0	11	0	10		Not estimable
Subtotal (95% CI)		**58**		**64**	**100.0%**	**0.41 [0.16 , 1.05]**
Total events:	5		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.85 (P = 0.06)						



Footnotes
(1) < 25 nmol/L
(2) < 37.5 nmol/L

Analysis 4.11. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 11: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: season of supplementation

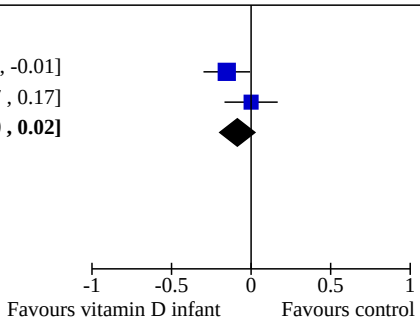
Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
4.11.1 Supplementation not seasonal						
Chandy 2016 (1)	5	47	14	54	56.6%	-0.15 [-0.30 , -0.01]
Moodley 2015 (2)	0	11	0	10	43.4%	0.00 [-0.17 , 0.17]
Subtotal (95% CI)		**58**		**64**	**100.0%**	**-0.09 [-0.20 , 0.02]**
Total events:	5		14			
Heterogeneity: Chi² = 1.82, df = 1 (P = 0.18); I² = 45%						
Test for overall effect: Z = 1.54 (P = 0.12)						



Footnotes
(1) < 25 nmol/L
(2) < 37.5 nmol/L

Analysis 4.12. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 12: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: D2 versus D3

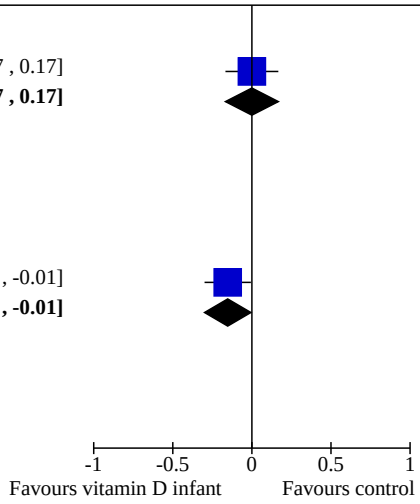
Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
4.12.1 Vitamin D3						
Chandy 2016 (1)	5	47	14	54	56.6%	-0.15 [-0.30 , -0.01]
Moodley 2015 (2)	0	11	0	10	43.4%	0.00 [-0.17 , 0.17]
Subtotal (95% CI)		**58**		**64**	**100.0%**	**-0.09 [-0.20 , 0.02]**
Total events:	5		14			
Heterogeneity: Chi² = 1.82, df = 1 (P = 0.18); I² = 45%						
Test for overall effect: Z = 1.54 (P = 0.12)						



Footnotes
(1) < 25 nmol/L
(2) < 37.5 nmol/L

Analysis 4.13. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 13: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: dosage

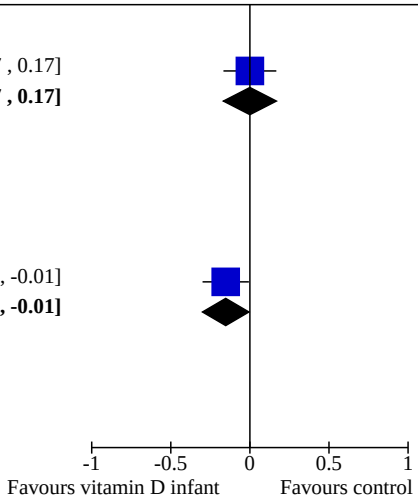
Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
4.13.1 Vitamin D single oral 50,000 IU at birth						
Moodley 2015 (1)	0	11	0	10	100.0%	0.00 [-0.17 , 0.17]
Subtotal (95% CI)		**11**		**10**	**100.0%**	**0.00 [-0.17 , 0.17]**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
4.13.2 Vitamin D dose 400 IU/day						
Chandy 2016 (2)	5	47	14	54	100.0%	-0.15 [-0.30 , -0.01]
Subtotal (95% CI)		**47**		**54**	**100.0%**	**-0.15 [-0.30 , -0.01]**
Total events:	5		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.05 (P = 0.04)						



Footnotes
(1) < 37.5 nmol/L
(2) < 25 nmol/L

Analysis 4.14. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 14: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: duration of supplementation

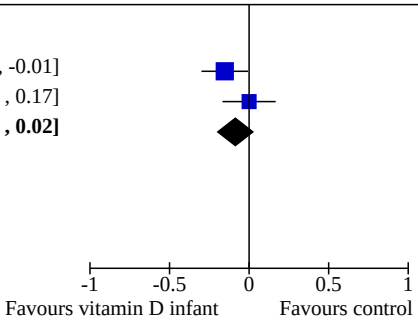
Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
4.14.1 Vitamin D single oral 50,000 IU at birth						
Moodley 2015 (1)	0	11	0	10	100.0%	0.00 [-0.17 , 0.17]
Subtotal (95% CI)		**11**		**10**	**100.0%**	**0.00 [-0.17 , 0.17]**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
4.14.2 > 6 months						
Chandy 2016 (2)	5	47	14	54	100.0%	-0.15 [-0.30 , -0.01]
Subtotal (95% CI)		**47**		**54**	**100.0%**	**-0.15 [-0.30 , -0.01]**
Total events:	5		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.05 (P = 0.04)						



Footnotes
(1) < 37.5 nmol/L
(2) < 25 nmol/L

Analysis 4.15. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 15: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: timing of commencement

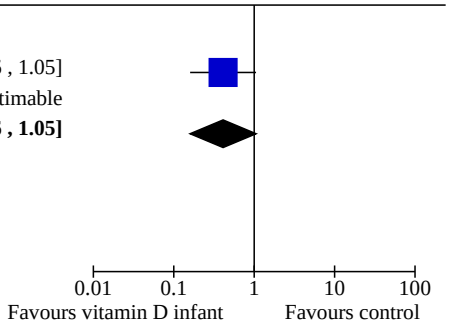
Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Difference IV, Fixed, 95% CI
4.15.1 From birth						
Chandy 2016 (1)	5	47	14	54	56.6%	-0.15 [-0.30 , -0.01]
Moodley 2015 (2)	0	11	0	10	43.4%	0.00 [-0.17 , 0.17]
Subtotal (95% CI)		**58**		**64**	**100.0%**	**-0.09 [-0.20 , 0.02]**
Total events:	5		14			
Heterogeneity: $Chi^2 = 1.82$, df = 1 (P = 0.18); $I^2 = 45\%$						
Test for overall effect: Z = 1.54 (P = 0.12)						



Footnotes
(1) < 25 nmol/L
(2) < 37.5 nmol/L

Analysis 4.16. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 16: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: sensitivity analysis

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
4.16.1 Other studies						
Chandy 2016 (1)	5	47	14	54	100.0%	0.41 [0.16 , 1.05]
Moodley 2015 (2)	0	11	0	10		Not estimable
Subtotal (95% CI)		**58**		**64**	**100.0%**	**0.41 [0.16 , 1.05]**
Total events:	5		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.85 (P = 0.06)						



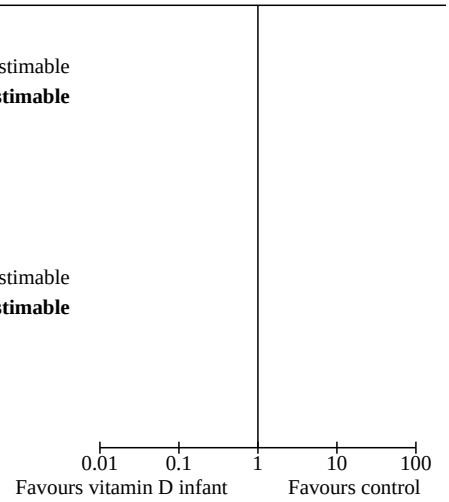
Footnotes

(1) < 25 nmol/L

(2) < 37.5 nmol/L

Analysis 4.17. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 17: Nutritional rickets: biochemical: subgroup analysis

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.17.1 Low-risk infants: D 200 IU/day birth to 6 months						
Ponnapakkam 2010 (1)	0	8	0	8		Not estimable
Subtotal (95% CI)		**8**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.17.2 Low-risk infants: D2 400 IU/day birth to 6 months; all seasons						
Greer 1981 (2)	0	9	0	9		Not estimable
Subtotal (95% CI)		**9**		**9**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



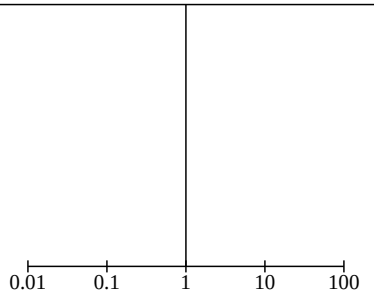
Footnotes

(1) Reported plasma alkaline phosphatase, calcium, phosphate and PTH

(2) Reported normal alkaline phosphatase, calcium and phosphate levels. None with clinical rickets

Analysis 4.18. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 18: Nutritional rickets: biochemical: sensitivity analysis

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.18.1 Other studies						
Greer 1981 (1)	0	9	0	9		Not estimable
Ponnapakkam 2010 (2)	0	8	0	8		Not estimable
Subtotal (95% CI)		**17**		**17**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



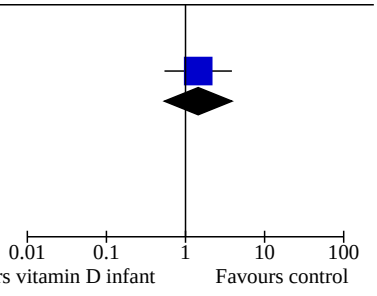
Footnotes

(1) Reported normal alkaline phosphatase, calcium and phosphate levels. None with clinical rickets

(2) Reported plasma alkaline phosphatase, calcium, phosphate and PTH

Analysis 4.19. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 19: Adverse effects (hypercalcaemia): subgroup and sensitivity analyses

Study or Subgroup	Vitamin D infant Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.19.1 Other studies: Vitamin D dose 400 IU/day birth to 9 months						
Chandy 2016 (1)	8	47	6	51	100.0%	1.45 [0.54 , 3.86]
Subtotal (95% CI)		**47**		**51**	**100.0%**	**1.45 [0.54 , 3.86]**
Total events:	8		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						

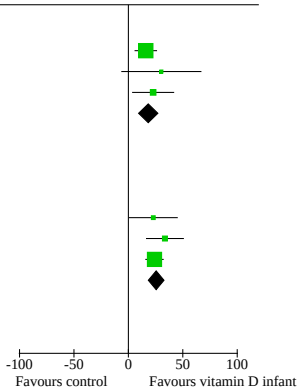


Footnotes

(1) Ca > 2.62 mmol/L

Analysis 4.20. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 20: Serum 25-OH vitamin D level at latest time reported to six months of age: infant risk

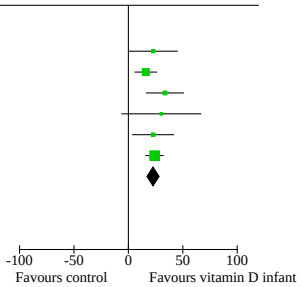
Study or Subgroup	Vitamin D infant Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
4.20.1 Higher-risk infants								
Chandy 2016	61.3	25.2	47	45.3	27.8	54	73.2%	16.00 [5.66 , 26.34]
Madar 2009	82.5	35.3	6	52.2	29.5	6	5.8%	30.30 [-6.51 , 67.11]
Moodley 2015	91.25	26	11	68.5	18.9	10	21.0%	22.75 [3.43 , 42.07]
Subtotal (95% CI)			**64**			**70**	**100.0%**	**18.24 [9.39 , 27.09]**
Heterogeneity: Chi² = 0.80, df = 2 (P = 0.67); I² = 0%								
Test for overall effect: Z = 4.04 (P < 0.0001)								
4.20.2 Lower-risk infants								
Alonso 2011	95	25.5	8	72.1	26.5	14	10.2%	22.90 [0.43 , 45.37]
Greer 1989	92.4	29.7	19	58.8	24.8	19	17.1%	33.60 [16.20 , 51.00]
Rueter 2019 (1)	83.2	27.8	68	59.2	22.7	72	72.7%	24.00 [15.56 , 32.44]
Subtotal (95% CI)			**95**			**105**	**100.0%**	**25.53 [18.34 , 32.72]**
Heterogeneity: Chi² = 1.01, df = 2 (P = 0.60); I² = 0%								
Test for overall effect: Z = 6.96 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.57, df = 1 (P = 0.21), I² = 36.2%								



Footnotes
(1) Reported at 3 months. Insufficient infants supplemented after 3 months.

Analysis 4.21. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 21: Serum 25-OH vitamin D level at latest time reported to six months of age: season of supplementation

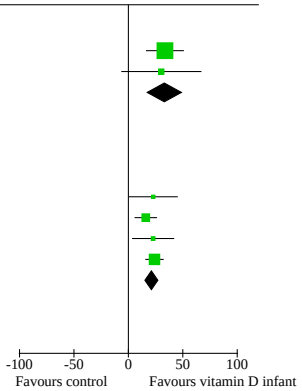
Study or Subgroup	Vitamin D infant Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
4.21.1 All year								
Alonso 2011	95	25.5	8	72.1	26.5	14	6.2%	22.90 [0.43 , 45.37]
Chandy 2016	61.3	25.2	47	45.3	27.8	54	29.1%	16.00 [5.66 , 26.34]
Greer 1989	92.4	29.7	19	58.8	24.8	19	10.3%	33.60 [16.20 , 51.00]
Madar 2009	82.5	35.3	6	52.2	29.5	6	2.3%	30.30 [-6.51 , 67.11]
Moodley 2015	91.25	26	11	68.5	18.9	10	8.3%	22.75 [3.43 , 42.07]
Rueter 2019 (1)	83.2	27.8	68	59.2	22.7	72	43.8%	24.00 [15.56 , 32.44]
Subtotal (95% CI)			**159**			**175**	**100.0%**	**22.63 [17.05 , 28.21]**
Heterogeneity: Chi² = 3.38, df = 5 (P = 0.64); I² = 0%								
Test for overall effect: Z = 7.95 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Footnotes
(1) Reported at 3 months. Insufficient infants supplemented after 3 months.

