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Effects of oral vitamin D supplementation on linear growth and other health outcomes among children under five years of age (Review)

Huey SL, Acharya N, Silver A, Sheni R, Yu EA, Peña-Rosas JP, Mehta S

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[Intervention Review]

Effects of oral vitamin D supplementation on linear growth and other health outcomes among children under five years of age

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ABSTRACT

Background

Vitamin D is a secosteroid hormone that is important for its role in calcium homeostasis to maintain skeletal health. Linear growth faltering and stunting remain pervasive indicators of poor nutrition status among infants and children under five years of age around the world, and low vitamin D status has been linked to poor growth. However, existing evidence on the effects of vitamin D supplementation on linear growth and other health outcomes among infants and children under five years of age has not been systematically reviewed.

Objectives

To assess effects of oral vitamin D supplementation on linear growth and other health outcomes among infants and children under five years of age.

Search methods

In December 2019, we searched CENTRAL, PubMed, Embase, 14 other electronic databases, and two trials registries. We also searched the reference lists of relevant publications for any relevant trials, and we contacted key organisations and authors to obtain information on relevant ongoing and unpublished trials.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs assessing the effects of oral vitamin D supplementation, with or without other micronutrients, compared to no intervention, placebo, a lower dose of vitamin D, or the same micronutrients alone (and not vitamin D) in infants and children under five years of age who lived in any country.

Data collection and analysis

We used standard Cochrane methodological procedures.

Main results

Out of 75 studies (187 reports; 12,122 participants) included in the qualitative analysis, 64 studies (169 reports; 10,854 participants) contributed data on our outcomes of interest for meta-analysis. A majority of included studies were conducted in India, USA, and Canada. Two studies reported for-profit funding, two were categorised as receiving mixed funding (non-profit and for-profit), five reported that they received no funding, 26 did not disclose funding sources, and the remaining studies were funded by non-profit funding. Certainty of evidence varied between high and very low across outcomes (all measured at endpoint) for each comparison.

Vitamin D supplementation versus placebo or no intervention (31 studies)

Compared to placebo or no intervention, vitamin D supplementation (at doses 200 to 2000 IU daily; or up to 300,000 IU bolus at enrolment) may make little to no difference in linear growth (measured length/height in cm) among children under five years of age (mean difference (MD) 0.66, 95% confidence interval (CI) -0.37 to 1.68; 3 studies, 240 participants; low-certainty evidence); probably improves length/height-for-age z-score (L/HAZ) (MD 0.11, 95% CI 0.001 to 0.22; 1 study, 1258 participants; moderate-certainty evidence); and probably makes little to no difference in stunting (risk ratio (RR) 0.90, 95% CI 0.80 to 1.01; 1 study, 1247 participants; moderate-certainty evidence).

In terms of adverse events, vitamin D supplementation probably makes little to no difference in developing hypercalciuria compared to placebo (RR 2.03, 95% CI 0.28 to 14.67; 2 studies, 68 participants; moderate-certainty evidence). It is uncertain whether vitamin D supplementation impacts the development of hypercalcaemia as the certainty of evidence was very low (RR 0.82, 95% CI 0.35 to 1.90; 2 studies, 367 participants).

Vitamin D supplementation (higher dose) versus vitamin D (lower dose) (34 studies)

Compared to a lower dose of vitamin D (100 to 1000 IU daily; or up to 300,000 IU bolus at enrolment), higher-dose vitamin D supplementation (200 to 6000 IU daily; or up to 600,000 IU bolus at enrolment) may have little to no effect on linear growth, but we are uncertain about this result (MD 1.00, 95% CI -2.22 to 0.21; 5 studies, 283 participants), and it may make little to no difference in L/HAZ (MD 0.40, 95% CI -0.06 to 0.86; 2 studies, 105 participants; low-certainty evidence). No studies evaluated stunting.

As regards adverse events, higher-dose vitamin D supplementation may make little to no difference in developing hypercalciuria (RR 1.16, 95% CI 1.00 to 1.35; 6 studies, 554 participants; low-certainty evidence) or in hypercalcaemia (RR 1.39, 95% CI 0.89 to 2.18; 5 studies, 986 participants; low-certainty evidence) compared to lower-dose vitamin D supplementation.

Vitamin D supplementation (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s) (9 studies)

Supplementation with a higher dose of vitamin D (400 to 2000 IU daily, or up to 300,000 IU bolus at enrolment) plus micronutrients, compared to a lower dose (200 to 2000 IU daily, or up to 90,000 IU bolus at enrolment) of vitamin D with the same micronutrients, may make little to no difference in linear growth (MD 0.60, 95% CI −3.33 to 4.53; 1 study, 25 participants; low-certainty evidence). No studies evaluated L/HAZ or stunting.