Analysis 4.22. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 22: Serum 25-OH vitamin D level at latest time reported to six months of age: D2 versus D3

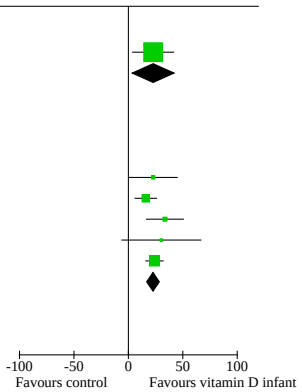
Study or Subgroup	Vitamin D infant Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
4.22.1 Vitamin D2 preparation								
Greer 1989	92.4	29.7	19	58.8	24.8	19	81.7%	33.60 [16.20 , 51.00]
Madar 2009	82.5	35.3	6	52.2	29.5	6	18.3%	30.30 [-6.51 , 67.11]
Subtotal (95% CI)			**25**			**25**	**100.0%**	**33.00 [17.27 , 48.73]**
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%								
Test for overall effect: Z = 4.11 (P < 0.0001)								
4.22.2 Vitamin D3 preparation								
Alonso 2011	95	25.5	8	72.1	26.5	14	7.1%	22.90 [0.43 , 45.37]
Chandy 2016	61.3	25.2	47	45.3	27.8	54	33.3%	16.00 [5.66 , 26.34]
Moodley 2015	91.25	26	11	68.5	18.9	10	9.5%	22.75 [3.43 , 42.07]
Rueter 2019 (1)	83.2	27.8	68	59.2	22.7	72	50.1%	24.00 [15.56 , 32.44]
Subtotal (95% CI)			**134**			**150**	**100.0%**	**21.14 [15.17 , 27.11]**
Heterogeneity: Chi² = 1.44, df = 3 (P = 0.70); I² = 0%								
Test for overall effect: Z = 6.94 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.91, df = 1 (P = 0.17), I² = 47.6%								



Footnotes
(1) Reported at 3 months. Insufficient infants supplemented after 3 months.

Analysis 4.23. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 23: Serum 25-OH vitamin D level at latest time reported to six months of age: dosage

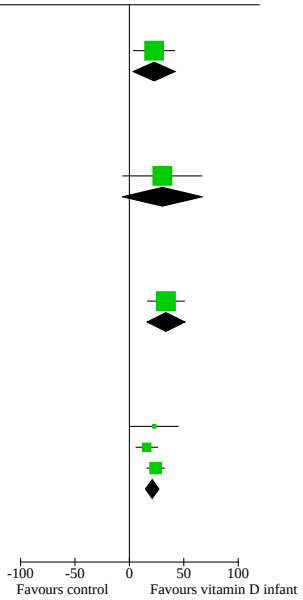
Study or Subgroup	Vitamin D infant Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
4.23.1 Vitamin D single oral 50,000 IU at birth								
Moodley 2015	91.25	26	11	68.5	18.9	10	100.0%	22.75 [3.43 , 42.07]
Subtotal (95% CI)			**11**			**10**	**100.0%**	**22.75 [3.43 , 42.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.31 (P = 0.02)								
4.23.2 Vitamin D 400 IU/day								
Alonso 2011	95	25.5	8	72.1	26.5	14	6.7%	22.90 [0.43 , 45.37]
Chandy 2016	61.3	25.2	47	45.3	27.8	54	31.8%	16.00 [5.66 , 26.34]
Greer 1989	92.4	29.7	19	58.8	24.8	19	11.2%	33.60 [16.20 , 51.00]
Madar 2009	82.5	35.3	6	52.2	29.5	6	2.5%	30.30 [-6.51 , 67.11]
Rueter 2019 (1)	83.2	27.8	68	59.2	22.7	72	47.8%	24.00 [15.56 , 32.44]
Subtotal (95% CI)			**148**			**165**	**100.0%**	**22.62 [16.79 , 28.45]**
Heterogeneity: Chi² = 3.38, df = 4 (P = 0.50); I² = 0%								
Test for overall effect: Z = 7.61 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%								



Footnotes
(1) Reported at 3 months. Insufficient infants supplemented after 3 months.

Analysis 4.24. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 24: Serum 25-OH vitamin D level at latest time reported to six months of age: duration of supplementation

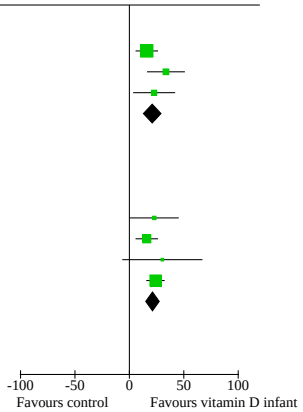
Study or Subgroup	Vitamin D infant Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
4.24.1 Vitamin D single oral 50,000 IU at birth								
Moodley 2015	91.25	26	11	68.5	18.9	10	100.0%	22.75 [3.43 , 42.07]
Subtotal (95% CI)			**11**			**10**	**100.0%**	**22.75 [3.43 , 42.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.31 (P = 0.02)								
4.24.2 1 to 2 months								
Madar 2009	82.5	35.3	6	52.2	29.5	6	100.0%	30.30 [-6.51 , 67.11]
Subtotal (95% CI)			**6**			**6**	**100.0%**	**30.30 [-6.51 , 67.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.61 (P = 0.11)								
4.24.3 4 to 6 months								
Greer 1989	92.4	29.7	19	58.8	24.8	19	100.0%	33.60 [16.20 , 51.00]
Subtotal (95% CI)			**19**			**19**	**100.0%**	**33.60 [16.20 , 51.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.79 (P = 0.0002)								
4.24.4 > 6 months								
Alonso 2011	95	25.5	8	72.1	26.5	14	7.8%	22.90 [0.43 , 45.37]
Chandy 2016	61.3	25.2	47	45.3	27.8	54	36.8%	16.00 [5.66 , 26.34]
Rueter 2019 (1)	83.2	27.8	68	59.2	22.7	72	55.4%	24.00 [15.56 , 32.44]
Subtotal (95% CI)			**123**			**140**	**100.0%**	**20.97 [14.69 , 27.24]**
Heterogeneity: Chi² = 1.41, df = 2 (P = 0.49); I² = 0%								
Test for overall effect: Z = 6.55 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.96, df = 3 (P = 0.58), I² = 0%								



Footnotes
(1) Reported at 3 months. Insufficient infants supplemented after 3 months.

Analysis 4.25. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 25: Serum 25-OH vitamin D level at latest time reported to six months of age: timing of commencement

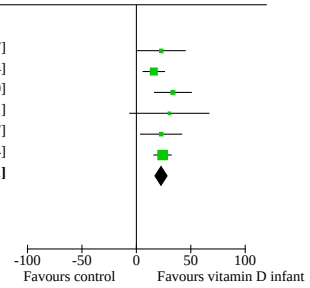
Study or Subgroup	Vitamin D infant Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
4.25.1 From birth								
Chandy 2016	61.3	25.2	47	45.3	27.8	54	61.0%	16.00 [5.66 , 26.34]
Greer 1989	92.4	29.7	19	58.8	24.8	19	21.5%	33.60 [16.20 , 51.00]
Moodley 2015	91.25	26	11	68.5	18.9	10	17.5%	22.75 [3.43 , 42.07]
Subtotal (95% CI)			**77**			**83**	**100.0%**	**20.97 [12.90 , 29.04]**
Heterogeneity: Chi² = 2.94, df = 2 (P = 0.23); I² = 32%								
Test for overall effect: Z = 5.09 (P < 0.00001)								
4.25.2 From 1 month age								
Alonso 2011	95	25.5	8	72.1	26.5	14	7.6%	22.90 [0.43 , 45.37]
Chandy 2016	61.3	25.2	47	45.3	27.8	54	35.8%	16.00 [5.66 , 26.34]
Madar 2009	82.5	35.3	6	52.2	29.5	6	2.8%	30.30 [-6.51 , 67.11]
Rueter 2019 (1)	83.2	27.8	68	59.2	22.7	72	53.8%	24.00 [15.56 , 32.44]
Subtotal (95% CI)			**129**			**146**	**100.0%**	**21.23 [15.04 , 27.42]**
Heterogeneity: Chi² = 1.65, df = 3 (P = 0.65); I² = 0%								
Test for overall effect: Z = 6.73 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%								



Footnotes
(1) Reported at 3 months. Insufficient infants supplemented after 3 months.

Analysis 4.26. Comparison 4: Vitamin D given to infants compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 26: Serum 25-OH vitamin D level at latest time reported to six months of age: sensitivity analysis

Study or Subgroup	Vitamin D infant Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
4.26.1 Other studies								
Alonso 2011	95	25.5	8	72.1	26.5	14	6.2%	22.90 [0.43 , 45.37]
Chandy 2016	61.3	25.2	47	45.3	27.8	54	29.1%	16.00 [5.66 , 26.34]
Greer 1989	92.4	29.7	19	58.8	24.8	19	10.3%	33.60 [16.20 , 51.00]
Madar 2009	82.5	35.3	6	52.2	29.5	6	2.3%	30.30 [-6.51 , 67.11]
Moodley 2015	91.25	26	11	68.5	18.9	10	8.3%	22.75 [3.43 , 42.07]
Rueter 2019 (1)	83.2	27.8	68	59.2	22.7	72	43.8%	24.00 [15.56 , 32.44]
Subtotal (95% CI)			**159**			**175**	**100.0%**	**22.63 [17.05 , 28.21]**
Heterogeneity: Chi² = 3.38, df = 5 (P = 0.64); I² = 0%								
Test for overall effect: Z = 7.95 (P < 0.00001)								



Footnotes
(1) Reported at 3 months. Insufficient infants supplemented after 3 months.

Comparison 5. Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): infant risk	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1.1 Higher-risk	5	512	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.39, 0.57]
5.2 Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): season of supplementation	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.2.1 Supplementation not seasonal	5	512	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.39, 0.57]
5.3 Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): D2 versus D3	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.3.1 Vitamin D3	5	512	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.39, 0.57]
5.4 Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): dosage	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.4.1 400 to 2000 IU/day	2	186	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.49, 1.03]
5.4.2 > 2000 to 4000 IU/day	2	216	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.34, 0.56]
5.4.3 > 4000 IU/day	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.20, 0.53]
5.5 Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): duration of supplementation	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.5.1 < 1 month	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.20, 0.53]
5.5.2 1 to 3 months	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.49, 0.75]
5.5.3 4 to 6 months	2	183	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.15, 0.53]
5.5.4 > 6 months	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.44, 0.99]
5.6 Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): timing of commencement	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.6.1 From birth	4	431	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.37, 0.55]
5.6.2 From 1 month age	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.40, 1.94]
5.7 Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): sensitivity analysis	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.7.1 Studies of good methodology	2	216	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.34, 0.56]
5.7.2 Other studies	3	296	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.39, 0.69]
5.8 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: infant risk	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.8.1 Higher-risk	5	512	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.09, 0.24]
5.9 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: season of supplementation	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.9.1 Supplementation not seasonal	5	512	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.09, 0.24]
5.10 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: D2 versus D3	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.10.1 Vitamin D3	5	512	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.09, 0.24]
5.11 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: dosage	5	512	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.09, 0.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.11.1 400 to 2000 IU/day	2	186	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.20, 0.81]
5.11.2 > 2000 to 4000 IU/day	2	216	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.02, 0.15]
5.11.3 > 4000 IU/day	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.06, 0.46]
5.12 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: duration of supplementation	5	512	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.09, 0.24]
5.12.1 < 1 month	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.06, 0.46]
5.12.2 1 to 3 months	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.02, 0.17]
5.12.3 4 to 6 months	2	183	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.05, 0.45]
5.12.4 > 6 months	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.19, 1.09]
5.13 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: timing of commencement	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.13.1 From birth	4	431	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.08, 0.23]
5.13.2 From 1 month age	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.10, 1.02]
5.14 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: sensitivity analysis	5	512	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.09, 0.24]
5.14.1 Studies of good methodology	2	216	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.02, 0.15]
5.14.2 Other studies	3	296	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.16, 0.50]
5.15 Nutritional rickets: biochemical: subgroup analyses	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.15.1 Higher-risk infants: Oral D3 60,000 IU/day for 10 days	1	115	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.84]
5.15.2 Higher-risk infants: Oral D3 60,000 IU postpartum and at 6, 10, and 14 weeks	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.29]

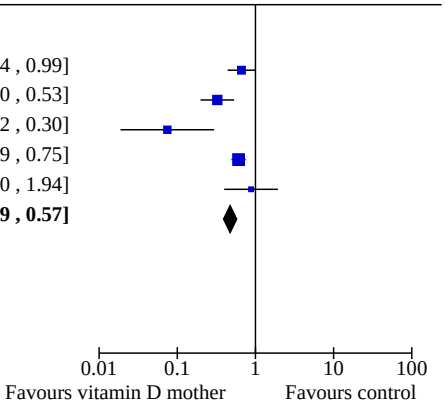
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.16 Nutritional rickets: biochemical: sensitivity analysis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.16.1 Studies of good methodology	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.29]
5.16.2 Other studies	1	115	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.84]
5.17 Nutritional rickets: radiological: infant risk	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.17.1 Higher-risk	3	536	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.18, 3.31]
5.18 Nutritional rickets: radiological: season of supplementation	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.18.1 Supplementation not seasonal	3	536	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.18, 3.31]
5.19 Nutritional rickets: radiological: D2 versus D3	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.19.1 Vitamin D3	3	536	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.18, 3.31]
5.20 Nutritional rickets: radiological: dosage	3	536	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.18, 3.31]
5.20.1 > 2000 to 4000 IU/day	2	421	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.05, 5.18]
5.20.2 > 4000 IU/day	1	115	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.15, 7.23]
5.21 Nutritional rickets: radiological: duration of supplementation	3	536	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.18, 3.31]
5.21.1 < 1 month	1	115	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.15, 7.23]
5.21.2 4 to 6 months	2	421	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.05, 5.18]
5.22 Nutritional rickets: radiological: timing of commencement	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.22.1 From birth	3	536	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.18, 3.31]
5.23 Nutritional rickets: radiological: sensitivity analysis	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.23.1 Studies of good methodology	2	421	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.05, 5.18]
5.23.2 All studies	1	115	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.15, 7.23]
5.24 Adverse effects (hypercalcaemia): subgroup analyses	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.24.1 Oral D3 120 000 IU within 7 days of delivery, then 1.5, 2.5 and 3.5 months, then monthly till 9 months (equivalent to D3 890 IU/day)	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.43, 3.29]
5.24.2 Oral D3 4000 IU/day till 26 weeks	1	371	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [0.18, 21.75]
5.24.3 Oral D3 50 000 IU monthly from 4 weeks to 16 weeks (equivalent to D3 1670 IU/day)	1	85	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.25 Adverse effects (hypercalcaemia): sensitivity analysis	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.25.1 Studies of good methodology	1	371	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [0.18, 21.75]
5.25.2 Other studies	2	186	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.43, 3.29]
5.26 Serum 25-OH vitamin D level at latest time reported to six months of age: infant risk	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.26.1 Higher-risk	5	516	Mean Difference (IV, Fixed, 95% CI)	26.87 [23.45, 30.29]
5.26.2 Lower-risk	2	81	Mean Difference (IV, Fixed, 95% CI)	17.01 [10.76, 23.26]
5.27 Serum 25-OH vitamin D level at latest time reported to six months of age: season of supplementation	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.27.1 Supplementation non-seasonal	7	597	Mean Difference (IV, Fixed, 95% CI)	24.60 [21.59, 27.60]
5.28 Serum 25-OH vitamin D level at latest time reported to six months of age: D2 versus D3	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.28.1 Vitamin D3	7	597	Mean Difference (IV, Fixed, 95% CI)	24.60 [21.59, 27.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.29 Serum 25-OH vitamin D level at latest time reported to six months of age: dosage	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.29.1 400 to 2000 IU/day	3	258	Mean Difference (IV, Fixed, 95% CI)	15.61 [9.83, 21.39]
5.29.2 > 2000 to 4000 IU/day	3	229	Mean Difference (IV, Fixed, 95% CI)	27.58 [23.97, 31.19]
5.29.3 > 4000 IU/day	1	110	Mean Difference (IV, Fixed, 95% CI)	33.65 [18.49, 48.81]
5.30 Serum 25-OH vitamin D level at latest time reported to six months of age: duration of supplementation	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.30.1 < 1 month	1	110	Mean Difference (IV, Fixed, 95% CI)	33.65 [18.49, 48.81]
5.30.2 1 to 3 months	2	81	Mean Difference (IV, Fixed, 95% CI)	17.01 [10.76, 23.26]
5.30.3 4 to 6 months	3	301	Mean Difference (IV, Fixed, 95% CI)	27.78 [24.07, 31.49]
5.30.4 >6 months	1	105	Mean Difference (IV, Fixed, 95% CI)	15.50 [4.62, 26.38]
5.31 Serum 25-OH vitamin D level at latest time reported to six months of age: timing of commencement	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.31.1 From birth	6	512	Mean Difference (IV, Fixed, 95% CI)	24.85 [21.82, 27.88]
5.31.2 From 1 month age	1	85	Mean Difference (IV, Fixed, 95% CI)	11.42 [-10.27, 33.11]
5.32 Serum 25-OH vitamin D level at latest time reported to six months of age: sensitivity analysis	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.32.1 Studies of good methodology	2	216	Mean Difference (IV, Fixed, 95% CI)	28.28 [24.51, 32.04]
5.32.2 Other studies	5	381	Mean Difference (IV, Fixed, 95% CI)	18.19 [13.22, 23.16]

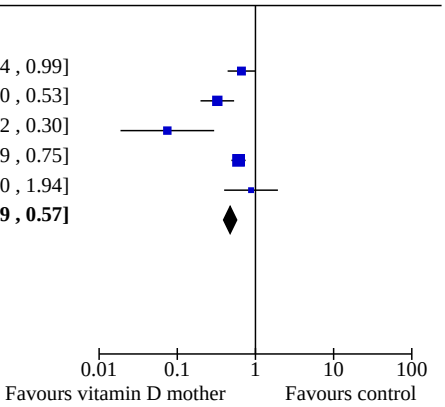
Analysis 5.1. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 1: Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): infant risk

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.1 Higher-risk						
Chandy 2016	20	51	32	54	18.6%	0.66 [0.44 , 0.99]
Naik 2017	13	53	43	57	24.8%	0.33 [0.20 , 0.53]
Roth 2016	2	49	29	53	16.6%	0.07 [0.02 , 0.30]
Trivedi 2020	35	58	56	56	34.3%	0.61 [0.49 , 0.75]
Wheeler 2016	13	55	7	26	5.7%	0.88 [0.40 , 1.94]
Subtotal (95% CI)		**266**		**246**	**100.0%**	**0.47 [0.39 , 0.57]**
Total events:	83		167			
Heterogeneity: Chi² = 19.41, df = 4 (P = 0.0007); I² = 79%						
Test for overall effect: Z = 7.61 (P < 0.00001)						



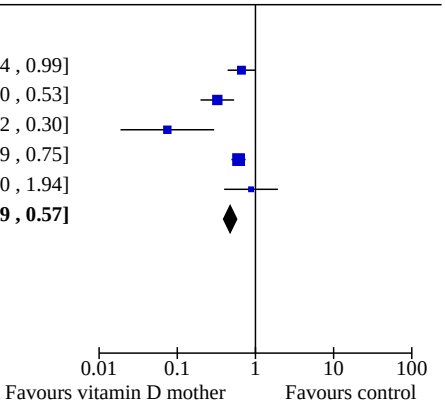
Analysis 5.2. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 2: Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): season of supplementation

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.2.1 Supplementation not seasonal						
Chandy 2016	20	51	32	54	18.6%	0.66 [0.44 , 0.99]
Naik 2017	13	53	43	57	24.8%	0.33 [0.20 , 0.53]
Roth 2016	2	49	29	53	16.6%	0.07 [0.02 , 0.30]
Trivedi 2020	35	58	56	56	34.3%	0.61 [0.49 , 0.75]
Wheeler 2016	13	55	7	26	5.7%	0.88 [0.40 , 1.94]
Subtotal (95% CI)		**266**		**246**	**100.0%**	**0.47 [0.39 , 0.57]**
Total events:	83		167			
Heterogeneity: Chi² = 19.41, df = 4 (P = 0.0007); I² = 79%						
Test for overall effect: Z = 7.61 (P < 0.00001)						



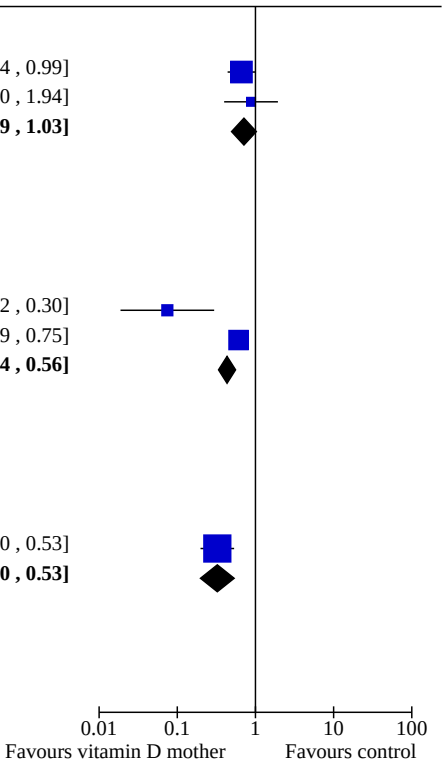
Analysis 5.3. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 3: Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): D2 versus D3

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.3.1 Vitamin D3						
Chandy 2016	20	51	32	54	18.6%	0.66 [0.44 , 0.99]
Naik 2017	13	53	43	57	24.8%	0.33 [0.20 , 0.53]
Roth 2016	2	49	29	53	16.6%	0.07 [0.02 , 0.30]
Trivedi 2020	35	58	56	56	34.3%	0.61 [0.49 , 0.75]
Wheeler 2016	13	55	7	26	5.7%	0.88 [0.40 , 1.94]
Subtotal (95% CI)		**266**		**246**	**100.0%**	**0.47 [0.39 , 0.57]**
Total events:	83		167			
Heterogeneity: Chi² = 19.41, df = 4 (P = 0.0007); I² = 79%						
Test for overall effect: Z = 7.61 (P < 0.00001)						



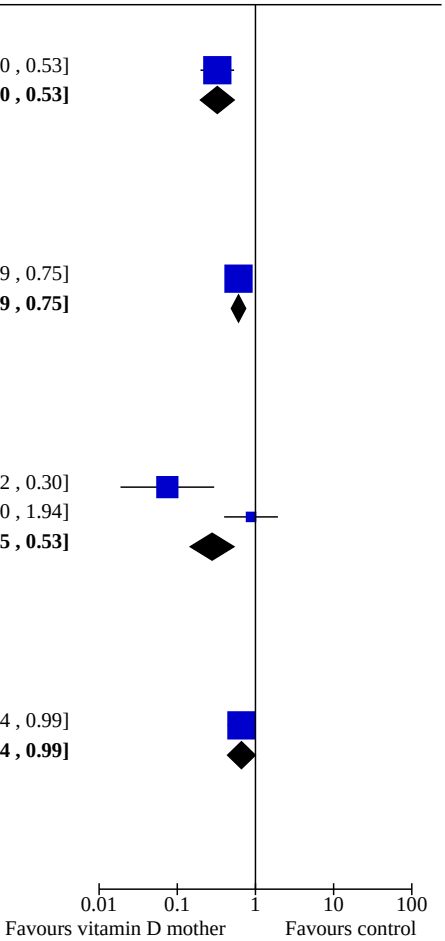
Analysis 5.4. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 4: Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): dosage

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.4.1 400 to 2000 IU/day						
Chandy 2016	20	51	32	54	76.6%	0.66 [0.44 , 0.99]
Wheeler 2016	13	55	7	26	23.4%	0.88 [0.40 , 1.94]
Subtotal (95% CI)		**106**		**80**	**100.0%**	**0.71 [0.49 , 1.03]**
Total events:	33		39			
Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%						
Test for overall effect: Z = 1.83 (P = 0.07)						
5.4.2 > 2000 to 4000 IU/day						
Roth 2016	2	49	29	53	32.7%	0.07 [0.02 , 0.30]
Trivedi 2020	35	58	56	56	67.3%	0.61 [0.49 , 0.75]
Subtotal (95% CI)		**107**		**109**	**100.0%**	**0.43 [0.34 , 0.56]**
Total events:	37		85			
Heterogeneity: Chi² = 16.26, df = 1 (P < 0.0001); I² = 94%						
Test for overall effect: Z = 6.55 (P < 0.00001)						
5.4.3 > 4000 IU/day						
Naik 2017	13	53	43	57	100.0%	0.33 [0.20 , 0.53]
Subtotal (95% CI)		**53**		**57**	**100.0%**	**0.33 [0.20 , 0.53]**
Total events:	13		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.45 (P < 0.00001)						
Test for subgroup differences: Chi² = 7.53, df = 2 (P = 0.02), I² = 73.4%						



Analysis 5.5. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 5: Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): duration of supplementation

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.5.1 < 1 month						
Naik 2017	13	53	43	57	100.0%	0.33 [0.20 , 0.53]
Subtotal (95% CI)		**53**		**57**	**100.0%**	**0.33 [0.20 , 0.53]**
Total events:	13		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.45 (P < 0.00001)						
5.5.2 1 to 3 months						
Trivedi 2020	35	58	56	56	100.0%	0.61 [0.49 , 0.75]
Subtotal (95% CI)		**58**		**56**	**100.0%**	**0.61 [0.49 , 0.75]**
Total events:	35		56			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.68 (P < 0.00001)						
5.5.3 4 to 6 months						
Roth 2016	2	49	29	53	74.6%	0.07 [0.02 , 0.30]
Wheeler 2016	13	55	7	26	25.4%	0.88 [0.40 , 1.94]
Subtotal (95% CI)		**104**		**79**	**100.0%**	**0.28 [0.15 , 0.53]**
Total events:	15		36			
Heterogeneity: Chi² = 11.57, df = 1 (P = 0.0007); I² = 91%						
Test for overall effect: Z = 3.91 (P < 0.0001)						
5.5.4 > 6 months						
Chandy 2016 (1)	20	51	32	54	100.0%	0.66 [0.44 , 0.99]
Subtotal (95% CI)		**51**		**54**	**100.0%**	**0.66 [0.44 , 0.99]**
Total events:	20		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
Test for subgroup differences: Chi² = 10.28, df = 3 (P = 0.02), I² = 70.8%						

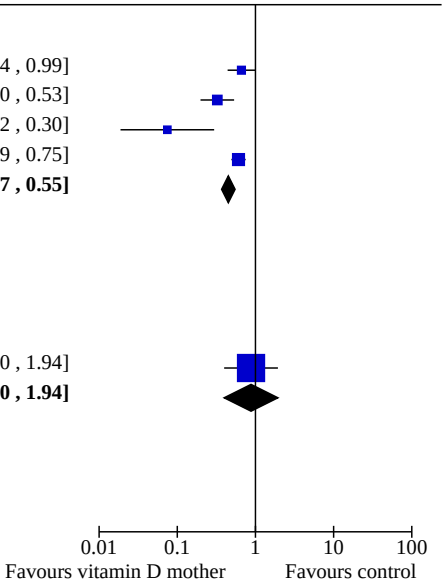


Footnotes

(1) < 25 nmol/L

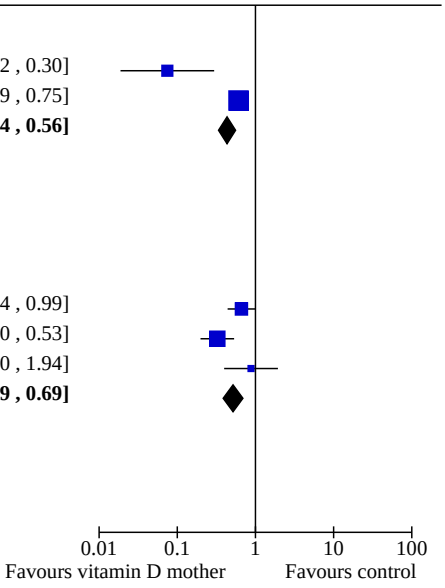
Analysis 5.6. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 6: Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): timing of commencement

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.6.1 From birth						
Chandy 2016	20	51	32	54	19.7%	0.66 [0.44 , 0.99]
Naik 2017	13	53	43	57	26.2%	0.33 [0.20 , 0.53]
Roth 2016	2	49	29	53	17.7%	0.07 [0.02 , 0.30]
Trivedi 2020	35	58	56	56	36.4%	0.61 [0.49 , 0.75]
Subtotal (95% CI)		**211**		**220**	**100.0%**	**0.45 [0.37 , 0.55]**
Total events:	70		160			
Heterogeneity: Chi² = 19.52, df = 3 (P = 0.0002); I² = 85%						
Test for overall effect: Z = 7.90 (P < 0.00001)						
5.6.2 From 1 month age						
Wheeler 2016	13	55	7	26	100.0%	0.88 [0.40 , 1.94]
Subtotal (95% CI)		**55**		**26**	**100.0%**	**0.88 [0.40 , 1.94]**
Total events:	13		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
Test for subgroup differences: Chi² = 2.58, df = 1 (P = 0.11), I² = 61.2%						



Analysis 5.7. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 7: Vitamin D insufficiency (25-OH vitamin D < 50 nmol/L): sensitivity analysis