In terms of adverse events, higher-dose vitamin D supplementation with micronutrients, compared to lower-dose vitamin D with the same micronutrients, may make little to no difference in developing hypercalciuria (RR 1.00, 95% CI 0.06 to 15.48; 1 study, 86 participants; low-certainty evidence) and probably makes little to no difference in developing hypercalcaemia (RR 1.00, 95% CI 0.90, 1.11; 2 studies, 126 participants; moderate-certainty evidence).

Four studies measured hyperphosphataemia and three studies measured kidney stones, but they reported no occurrences and therefore were not included in the comparison for these outcomes.

Authors' conclusions

Evidence suggests that oral vitamin D supplementation may result in little to no difference in linear growth, stunting, hypercalciuria, or hypercalcaemia, compared to placebo or no intervention, but may result in a slight increase in length/height-for-age z-score (L/HAZ). Additionally, evidence suggests that compared to lower doses of vitamin D, with or without micronutrients, vitamin D supplementation may result in little to no difference in linear growth, L/HAZ, stunting, hypercalciuria, or hypercalcaemia. Small sample sizes, substantial heterogeneity in terms of population and intervention parameters, and high risk of bias across many of the included studies limit our ability to confirm with any certainty the effects of vitamin D on our outcomes. Larger, well-designed studies of long duration (several months to years) are recommended to confirm whether or not oral vitamin D supplementation may impact linear growth in children under five years of age, among both those who are healthy and those with underlying infectious or non-communicable health conditions.

PLAIN LANGUAGE SUMMARY

Effects of vitamin D on linear growth and other health outcomes among children under 5 years of age

Background

Vitamin D is an essential nutrient that plays a major role in skeletal health. Deficiency in vitamin D has also been linked to non-skeletal health outcomes such as growth. Stunting and poor growth among children under five years of age remain a major global challenge. Previous literature has shown that blood vitamin D level is associated with stunting and poor growth. We examined the evidence regarding vitamin D supplements and their potential effects on linear growth. We also explored other outcomes related to vitamin D status, including adverse effects.

Study characteristics

We included 187 reports representing 75 studies (12,122 participants), conducted most frequently in India, USA, and Canada, among children under five years of age. In addition, 33 studies were classified as currently being conducted (ongoing) and 21 studies as 'awaiting classification' because they did not provide enough information to be categorised as included, ongoing, or excluded. Comparisons included oral vitamin D supplementation versus placebo (dummy pill) or no intervention; higher-dose vitamin D versus lower-dose vitamin D; vitamin D plus micronutrients (vitamins or minerals or both) compared to the same micronutrients alone; and higher-dose vitamin D plus micronutrients (vitamins or minerals or both) compared to lower-dose vitamin D plus the same micronutrients. Two studies reported for-profit funding, two were categorised as mixed funding (non-profit and for-profit), five reported that they had received no funding, 26 did not disclose funding sources, and the remaining studies were supported by non-profit funding.

Key findings

Supplementation with vitamin D in comparison with placebo or no intervention probably makes little to no difference in developing hypercalciuria, probably improves length or height compared to the child's age, probably makes little to no difference in stunting, and may make little to no difference in child length or height. It is uncertain whether vitamin D in comparison with placebo or no intervention impacts the development of hypercalcaemia.

Supplementation with a higher dose of vitamin D compared to a lower dose of vitamin D may make little to no difference in length or height compared to the child's age and developing hypercalciuria, or hypercalcaemia; and we are uncertain about the effects of higher-dose vitamin D on linear growth.

Supplementation with a higher dose of vitamin D along with micronutrients (vitamins or minerals, or both) compared to a lower dose of vitamin D and the same micronutrients may make little to no difference in linear growth in children under five years of age and developing hypercalciuria, and probably makes little to no difference in developing hypercalcaemia.

Conclusions

Current evidence suggests that vitamin D probably slightly improves length/height-for-age z-score compared to placebo; however, because of the quality of the evidence, we are uncertain about the true effects of vitamin D on linear growth or adverse effects among children under five years of age compared to placebo, no intervention, or lower doses of vitamin D, with or without micronutrients.