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.7.1 Studies of good methodology						
Roth 2016	2	49	29	53	32.7%	0.07 [0.02 , 0.30]
Trivedi 2020	35	58	56	56	67.3%	0.61 [0.49 , 0.75]
Subtotal (95% CI)		**107**		**109**	**100.0%**	**0.43 [0.34 , 0.56]**
Total events:	37		85			
Heterogeneity: Chi² = 16.26, df = 1 (P < 0.0001); I² = 94%						
Test for overall effect: Z = 6.55 (P < 0.00001)						
5.7.2 Other studies						
Chandy 2016	20	51	32	54	37.9%	0.66 [0.44 , 0.99]
Naik 2017 (1)	13	53	43	57	50.5%	0.33 [0.20 , 0.53]
Wheeler 2016	13	55	7	26	11.6%	0.88 [0.40 , 1.94]
Subtotal (95% CI)		**159**		**137**	**100.0%**	**0.52 [0.39 , 0.69]**
Total events:	46		82			
Heterogeneity: Chi² = 6.51, df = 2 (P = 0.04); I² = 69%						
Test for overall effect: Z = 4.46 (P < 0.00001)						

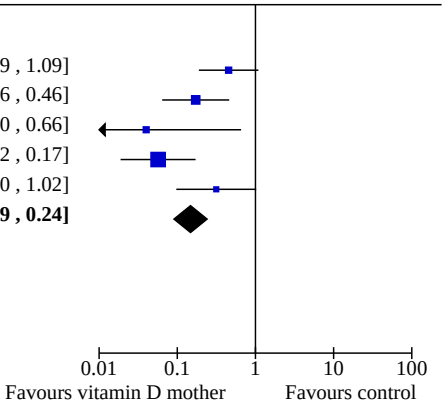


Footnotes

(1) < 50 nmol/L

Analysis 5.8. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 8: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: infant risk

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.8.1 Higher-risk						
Chandy 2016	6	51	14	54	12.3%	0.45 [0.19 , 1.09]
Naik 2017 (1)	4	53	25	57	21.8%	0.17 [0.06 , 0.46]
Roth 2016	0	49	13	53	11.7%	0.04 [0.00 , 0.66]
Trivedi 2020	3	58	51	56	46.9%	0.06 [0.02 , 0.17]
Wheeler 2016	4	55	6	26	7.4%	0.32 [0.10 , 1.02]
Subtotal (95% CI)		**266**		**246**	**100.0%**	**0.15 [0.09 , 0.24]**
Total events:	17		109			
Heterogeneity: Chi² = 11.70, df = 4 (P = 0.02); I² = 66%						
Test for overall effect: Z = 7.69 (P < 0.00001)						

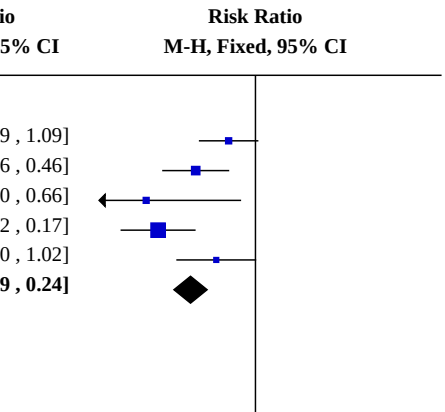


Footnotes

(1) < 27.5 nmol/L

Analysis 5.9. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 9: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: season of supplementation

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.9.1 Supplementation not seasonal						
Chandy 2016	6	51	14	54	12.3%	0.45 [0.19 , 1.09]
Naik 2017 (1)	4	53	25	57	21.8%	0.17 [0.06 , 0.46]
Roth 2016	0	49	13	53	11.7%	0.04 [0.00 , 0.66]
Trivedi 2020	3	58	51	56	46.9%	0.06 [0.02 , 0.17]
Wheeler 2016	4	55	6	26	7.4%	0.32 [0.10 , 1.02]
Subtotal (95% CI)		**266**		**246**	**100.0%**	**0.15 [0.09 , 0.24]**
Total events:	17		109			
Heterogeneity: Chi² = 11.70, df = 4 (P = 0.02); I² = 66%						
Test for overall effect: Z = 7.69 (P < 0.00001)						



Footnotes

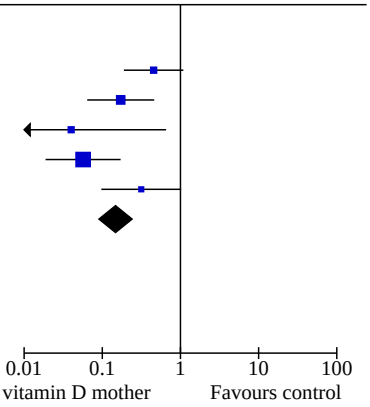
(1) < 27.5 nmol/L

Analysis 5.10. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 10: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: D2 versus D3

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.10.1 Vitamin D3						
Chandy 2016	6	51	14	54	12.3%	0.45 [0.19 , 1.09]
Naik 2017 (1)	4	53	25	57	21.8%	0.17 [0.06 , 0.46]
Roth 2016	0	49	13	53	11.7%	0.04 [0.00 , 0.66]
Trivedi 2020	3	58	51	56	46.9%	0.06 [0.02 , 0.17]
Wheeler 2016	4	55	6	26	7.4%	0.32 [0.10 , 1.02]
Subtotal (95% CI)		**266**		**246**	**100.0%**	**0.15 [0.09 , 0.24]**
Total events:	17		109			

Heterogeneity: Chi² = 11.70, df = 4 (P = 0.02); I² = 66%

Test for overall effect: Z = 7.69 (P < 0.00001)

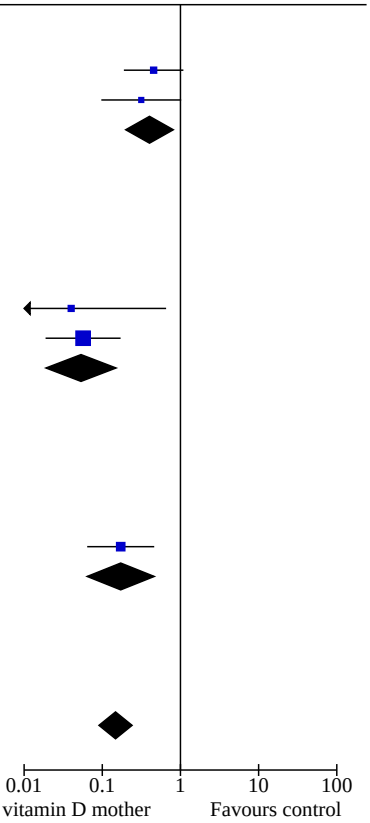


Footnotes

(1) < 27.5 nmol/L

Analysis 5.11. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 11: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: dosage

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.11.1 400 to 2000 IU/day						
Chandy 2016	6	51	14	54	12.3%	0.45 [0.19 , 1.09]
Wheeler 2016	4	55	6	26	7.4%	0.32 [0.10 , 1.02]
Subtotal (95% CI)		**106**		**80**	**19.6%**	**0.40 [0.20 , 0.81]**
Total events:	10		20			
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 2.55 (P = 0.01)						
5.11.2 > 2000 to 4000 IU/day						
Roth 2016	0	49	13	53	11.7%	0.04 [0.00 , 0.66]
Trivedi 2020	3	58	51	56	46.9%	0.06 [0.02 , 0.17]
Subtotal (95% CI)		**107**		**109**	**58.6%**	**0.05 [0.02 , 0.15]**
Total events:	3		64			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 5.56 (P < 0.00001)						
5.11.3 > 4000 IU/day						
Naik 2017 (1)	4	53	25	57	21.8%	0.17 [0.06 , 0.46]
Subtotal (95% CI)		**53**		**57**	**21.8%**	**0.17 [0.06 , 0.46]**
Total events:	4		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.49 (P = 0.0005)						
Total (95% CI)		**266**		**246**	**100.0%**	**0.15 [0.09 , 0.24]**
Total events:	17		109			
Heterogeneity: Chi² = 11.70, df = 4 (P = 0.02); I² = 66%						
Test for overall effect: Z = 7.69 (P < 0.00001)						
Test for subgroup differences: Chi² = 10.18, df = 2 (P = 0.006), I² = 80.4%						

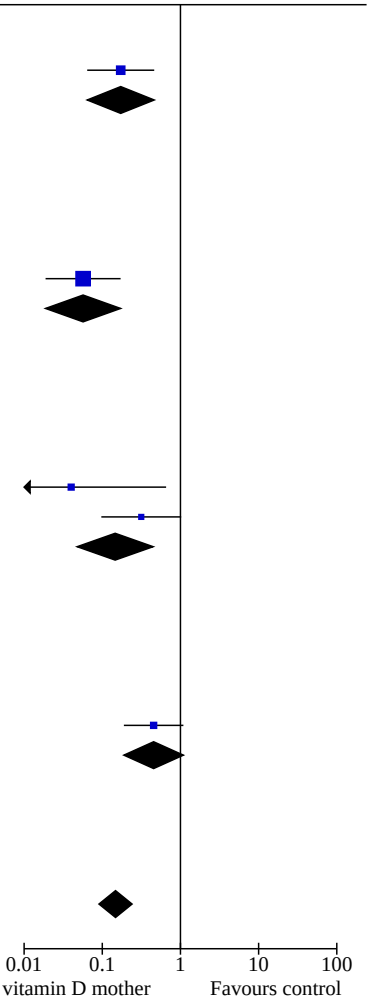


Footnotes

(1) < 27.5 nmol/L

Analysis 5.12. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 12: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: duration of supplementation

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.12.1 < 1 month						
Naik 2017 (1)	4	53	25	57	21.8%	0.17 [0.06 , 0.46]
Subtotal (95% CI)		**53**		**57**	**21.8%**	**0.17 [0.06 , 0.46]**
Total events:	4		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.49 (P = 0.0005)						
5.12.2 1 to 3 months						
Trivedi 2020	3	58	51	56	46.9%	0.06 [0.02 , 0.17]
Subtotal (95% CI)		**58**		**56**	**46.9%**	**0.06 [0.02 , 0.17]**
Total events:	3		51			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.09 (P < 0.00001)						
5.12.3 4 to 6 months						
Roth 2016	0	49	13	53	11.7%	0.04 [0.00 , 0.66]
Wheeler 2016	4	55	6	26	7.4%	0.32 [0.10 , 1.02]
Subtotal (95% CI)		**104**		**79**	**19.1%**	**0.15 [0.05 , 0.45]**
Total events:	4		19			
Heterogeneity: Chi² = 2.47, df = 1 (P = 0.12); I² = 59%						
Test for overall effect: Z = 3.37 (P = 0.0008)						
5.12.4 > 6 months						
Chandy 2016	6	51	14	54	12.3%	0.45 [0.19 , 1.09]
Subtotal (95% CI)		**51**		**54**	**12.3%**	**0.45 [0.19 , 1.09]**
Total events:	6		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.77 (P = 0.08)						
Total (95% CI)		**266**		**246**	**100.0%**	**0.15 [0.09 , 0.24]**
Total events:	17		109			
Heterogeneity: Chi² = 11.70, df = 4 (P = 0.02); I² = 66%						
Test for overall effect: Z = 7.69 (P < 0.00001)						
Test for subgroup differences: Chi² = 8.60, df = 3 (P = 0.04), I² = 65.1%						

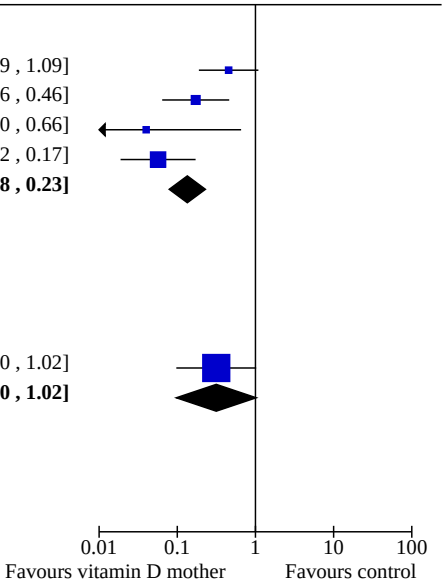


Footnotes

(1) < 27.5 nmol/L

Analysis 5.13. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 13: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: timing of commencement

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.13.1 From birth						
Chandy 2016	6	51	14	54	13.3%	0.45 [0.19 , 1.09]
Naik 2017 (1)	4	53	25	57	23.5%	0.17 [0.06 , 0.46]
Roth 2016	0	49	13	53	12.7%	0.04 [0.00 , 0.66]
Trivedi 2020	3	58	51	56	50.6%	0.06 [0.02 , 0.17]
Subtotal (95% CI)		**211**		**220**	**100.0%**	**0.13 [0.08 , 0.23]**
Total events:	13		103			
Heterogeneity: Chi² = 10.70, df = 3 (P = 0.01); I² = 72%						
Test for overall effect: Z = 7.38 (P < 0.00001)						
5.13.2 From 1 month age						
Wheeler 2016	4	55	6	26	100.0%	0.32 [0.10 , 1.02]
Subtotal (95% CI)		**55**		**26**	**100.0%**	**0.32 [0.10 , 1.02]**
Total events:	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.92 (P = 0.05)						

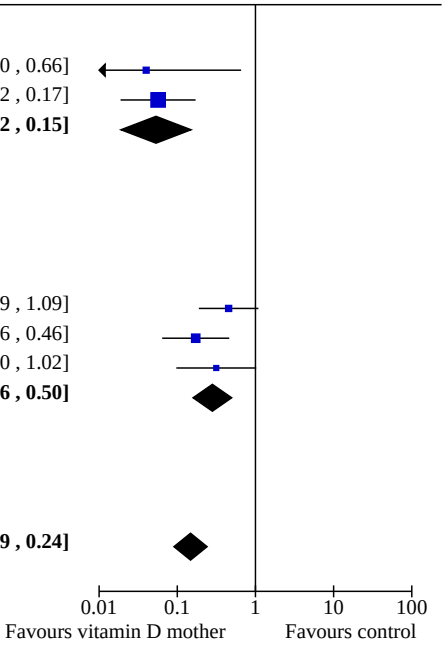


Footnotes

(1) < 27.5 nmol/L

Analysis 5.14. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 14: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: sensitivity analysis

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.14.1 Studies of good methodology						
Roth 2016	0	49	13	53	11.7%	0.04 [0.00 , 0.66]
Trivedi 2020	3	58	51	56	46.9%	0.06 [0.02 , 0.17]
Subtotal (95% CI)		**107**		**109**	**58.6%**	**0.05 [0.02 , 0.15]**
Total events:	3		64			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 5.56 (P < 0.00001)						
5.14.2 Other studies						
Chandy 2016	6	51	14	54	12.3%	0.45 [0.19 , 1.09]
Naik 2017 (1)	4	53	25	57	21.8%	0.17 [0.06 , 0.46]
Wheeler 2016	4	55	6	26	7.4%	0.32 [0.10 , 1.02]
Subtotal (95% CI)		**159**		**137**	**41.4%**	**0.28 [0.16 , 0.50]**
Total events:	14		45			
Heterogeneity: Chi² = 2.13, df = 2 (P = 0.34); I² = 6%						
Test for overall effect: Z = 4.38 (P < 0.0001)						
Total (95% CI)		**266**		**246**	**100.0%**	**0.15 [0.09 , 0.24]**
Total events:	17		109			
Heterogeneity: Chi² = 11.70, df = 4 (P = 0.02); I² = 66%						
Test for overall effect: Z = 7.69 (P < 0.00001)						
Test for subgroup differences: Chi² = 7.63, df = 1 (P = 0.006), I² = 86.9%						

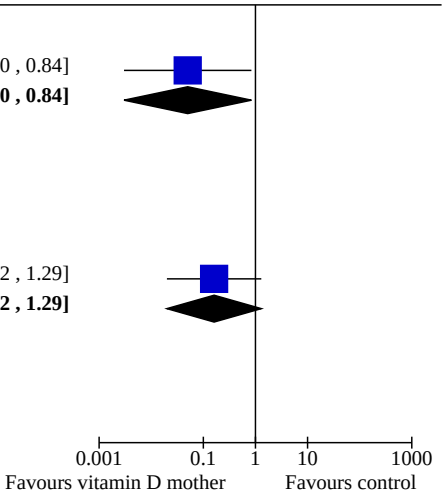


Footnotes

(1) < 27.5 nmol/L

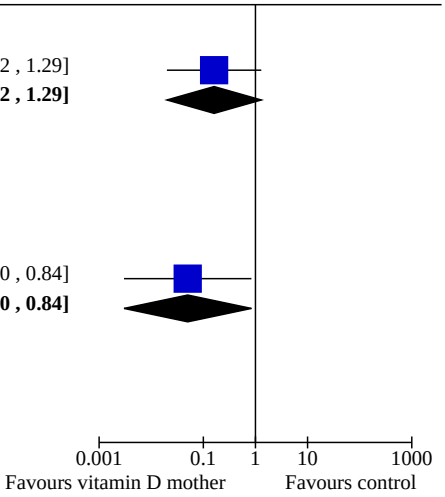
Analysis 5.15. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 15: Nutritional rickets: biochemical: subgroup analyses

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.15.1 Higher-risk infants: Oral D3 60,000 IU/day for 10 days						
Naik 2017	0	56	10	59	100.0%	0.05 [0.00 , 0.84]
Subtotal (95% CI)		**56**		**59**	**100.0%**	**0.05 [0.00 , 0.84]**
Total events:	0		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.08 (P = 0.04)						
5.15.2 Higher-risk infants: Oral D3 60,000 IU postpartum and at 6, 10, and 14 weeks						
Trivedi 2020	1	58	6	56	100.0%	0.16 [0.02 , 1.29]
Subtotal (95% CI)		**58**		**56**	**100.0%**	**0.16 [0.02 , 1.29]**
Total events:	1		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.72 (P = 0.09)						
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%						



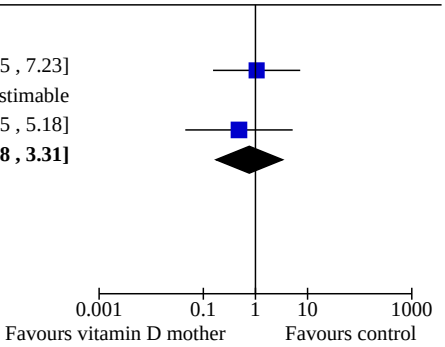
Analysis 5.16. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 16: Nutritional rickets: biochemical: sensitivity analysis

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.16.1 Studies of good methodology						
Trivedi 2020	1	58	6	56	100.0%	0.16 [0.02 , 1.29]
Subtotal (95% CI)		**58**		**56**	**100.0%**	**0.16 [0.02 , 1.29]**
Total events:	1		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.72 (P = 0.09)						
5.16.2 Other studies						
Naik 2017	0	56	10	59	100.0%	0.05 [0.00 , 0.84]
Subtotal (95% CI)		**56**		**59**	**100.0%**	**0.05 [0.00 , 0.84]**
Total events:	0		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.08 (P = 0.04)						



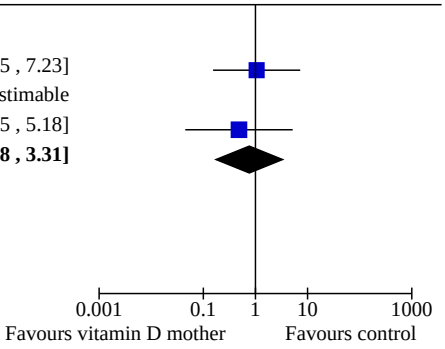
Analysis 5.17. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 17: Nutritional rickets: radiological: infant risk

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.17.1 Higher-risk						
Naik 2017	2	56	2	59	48.9%	1.05 [0.15 , 7.23]
Roth 2016	0	152	0	155		Not estimable
Trivedi 2020	1	58	2	56	51.1%	0.48 [0.05 , 5.18]
Subtotal (95% CI)		**266**		**270**	**100.0%**	**0.76 [0.18 , 3.31]**
Total events:	3		4			
Heterogeneity: $Chi^2 = 0.25$, df = 1 (P = 0.62); $I^2 = 0\%$						
Test for overall effect: Z = 0.36 (P = 0.72)						



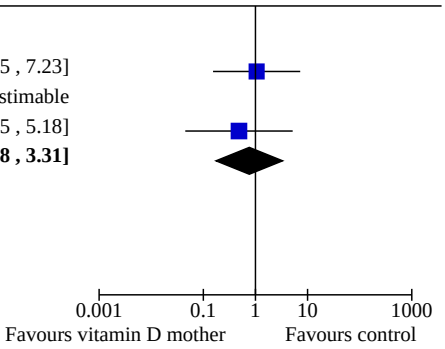
Analysis 5.18. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 18: Nutritional rickets: radiological: season of supplementation

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.18.1 Supplementation not seasonal						
Naik 2017	2	56	2	59	48.9%	1.05 [0.15 , 7.23]
Roth 2016	0	152	0	155		Not estimable
Trivedi 2020	1	58	2	56	51.1%	0.48 [0.05 , 5.18]
Subtotal (95% CI)		**266**		**270**	**100.0%**	**0.76 [0.18 , 3.31]**
Total events:	3		4			
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						



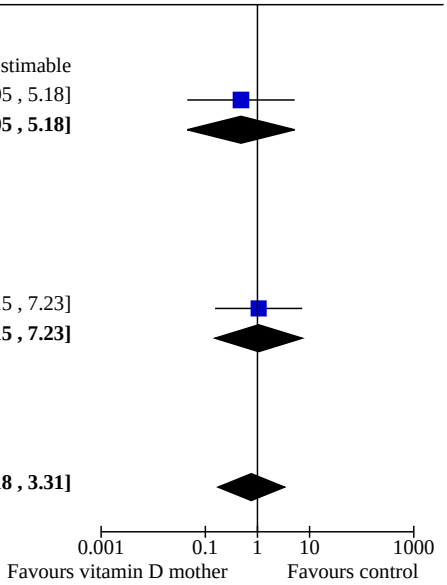
Analysis 5.19. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 19: Nutritional rickets: radiological: D2 versus D3

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.19.1 Vitamin D3						
Naik 2017	2	56	2	59	48.9%	1.05 [0.15 , 7.23]
Roth 2016	0	152	0	155		Not estimable
Trivedi 2020	1	58	2	56	51.1%	0.48 [0.05 , 5.18]
Subtotal (95% CI)		**266**		**270**	**100.0%**	**0.76 [0.18 , 3.31]**
Total events:	3		4			
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						



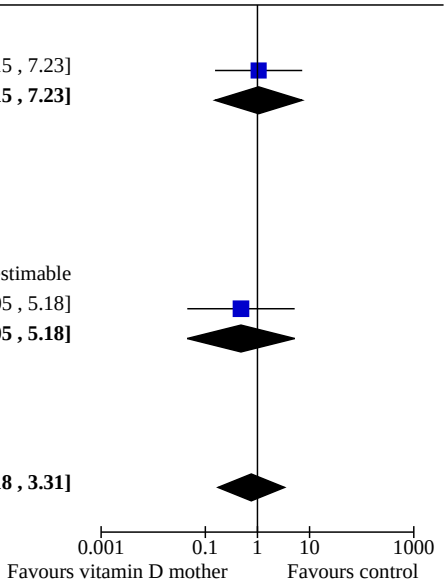
Analysis 5.20. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 20: Nutritional rickets: radiological: dosage

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.20.1 > 2000 to 4000 IU/day						
Roth 2016	0	152	0	155		Not estimable
Trivedi 2020	1	58	2	56	51.1%	0.48 [0.05 , 5.18]
Subtotal (95% CI)		**210**		**211**	**51.1%**	**0.48 [0.05 , 5.18]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
5.20.2 > 4000 IU/day						
Naik 2017	2	56	2	59	48.9%	1.05 [0.15 , 7.23]
Subtotal (95% CI)		**56**		**59**	**48.9%**	**1.05 [0.15 , 7.23]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
Total (95% CI)		**266**		**270**	**100.0%**	**0.76 [0.18 , 3.31]**
Total events:	3		4			
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%						



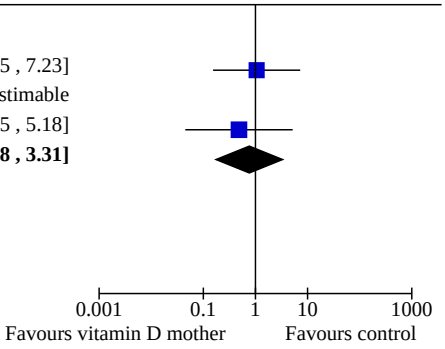
Analysis 5.21. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 21: Nutritional rickets: radiological: duration of supplementation

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.21.1 < 1 month						
Naik 2017	2	56	2	59	48.9%	1.05 [0.15 , 7.23]
Subtotal (95% CI)		**56**		**59**	**48.9%**	**1.05 [0.15 , 7.23]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
5.21.2 4 to 6 months						
Roth 2016	0	152	0	155		Not estimable
Trivedi 2020	1	58	2	56	51.1%	0.48 [0.05 , 5.18]
Subtotal (95% CI)		**210**		**211**	**51.1%**	**0.48 [0.05 , 5.18]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
Total (95% CI)		**266**		**270**	**100.0%**	**0.76 [0.18 , 3.31]**
Total events:	3		4			
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%						



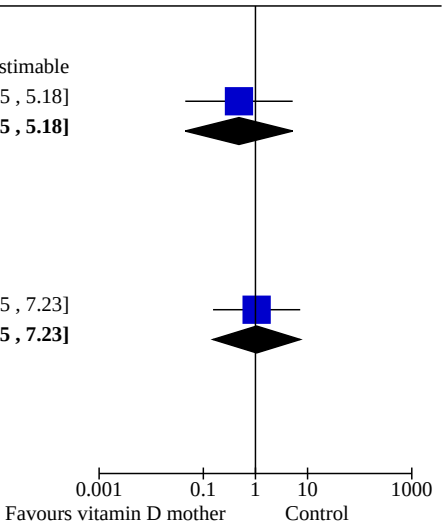
Analysis 5.22. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 22: Nutritional rickets: radiological: timing of commencement

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.22.1 From birth						
Naik 2017	2	56	2	59	48.9%	1.05 [0.15 , 7.23]
Roth 2016	0	152	0	155		Not estimable
Trivedi 2020	1	58	2	56	51.1%	0.48 [0.05 , 5.18]
Subtotal (95% CI)		**266**		**270**	**100.0%**	**0.76 [0.18 , 3.31]**
Total events:	3		4			
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						



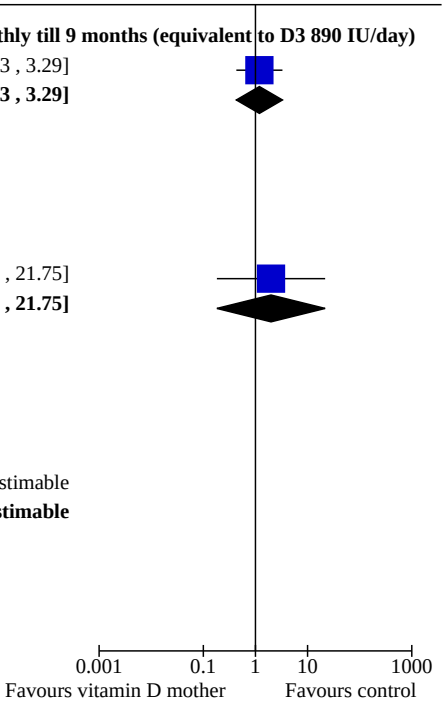
Analysis 5.23. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 23: Nutritional rickets: radiological: sensitivity analysis

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.23.1 Studies of good methodology						
Roth 2016	0	152	0	155		Not estimable
Trivedi 2020	1	58	2	56	100.0%	0.48 [0.05 , 5.18]
Subtotal (95% CI)		**210**		**211**	**100.0%**	**0.48 [0.05 , 5.18]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
5.23.2 All studies						
Naik 2017	2	56	2	59	100.0%	1.05 [0.15 , 7.23]
Subtotal (95% CI)		**56**		**59**	**100.0%**	**1.05 [0.15 , 7.23]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						



Analysis 5.24. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 24: Adverse effects (hypercalcaemia): subgroup analyses

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.24.1 Oral D3 120 000 IU within 7 days of delivery, then 1.5, 2.5 and 3.5 months, then monthly till 9 months (equivalent to D3 890 IU/day)						
Chandy 2016 (1)	7	50	6	51	100.0%	1.19 [0.43 , 3.29]
Subtotal (95% CI)		**50**		**51**	**100.0%**	**1.19 [0.43 , 3.29]**
Total events:	7		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
5.24.2 Oral D3 4000 IU/day till 26 weeks						
Roth 2016 (2)	2	186	1	185	100.0%	1.99 [0.18 , 21.75]
Subtotal (95% CI)		**186**		**185**	**100.0%**	**1.99 [0.18 , 21.75]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.57)						
5.24.3 Oral D3 50 000 IU monthly from 4 weeks to 16 weeks (equivalent to D3 1670 IU/day)						
Wheeler 2016	0	57	0	28		Not estimable
Subtotal (95% CI)		**57**		**28**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: $Chi^2 = 0.15$, df = 1 (P = 0.70), $I^2 = 0\%$						



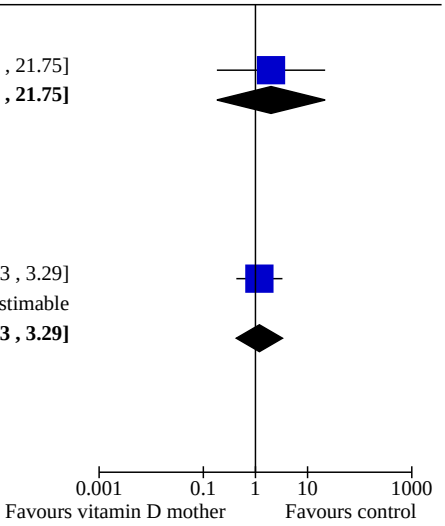
Footnotes

(1) Ca > 2.62 mmol/L

(2) Single reading of Ca > 2.8 mmol/L or 2 readings of Ca > 2.6 mmol/L

Analysis 5.25. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 25: Adverse effects (hypercalcaemia): sensitivity analysis

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.25.1 Studies of good methodology						
Roth 2016 (1)	2	186	1	185	100.0%	1.99 [0.18 , 21.75]
Subtotal (95% CI)		**186**		**185**	**100.0%**	**1.99 [0.18 , 21.75]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.57)						
5.25.2 Other studies						
Chandy 2016 (2)	7	50	6	51	100.0%	1.19 [0.43 , 3.29]
Wheeler 2016	0	57	0	28		Not estimable
Subtotal (95% CI)		**107**		**79**	**100.0%**	**1.19 [0.43 , 3.29]**
Total events:	7		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						



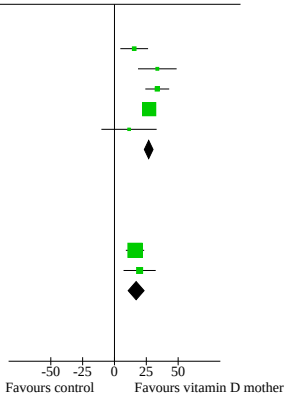
Footnotes

(1) Single reading of Ca > 2.8 mmol/L or 2 readings of Ca > 2.6 mmol/L

(2) Ca > 2.62 mmol/l

Analysis 5.26. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 26: Serum 25-OH vitamin D level at latest time reported to six months of age: infant risk

Study or Subgroup	Vitamin D mother Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
5.26.1 Higher-risk								
Chandy 2016 (1)	60.8	29.037	51	45.3	27.777	54	9.9%	15.50 [4.62 , 26.38]
Naik 2017	72.975	36.675	53	39.325	44.325	57	5.1%	33.65 [18.49 , 48.81]
Roth 2016	80.4	21.8	49	46.8	26.4	53	13.3%	33.60 [24.23 , 42.97]
Trivedi 2020	43.327	12.8	58	16.075	9.4	56	69.2%	27.25 [23.14 , 31.36]
Wheeler 2016	48.8211	38.7	57	37.4	51.9	28	2.5%	11.42 [-10.27 , 33.11]
Subtotal (95% CI)			**268**			**248**	**100.0%**	**26.87 [23.45 , 30.29]**
Heterogeneity: Chi² = 8.93, df = 4 (P = 0.06); I² = 55%								
Test for overall effect: Z = 15.39 (P < 0.00001)								
5.26.2 Lower-risk								
Niramitmahapanya 2017	40.4	12.56	35	24.28	17.2	33	75.5%	16.12 [8.93 , 23.31]
Thiele 2017	62.225	11.075	7	42.475	11.975	6	24.5%	19.75 [7.14 , 32.36]
Subtotal (95% CI)			**42**			**39**	**100.0%**	**17.01 [10.76 , 23.26]**
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%								
Test for overall effect: Z = 5.34 (P < 0.00001)								
Test for subgroup differences: Chi² = 7.35, df = 1 (P = 0.007), I² = 86.4%								

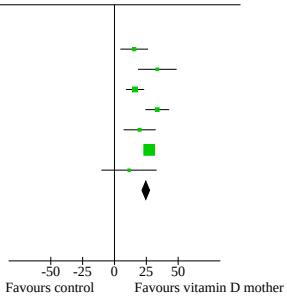


Footnotes

(1) Converted from median and IQR

Analysis 5.27. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 27: Serum 25-OH vitamin D level at latest time reported to six months of age: season of supplementation

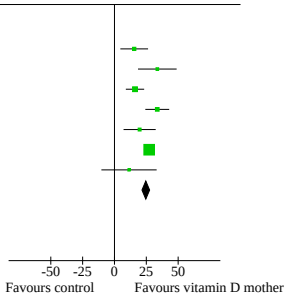
Study or Subgroup	Vitamin D mother Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
5.27.1 Supplementation non-seasonal								
Chandy 2016 (1)	60.8	29.037	51	45.3	27.777	54	7.6%	15.50 [4.62 , 26.38]
Naik 2017	72.975	36.675	53	39.325	44.325	57	3.9%	33.65 [18.49 , 48.81]
Niramitmahapanya 2017	40.4	12.56	35	24.28	17.2	33	17.4%	16.12 [8.93 , 23.31]
Roth 2016	80.4	21.8	49	46.8	26.4	53	10.3%	33.60 [24.23 , 42.97]
Thiele 2017	62.225	11.075	7	42.475	11.975	6	5.7%	19.75 [7.14 , 32.36]
Trivedi 2020	43.327	12.8	58	16.075	9.4	56	53.2%	27.25 [23.14 , 31.36]
Wheeler 2016	48.8211	38.7	57	37.4	51.9	28	1.9%	11.42 [-10.27 , 33.11]
Subtotal (95% CI)			**310**			**287**	**100.0%**	**24.60 [21.59 , 27.60]**
Heterogeneity: Chi² = 16.52, df = 6 (P = 0.01); I² = 64%								
Test for overall effect: Z = 16.06 (P < 0.00001)								



Footnotes
(1) Converted from median and IQR

Analysis 5.28. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 28: Serum 25-OH vitamin D level at latest time reported to six months of age: D2 versus D3

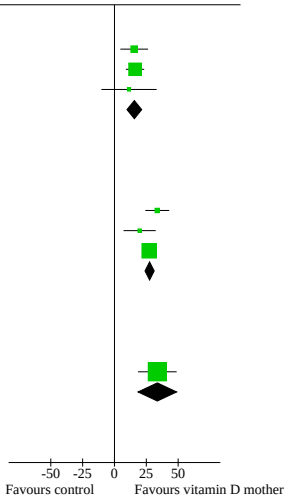
Study or Subgroup	Vitamin D mother Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
5.28.1 Vitamin D3								
Chandy 2016 (1)	60.8	29.037	51	45.3	27.777	54	7.6%	15.50 [4.62 , 26.38]
Naik 2017	72.975	36.675	53	39.325	44.325	57	3.9%	33.65 [18.49 , 48.81]
Niramitmahapanya 2017	40.4	12.56	35	24.28	17.2	33	17.4%	16.12 [8.93 , 23.31]
Roth 2016	80.4	21.8	49	46.8	26.4	53	10.3%	33.60 [24.23 , 42.97]
Thiele 2017	62.225	11.075	7	42.475	11.975	6	5.7%	19.75 [7.14 , 32.36]
Trivedi 2020	43.327	12.8	58	16.075	9.4	56	53.2%	27.25 [23.14 , 31.36]
Wheeler 2016	48.8211	38.7	57	37.4	51.9	28	1.9%	11.42 [-10.27 , 33.11]
Subtotal (95% CI)			**310**			**287**	**100.0%**	**24.60 [21.59 , 27.60]**
Heterogeneity: Chi² = 16.52, df = 6 (P = 0.01); I² = 64%								
Test for overall effect: Z = 16.06 (P < 0.00001)								



Footnotes
(1) Converted from median and IQR

Analysis 5.29. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 29: Serum 25-OH vitamin D level at latest time reported to six months of age: dosage

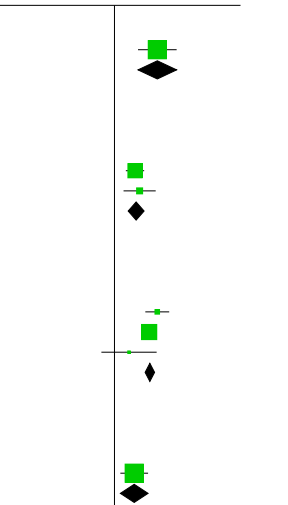
Study or Subgroup	Vitamin D mother Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
5.29.1 400 to 2000 IU/day								
Chandy 2016 (1)	60.8	29.037	51	45.3	27.777	54	28.3%	15.50 [4.62 , 26.38]
Niramitmahapanya 2017	40.4	12.56	35	24.28	17.2	33	64.6%	16.12 [8.93 , 23.31]
Wheeler 2016	48.8211	38.7	57	37.4	51.9	28	7.1%	11.42 [-10.27 , 33.11]
Subtotal (95% CI)			**143**			**115**	**100.0%**	**15.61 [9.83 , 21.39]**
Heterogeneity: Chi² = 0.16, df = 2 (P = 0.92); I² = 0%								
Test for overall effect: Z = 5.29 (P < 0.00001)								
5.29.2 > 2000 to 4000 IU/day								
Roth 2016	80.4	21.8	49	46.8	26.4	53	14.8%	33.60 [24.23 , 42.97]
Thiele 2017	62.225	11.075	7	42.475	11.975	6	8.2%	19.75 [7.14 , 32.36]
Trivedi 2020	43.327	12.8	58	16.075	9.4	56	77.0%	27.25 [23.14 , 31.36]
Subtotal (95% CI)			**114**			**115**	**100.0%**	**27.58 [23.97 , 31.19]**
Heterogeneity: Chi² = 3.09, df = 2 (P = 0.21); I² = 35%								
Test for overall effect: Z = 14.98 (P < 0.00001)								
5.29.3 > 4000 IU/day								
Naik 2017	72.975	36.675	53	39.325	44.325	57	100.0%	33.65 [18.49 , 48.81]
Subtotal (95% CI)			**53**			**57**	**100.0%**	**33.65 [18.49 , 48.81]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.35 (P < 0.0001)								
Test for subgroup differences: Chi² = 13.27, df = 2 (P = 0.001), I² = 84.9%								



Footnotes
(1) Converted from median and IQR

Analysis 5.30. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 30: Serum 25-OH vitamin D level at latest time reported to six months of age: duration of supplementation

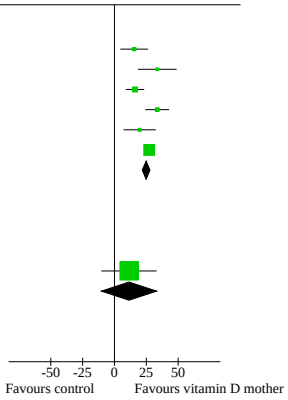
Study or Subgroup	Vitamin D mother Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
5.30.1 < 1 month								
Naik 2017	72.975	36.675	53	39.325	44.325	57	100.0%	33.65 [18.49 , 48.81]
Subtotal (95% CI)			**53**			**57**	**100.0%**	**33.65 [18.49 , 48.81]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.35 (P < 0.0001)								
5.30.2 1 to 3 months								
Niramitmahapanya 2017	40.4	12.56	35	24.28	17.2	33	75.5%	16.12 [8.93 , 23.31]
Thiele 2017	62.225	11.075	7	42.475	11.975	6	24.5%	19.75 [7.14 , 32.36]
Subtotal (95% CI)			**42**			**39**	**100.0%**	**17.01 [10.76 , 23.26]**
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%								
Test for overall effect: Z = 5.34 (P < 0.00001)								
5.30.3 4 to 6 months								
Roth 2016	80.4	21.8	49	46.8	26.4	53	15.7%	33.60 [24.23 , 42.97]
Trivedi 2020	43.327	12.8	58	16.075	9.4	56	81.4%	27.25 [23.14 , 31.36]
Wheeler 2016	48.8211	38.7	57	37.4	51.9	28	2.9%	11.42 [-10.27 , 33.11]
Subtotal (95% CI)			**164**			**137**	**100.0%**	**27.78 [24.07 , 31.49]**
Heterogeneity: Chi² = 3.73, df = 2 (P = 0.15); I² = 46%								
Test for overall effect: Z = 14.68 (P < 0.00001)								
5.30.4 >6 months								
Chandy 2016 (1)	60.8	29.037	51	45.3	27.777	54	100.0%	15.50 [4.62 , 26.38]
Subtotal (95% CI)			**51**			**54**	**100.0%**	**15.50 [4.62 , 26.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.79 (P = 0.005)								
Test for subgroup differences: Chi² = 12.55, df = 3 (P = 0.006), I² = 76.1%								



Footnotes
(1) Converted from median and IQR

Analysis 5.31. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 31: Serum 25-OH vitamin D level at latest time reported to six months of age: timing of commencement

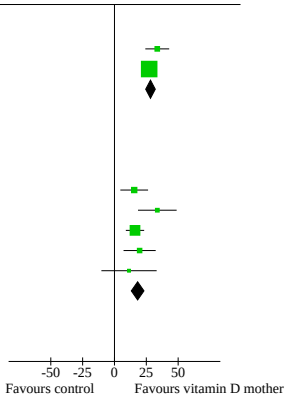
Study or Subgroup	Vitamin D mother Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
5.31.1 From birth								
Chandy 2016 (1)	60.8	29.037	51	45.3	27.777	54	7.8%	15.50 [4.62 , 26.38]
Naik 2017	72.975	36.675	53	39.325	44.325	57	4.0%	33.65 [18.49 , 48.81]
Niramitmahapanya 2017	40.4	12.56	35	24.28	17.2	33	17.7%	16.12 [8.93 , 23.31]
Roth 2016	80.4	21.8	49	46.8	26.4	53	10.5%	33.60 [24.23 , 42.97]
Thiele 2017	62.225	11.075	7	42.475	11.975	6	5.8%	19.75 [7.14 , 32.36]
Trivedi 2020	43.327	12.8	58	16.075	9.4	56	54.3%	27.25 [23.14 , 31.36]
Subtotal (95% CI)			**253**			**259**	**100.0%**	**24.85 [21.82 , 27.88]**
Heterogeneity: Chi² = 15.08, df = 5 (P = 0.01); I² = 67%								
Test for overall effect: Z = 16.08 (P < 0.00001)								
5.31.2 From 1 month age								
Wheeler 2016	48.8211	38.7	57	37.4	51.9	28	100.0%	11.42 [-10.27 , 33.11]
Subtotal (95% CI)			**57**			**28**	**100.0%**	**11.42 [-10.27 , 33.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.03 (P = 0.30)								
Test for subgroup differences: Chi² = 1.44, df = 1 (P = 0.23), I² = 30.8%								



Footnotes
(1) Converted from median and IQR

Analysis 5.32. Comparison 5: Vitamin D given to lactating mothers compared to placebo or no treatment: subgroup and sensitivity analyses, Outcome 32: Serum 25-OH vitamin D level at latest time reported to six months of age: sensitivity analysis

Study or Subgroup	Vitamin D mother Mean [nmol/L]	SD [nmol/L]	Total	Control Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
5.32.1 Studies of good methodology								
Roth 2016	80.4	21.8	49	46.8	26.4	53	16.2%	33.60 [24.23 , 42.97]
Trivedi 2020	43.327	12.8	58	16.075	9.4	56	83.8%	27.25 [23.14 , 31.36]
Subtotal (95% CI)			**107**			**109**	**100.0%**	**28.28 [24.51 , 32.04]**
Heterogeneity: Chi² = 1.48, df = 1 (P = 0.22); I² = 32%								
Test for overall effect: Z = 14.72 (P < 0.00001)								
5.32.2 Other studies								
Chandy 2016 (1)	60.8	29.037	51	45.3	27.777	54	20.8%	15.50 [4.62 , 26.38]
Naik 2017	72.975	36.675	53	39.325	44.325	57	10.7%	33.65 [18.49 , 48.81]
Niramitmahapanya 2017	40.4	12.56	35	24.28	17.2	33	47.7%	16.12 [8.93 , 23.31]
Thiele 2017	62.225	11.075	7	42.475	11.975	6	15.5%	19.75 [7.14 , 32.36]
Wheeler 2016	48.8211	38.7	57	37.4	51.9	28	5.2%	11.42 [-10.27 , 33.11]
Subtotal (95% CI)			**203**			**178**	**100.0%**	**18.19 [13.22 , 23.16]**
Heterogeneity: Chi² = 4.98, df = 4 (P = 0.29); I² = 20%								
Test for overall effect: Z = 7.18 (P < 0.00001)								



Footnotes
(1) Converted from median and IQR

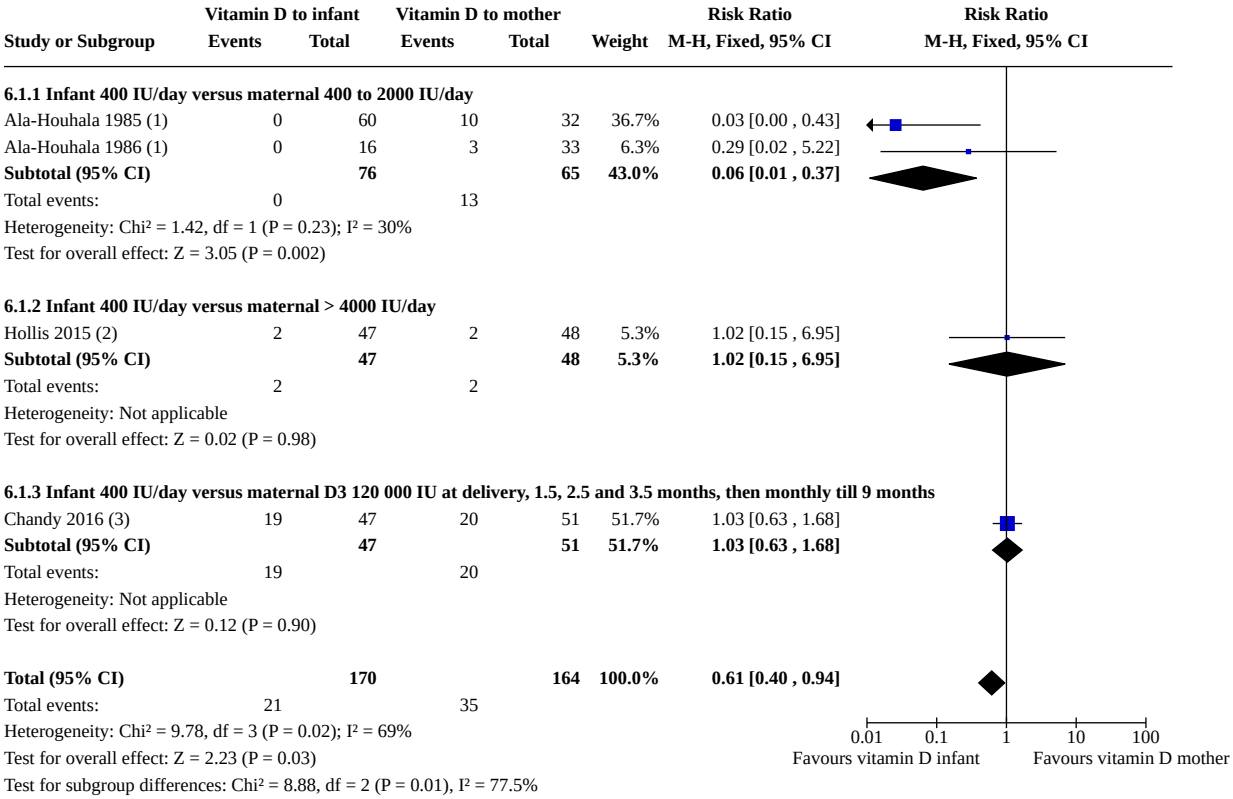
Comparison 6. Vitamin D given to infants compared to vitamin D given to lactating mothers: sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L: subgroup analysis	4	334	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.40, 0.94]
6.1.1 Infant 400 IU/day versus maternal 400 to 2000 IU/day	2	141	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.37]
6.1.2 Infant 400 IU/day versus maternal > 4000 IU/day	1	95	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.15, 6.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1.3 Infant 400 IU/day versus maternal D3 120 000 IU at delivery, 1.5, 2.5 and 3.5 months, then monthly till 9 months	1	98	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.63, 1.68]
6.2 Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L: sensitivity analysis	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.2.1 Other studies	4	334	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.40, 0.94]
6.3 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: subgroup analysis	4	334	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.17, 0.72]
6.3.1 Infant 400 IU/day versus maternal 400 to 2000 IU/day	2	141	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.37]
6.3.2 Infant 400 IU/day versus maternal > 4000 IU/day	1	95	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.15, 6.95]
6.3.3 Infant 400 IU/day versus maternal D3 120 000 IU at delivery, 1.5, 2.5 and 3.5 months, then monthly till 9 months	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.30, 2.77]
6.4 Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: sensitivity analysis	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.4.1 Other studies	4	334	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.17, 0.72]
6.5 Nutritional rickets: biochemical: sensitivity analysis	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.5.1 Other studies	1	92	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.6 Adverse effects (hypercalcaemia): subgroup and sensitivity analyses	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.6.1 Other studies: infant D3 400 IU/day versus maternal D3 3000 µg (120 000 IU) at birth, 1.5, 2.5 and 3.5 months, then monthly to 9 months	1	97	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.48, 3.09]
6.7 Serum 25-OH vitamin D level at latest time reported to six months of age: subgroup analysis	4	269	Mean Difference (IV, Fixed, 95% CI)	14.35 [9.64, 19.06]
6.7.1 Infant 400 IU/day versus maternal 400 to 2000 IU/day	1	47	Mean Difference (IV, Fixed, 95% CI)	36.80 [26.78, 46.82]
6.7.2 Infant 400 IU/day versus maternal > 2000 to 4000 IU/day	1	30	Mean Difference (IV, Fixed, 95% CI)	13.50 [6.45, 20.55]
6.7.3 Infant 400 IU/day versus maternal > 4000 IU/day	1	95	Mean Difference (IV, Fixed, 95% CI)	0.60 [-13.48, 14.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.7.4 Infant 400 IU/day versus maternal D3 120 000 IU at delivery, 1.5, 2.5 and 3.5 months, then monthly till 9 months	1	97	Mean Difference (IV, Fixed, 95% CI)	0.50 [-9.54, 10.54]
6.8 Serum 25-OH vitamin D level at latest time reported to six months of age: sensitivity analysis	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.8.1 Other studies	4	269	Mean Difference (IV, Fixed, 95% CI)	14.35 [9.64, 19.06]

Analysis 6.1. Comparison 6: Vitamin D given to infants compared to vitamin D given to lactating mothers: sensitivity analysis, Outcome 1: Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L: subgroup analysis

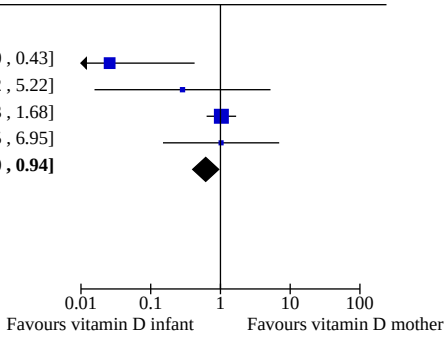


Footnotes

(1) < 12.5 nmol/L
(2) < 50 nmol/L
(3) <25 nmol/l

Analysis 6.2. Comparison 6: Vitamin D given to infants compared to vitamin D given to lactating mothers: sensitivity analysis, Outcome 2: Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L: sensitivity analysis

Study or Subgroup	Vitamin D to infant Events	Total	Vitamin D to mother Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.2.1 Other studies						
Ala-Houhala 1985 (1)	0	60	10	32	36.7%	0.03 [0.00 , 0.43]
Ala-Houhala 1986 (1)	0	16	3	33	6.3%	0.29 [0.02 , 5.22]
Chandy 2016 (2)	19	47	20	51	51.7%	1.03 [0.63 , 1.68]
Hollis 2015 (3)	2	47	2	48	5.3%	1.02 [0.15 , 6.95]
Subtotal (95% CI)		**170**		**164**	**100.0%**	**0.61 [0.40 , 0.94]**
Total events:	21		35			
Heterogeneity: Chi² = 9.78, df = 3 (P = 0.02); I² = 69%						
Test for overall effect: Z = 2.23 (P = 0.03)						

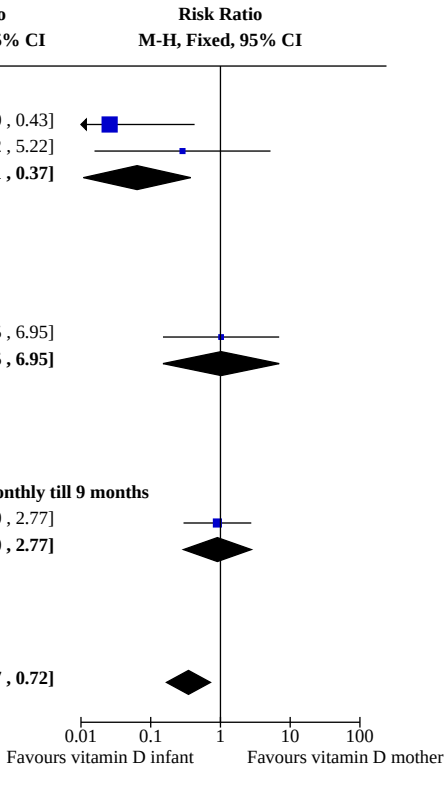


Footnotes

(1) < 12.5 nmol/L
(2) < 25 nmol/L
(3) < 50 nmol/L

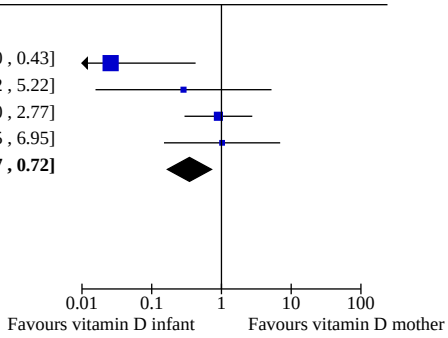
Analysis 6.3. Comparison 6: Vitamin D given to infants compared to vitamin D given to lactating mothers: sensitivity analysis, Outcome 3: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: subgroup analysis

Study or Subgroup	Vitamin D to infant Events	Total	Vitamin D to mother Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.3.1 Infant 400 IU/day versus maternal 400 to 2000 IU/day						
Ala-Houhala 1985	0	60	10	32	57.5%	0.03 [0.00 , 0.43]
Ala-Houhala 1986	0	16	3	33	9.8%	0.29 [0.02 , 5.22]
Subtotal (95% CI)		**76**		**65**	**67.4%**	**0.06 [0.01 , 0.37]**
Total events:	0		13			
Heterogeneity: Chi² = 1.42, df = 1 (P = 0.23); I² = 30%						
Test for overall effect: Z = 3.05 (P = 0.002)						
6.3.2 Infant 400 IU/day versus maternal > 4000 IU/day						
Hollis 2015	2	47	2	48	8.4%	1.02 [0.15 , 6.95]
Subtotal (95% CI)		**47**		**48**	**8.4%**	**1.02 [0.15 , 6.95]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
6.3.3 Infant 400 IU/day versus maternal D3 120 000 IU at delivery, 1.5, 2.5 and 3.5 months, then monthly till 9 months						
Chandy 2016	5	47	6	51	24.3%	0.90 [0.30 , 2.77]
Subtotal (95% CI)		**47**		**51**	**24.3%**	**0.90 [0.30 , 2.77]**
Total events:	5		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.86)						
Total (95% CI)		**170**		**164**	**100.0%**	**0.35 [0.17 , 0.72]**
Total events:	7		21			
Heterogeneity: Chi² = 7.34, df = 3 (P = 0.06); I² = 59%						
Test for overall effect: Z = 2.85 (P = 0.004)						
Test for subgroup differences: Chi² = 6.82, df = 2 (P = 0.03), I² = 70.7%						



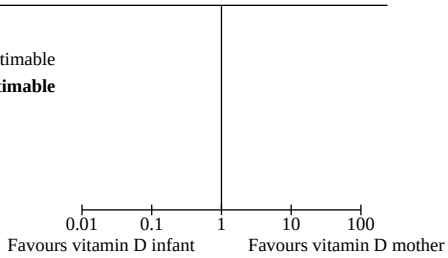
Analysis 6.4. Comparison 6: Vitamin D given to infants compared to vitamin D given to lactating mothers: sensitivity analysis, Outcome 4: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L: sensitivity analysis

Study or Subgroup	Vitamin D to infant Events	Total	Vitamin D to mother Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.4.1 Other studies						
Ala-Houhala 1985	0	60	10	32	57.5%	0.03 [0.00 , 0.43]
Ala-Houhala 1986	0	16	3	33	9.8%	0.29 [0.02 , 5.22]
Chandy 2016	5	47	6	51	24.3%	0.90 [0.30 , 2.77]
Hollis 2015	2	47	2	48	8.4%	1.02 [0.15 , 6.95]
Subtotal (95% CI)		**170**		**164**	**100.0%**	**0.35 [0.17 , 0.72]**
Total events:	7		21			
Heterogeneity: Chi² = 7.34, df = 3 (P = 0.06); I² = 59%						
Test for overall effect: Z = 2.85 (P = 0.004)						



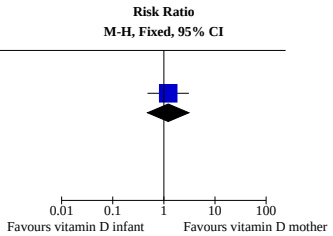
Analysis 6.5. Comparison 6: Vitamin D given to infants compared to vitamin D given to lactating mothers: sensitivity analysis, Outcome 5: Nutritional rickets: biochemical: sensitivity analysis

Study or Subgroup	Vitamin D to infant Events	Total	Vitamin D to mother Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.5.1 Other studies						
Ala-Houhala 1985	0	60	0	32		Not estimable
Subtotal (95% CI)		**60**		**32**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



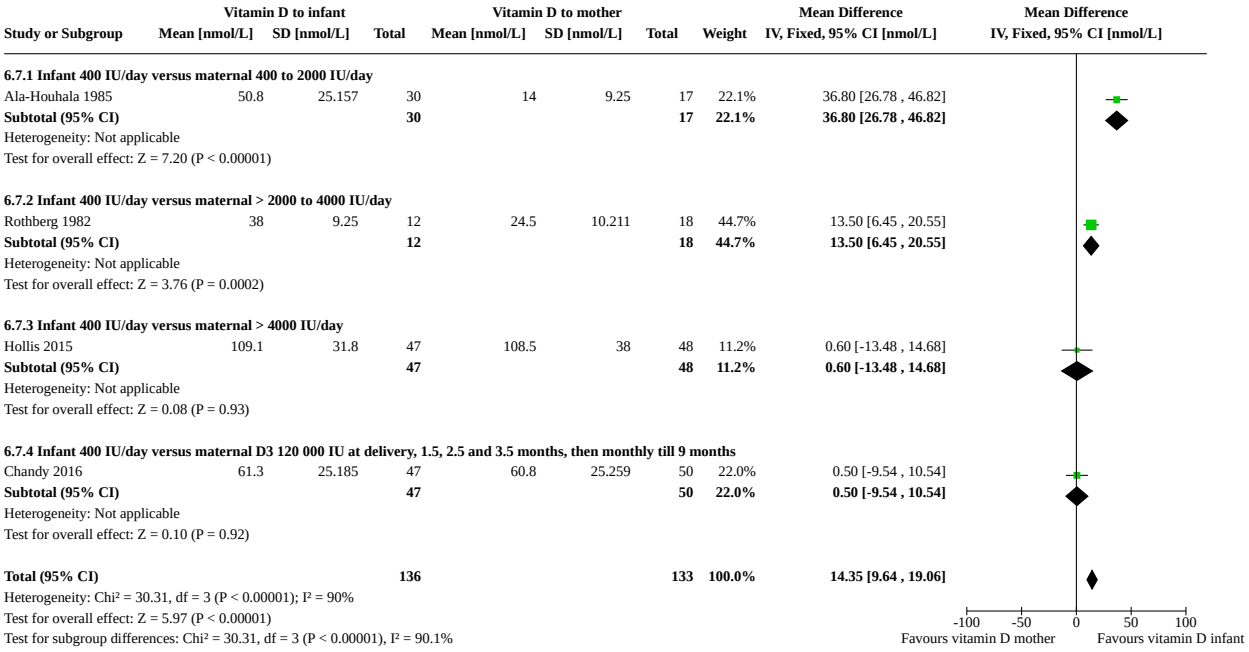
Analysis 6.6. Comparison 6: Vitamin D given to infants compared to vitamin D given to lactating mothers: sensitivity analysis, Outcome 6: Adverse effects (hypercalcaemia): subgroup and sensitivity analyses

Study or Subgroup	Vitamin D to infant Events	Total	Vitamin D to mother Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.6.1 Other studies: infant D3 400 IU/day versus maternal D3 3000 µg (120 000 IU) at birth, 1.5, 2.5 and 3.5 months, then monthly to 9 months						
Chandy 2016 (1)	8	47	7	50	100.0%	1.22 [0.48 , 3.09]
Subtotal (95% CI)		**47**		**50**	**100.0%**	**1.22 [0.48 , 3.09]**
Total events:	8		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						



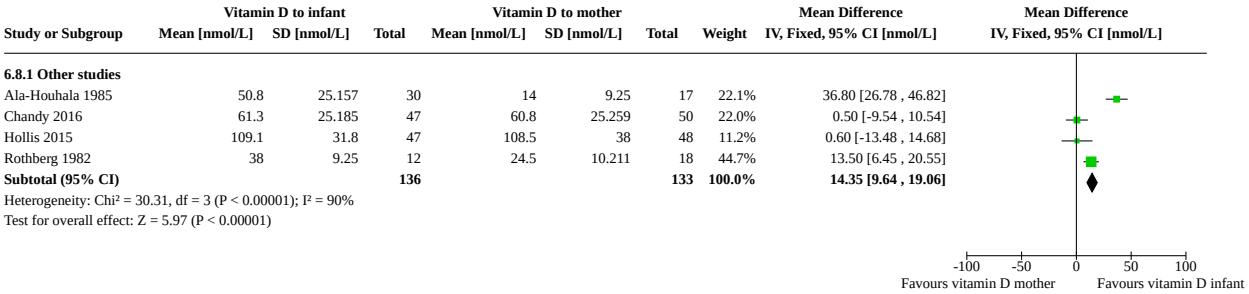
Footnotes
(1) > 2.62 mmol/L

Analysis 6.7. Comparison 6: Vitamin D given to infants compared to vitamin D given to lactating mothers: sensitivity analysis, Outcome 7: Serum 25-OH vitamin D level at latest time reported to six months of age: subgroup analysis



Study or Subgroup	Vitamin D to infant Mean [nmol/L]	SD [nmol/L]	Total	Vitamin D to mother Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
6.7.1 Infant 400 IU/day versus maternal 400 to 2000 IU/day								
Ala-Houhala 1985	50.8	25.157	30	14	9.25	17	22.1%	36.80 [26.78 , 46.82]
Subtotal (95% CI)			**30**			**17**	**22.1%**	**36.80 [26.78 , 46.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 7.20 (P < 0.00001)								
6.7.2 Infant 400 IU/day versus maternal > 2000 to 4000 IU/day								
Rothberg 1982	38	9.25	12	24.5	10.211	18	44.7%	13.50 [6.45 , 20.55]
Subtotal (95% CI)			**12**			**18**	**44.7%**	**13.50 [6.45 , 20.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.76 (P = 0.0002)								
6.7.3 Infant 400 IU/day versus maternal > 4000 IU/day								
Hollis 2015	109.1	31.8	47	108.5	38	48	11.2%	0.60 [-13.48 , 14.68]
Subtotal (95% CI)			**47**			**48**	**11.2%**	**0.60 [-13.48 , 14.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.08 (P = 0.93)								
6.7.4 Infant 400 IU/day versus maternal D3 120 000 IU at delivery, 1.5, 2.5 and 3.5 months, then monthly till 9 months								
Chandy 2016	61.3	25.185	47	60.8	25.259	50	22.0%	0.50 [-9.54 , 10.54]
Subtotal (95% CI)			**47**			**50**	**22.0%**	**0.50 [-9.54 , 10.54]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								
Total (95% CI)			**136**			**133**	**100.0%**	**14.35 [9.64 , 19.06]**
Heterogeneity: Chi² = 30.31, df = 3 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 5.97 (P < 0.00001)								
Test for subgroup differences: Chi² = 30.31, df = 3 (P < 0.00001), I² = 90.1%								

Analysis 6.8. Comparison 6: Vitamin D given to infants compared to vitamin D given to lactating mothers: sensitivity analysis, Outcome 8: Serum 25-OH vitamin D level at latest time reported to six months of age: sensitivity analysis



Study or Subgroup	Vitamin D to infant Mean [nmol/L]	SD [nmol/L]	Total	Vitamin D to mother Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
6.8.1 Other studies								
Ala-Houhala 1985	50.8	25.157	30	14	9.25	17	22.1%	36.80 [26.78 , 46.82]
Chandy 2016	61.3	25.185	47	60.8	25.259	50	22.0%	0.50 [-9.54 , 10.54]
Hollis 2015	109.1	31.8	47	108.5	38	48	11.2%	0.60 [-13.48 , 14.68]
Rothberg 1982	38	9.25	12	24.5	10.211	18	44.7%	13.50 [6.45 , 20.55]
Subtotal (95% CI)			**136**			**133**	**100.0%**	**14.35 [9.64 , 19.06]**
Heterogeneity: Chi² = 30.31, df = 3 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 5.97 (P < 0.00001)								

APPENDICES

Appendix 1. Cochrane Neonatal standard search strategy

Searches were performed 29th May 2020 of the following databases using the search terms 'exp vitamin D/ or vitamin D.mp.; cholecalciferol.mp. or exp colecalciferol/; colecalciferol.mp' adapted for the database. Additional searches were performed as documented in Appendix 2; Appendix 3; Appendix 4; and Appendix 5.

CENTRAL via CRS Web:

1. MESH DESCRIPTOR Infant, Newborn EXPLODE ALL AND CENTRAL:TARGET

2. infant or infants or infant's or "infant s" or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU AND CENTRAL:TARGET

3. #2 OR #1

MEDLINE via Ovid - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R):

1. exp infant, newborn/

2. (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or 'infant s' or infant's or infantile or infancy or neonat*).ti,ab.

3. 1 or 2

4. randomized controlled trial.pt.

5. controlled clinical trial.pt.

6. randomized.ab.

7. placebo.ab.

8. drug therapy.fs.

9. randomly.ab.

10. trial.ab.

11. groups.ab.

12. or/4-11

13. exp animals/ not humans.sh.

14. 12 not 13

15. 3 and 14

16. randomi?ed.ti,ab.

17. randomly.ti,ab.

18. trial.ti,ab.

19. groups.ti,ab.

20. ((single or doubl* or tripl* or treb*) and (blind* or mask*)).ti,ab.

21. placebo*.ti,ab.

22. 16 or 17 or 18 or 19 or 20 or 21

23. 2 and 22

24. limit 23 to yr="2018 -Current"

25. 15 or 24

CINAHL via EBSCOhost:

(infant or infants or infant's or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW) AND (randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Appendix 2. CENTRAL search strategy

EBM Reviews - Cochrane Central Register of Controlled Trials April 2020

1 newborn.mp. or exp Infant, Newborn/

2 neonat*.mp.

3 infant.mp. or exp Infant/

4 infan*.mp.

5 1 or 2 or 3 or 4

6 exp Vitamin D/ or exp Cholecalciferol/ or vitamin d.mp.

7 colecalciferol.mp.

8 cholecalciferol.mp.

9 6 or 7 or 8

10 5 and 9

11 limit 10 to (clinical trial or controlled clinical trial or randomized controlled trial)

12 random*.mp.

13 10 and 12

14 11 or 13

Appendix 3. Embase search strategy

Embase 1974 to 2020 May 29

1 exp infant/ or infant.mp.

2 exp newborn/ or newborn.mp.

3 neonat*.mp.

5 exp vitamin D/ or vitamin D.mp.

6 cholecalciferol.mp. or exp colecalciferol/

7 colecalciferol.mp.

8 5 or 6 or 7

9 4 and 8 n=422

10 limit 9 to (clinical trial or randomized controlled trial or controlled clinical trial)

Appendix 4. MEDLINE search strategy

MEDLINE(R) All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946-current

1 exp infant/ or infant.mp.

2 exp newborn/ or newborn.mp.

3 neonat*.mp.

4 1 or 2 or 3

5 exp vitamin D/ or vitamin D.mp.

6 cholecalciferol.mp. or exp colecalciferol/

7 colecalciferol.mp.

8 5 or 6 or 7

9 4 and 8

10 limit 9 to randomized controlled trial n=290

11 limit 10 to yr="2018 -Current"

Appendix 5. MIDIRS search strategy

Maternity & Infant Care Database (MIDIRS) 1971 to April 2020

1 newborn.mp. [mp=abstract, heading word, title]

2 neonat*.mp. [mp=abstract, heading word, title]

3 infan*.mp. [mp=abstract, heading word, title]

4 1 or 2 or 3

5 vitamin D.mp. [mp=abstract, heading word, title]

6 colecalciferol.mp. [mp=abstract, heading word, title]

7 cholecalciferol.mp. [mp=abstract, heading word, title]

8 5 or 6 or 7

9 4 and 8

10 random*.mp. [mp=abstract, heading word, title]

11 9 and 10

12 limit 9 to randomised controlled trial

13 11 or 12

Appendix 6. 'Risk of bias' tool

We used the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality of the trials. For each trial, we sought information regarding the method of randomisation, blinding and reporting of all outcomes of all the infants enrolled in the trial. We assessed each criterion as being at a low, high, or unclear risk of bias. Two review authors separately assessed each study. Disagreements were resolved by discussion. We added this information to the table Characteristics of included studies. We evaluated the following issues and entered the findings into the 'Risk of bias' table:

Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk.

Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk, high risk or unclear risk for participants; and
- low risk, high risk or unclear risk for personnel.

Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or
- unclear risk.

Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk;
- unclear risk.

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

HISTORY

Protocol first published: Issue 6, 2018
Review first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

MLT, DO and SA contributed to protocol development (Tan 2018), and all stages of the review. MLT was the primary author of the protocol and review. All data and text was cross-checked by DO.

DECLARATIONS OF INTEREST

MLT has no interest to declare.

SAA was an Advisory Board member for the Milk Processors Educational Program (MilkPep), and received consultancy as a scientific advisor. This relationship ended in December 2018.

DAO has no interest to declare.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Australian Satellite of Cochrane Neonatal, Australia

  Supported by a bridging funding grant from Cochrane 2017-8
- Vermont Oxford Network, USA

  Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol (Tan 2018).

- We have reported both bone mineral density and bone mineral content as bone mineral density was not reliably reported, and both measures are accepted by the International Society for Clinical Densitometry as indicators of bone health in paediatric populations (Crabtree 2014).
- Vitamin D insufficiency and deficiency were both included in SoF table analysis to address the objectives of the review. Nutritional rickets was defined as either biochemical or radiological rickets as combined outcomes were not reported.
- Latitude for high-risk populations for vitamin D deficiency was defined as above 52ÃÂ°N or below 52ÃÂ°S as these populations have insufficient UV intensity most of the year.
- Subgroup analysis of doses of vitamin D to mothers was stratified as 400 to 2000 IU/day; 2000 to 4000 IU/day; and > 4000 IU/day. Single and intermittent high-dose studies were incorporated by calculating the average daily dose equivalent.
- Certainty of evidence for surrogate outcomes was downgraded due to indirectness. This included 25-OH vitamin D levels and vitamin D insufficiency which may not be predictive of vitamin D deficiency or bone health (Munns 2016).

INDEX TERMS

Medical Subject Headings (MeSH)

25-Hydroxyvitamin D 2 [blood]; Bone and Bones [*physiology]; Bone Density; *Breast Feeding; Hypercalcemia [etiology]; Lactation; *Mothers; Randomized Controlled Trials as Topic; Rickets [blood]; Term Birth; Vitamin D [*administration & dosage] [adverse effects]; Vitamin D Deficiency [epidemiology] [*prevention & control]; Vitamins [*administration & dosage] [adverse effects]

MeSH check words

Female; Humans; Infant