SUMMARY OF FINDINGS

Summary of findings 1. Vitamin D versus placebo or no intervention

Vitamin D versus placebo or no intervention

Patient or population: children under 5 years of age
Setting: any country
Intervention: oral vitamin D (doses: 200 to 2000 IU daily; or up to 300,000 IU bolus at enrolment)
Comparison: placebo or no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with placebo or no intervention	Risk with vitamin D				
Linear growth (length/height) Unit: cm Time frame: 6.3 months (mean)	Mean length in control group was **62.7 cm**	Mean length in intervention group was **0.66 cm** longer (0.37 shorter to 1.68 longer).	-	240 (3 RCTs)	⊕⊕⊖⊖ **Low**[a]	Two studies showed an increase in linear growth, and 1 study found a decrease in linear growth. However, no difference was found overall
Length/height-for-age z-score (L/HAZ) Time frame: 6 months	Mean height-for-age z-score in control group was **-1.95**	Mean height-for-age z-score in intervention group was **0.11 units higher** (0.001 to 0.22 higher).	-	1258 (1 RCT)	⊕⊕⊕⊖ **Moderate**[b]	HAZ was higher among those receiving vitamin D
Stunting Definition: L/HAZ < -2 Time frame: 6 months	**Study population**		**RR 0.90 (0.80 to 1.01)**	1247 (1 RCT)	⊕⊕⊕⊖ **Moderate**[b]	
	490 per 1000	**441 per 1000** (392 to 495)				
Adverse effect: hypercalciuria As defined by trialists Time frame: 6.5 months (mean)	**Study population**		**RR 2.03 (0.28 to 14.67)**	68 (2 RCTs)	⊕⊕⊕⊖ **Moderate**[c]	There was no greater risk of increased calcium secretion in urine in groups receiving vitamin D
	29 per 1000	**60 per 1000** (1 to 238)				
Adverse effect: hypercalcaemia As defined by trialists Time frame: 7.5 months (mean)	**Study population**		**RR 0.82 (0.35 to 1.90)**	367 (2 RCTs)	⊕⊖⊖⊖ **Very low**[d]	There was no greater risk of increased calcium concentration in blood in groups receiving vitamin D
	124 per 1000	**101 per 1000** (43 to 235)				

Adverse effect: hyperphosphataemia[e]	-	-	-	-	-	Not measured
Adverse effect: kidney stones[e]	-	-	-	-	-	Not measured

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RCT: randomised controlled trial; 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.

[a]Downgraded one level due to serious risk of bias. Evidence was downgraded an additional level due to inconsistency (as indicated by an I^2 value of 49%; P = 0.14), suggesting moderate heterogeneity.
[b]Downgraded one level due to indirectness as only one study conducted in India was included, restricting the population analysed.
[c]Downgraded one level due to imprecision, as the confidence interval was wide around the effect size which included 1.0, the null value.
[d]Downgraded one level due to serious risk of bias. Evidence was downgraded an additional level due to imprecision, as the confidence interval around the effect size included 1.0, the null value. Evidence was downgraded an additional level due to inconsistency (as indicated by an I^2 value of 48%; P = 0.64), suggesting moderate heterogeneity.
[e]No data were available for this outcome.

Summary of findings 2. Vitamin D (higher dose) versus vitamin D (lower dose)

Vitamin D (higher dose) versus vitamin D (lower dose)

Patient or population: children under 5 years of age
Setting: any country
Intervention: oral vitamin D (higher dose: 200 to 6000 IU daily; or up to 600,000 IU bolus at enrolment)
Comparison: oral vitamin D (lower dose: 100 to 1000 IU daily; or up to 300,000 IU bolus at enrolment)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with lower-dose vitamin D	Risk with higher-dose vitamin D				
Linear growth (length/height) Unit: cm	Mean length in control group was **57.8 cm**.	Mean length in intervention group was **1.00 cm shorter**	-	283 (5 RCTs)	⊕⊖⊖⊖ **Very low[a]**	Two studies showed an increase in linear growth, and 3 studies found a decrease in linear

Time frame: 4.2 months (mean)		(2.22 shorter to 0.21 longer).				growth. However, no difference was found overall
Length/height-for-age z-score (L/HAZ) Unitless Time frame: 7 months (mean)	Mean height-for-age z-score in control group was -**0.35**.	Mean height-for-age z-score in intervention group was**0.40 units higher** (0.06 units lower to 0.86 units higher).	-	105 (2 RCTs)	⊕⊕⊖⊖ **Low**[b]	No difference in HAZ was found between groups
Stunting[c]	-	-	-	-	-	Not measured
Adverse effect: hypercalciuria As defined by trialists Time frame: 3.9 months (mean)	**Study population** **276 per 1000**	**320 per 1000** (276 to 372)	**RR 1.16 (1.00 to 1.35)**	554 (6 RCTs)	⊕⊕⊖⊖ **Low**[b]	There was no greater risk of increased calcium secretion in urine in groups receiving vitamin D
Adverse effect: hypercalcaemia As defined by trialists Time frame: 8.6 months (mean)	**Study population** **64 per 1000**	**88 per 1000** (57 to 139)	**RR 1.39 (0.89 to 2.18)**	986 (5 RCTs)	⊕⊕⊖⊖ **Low**[b]	There was no greater risk of increased calcium concentrations in blood in groups receiving vitamin D
Adverse effect: hyperphosphataemia[c]	-	-	-	-	-	Not measured
Adverse effect: kidney stones[c]	-	-	-	-	-	Not measured

*__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; RCT: randomised controlled trial; 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.

[a]Downgraded one level due to serious risk of bias. Evidence was downgraded an additional level due to imprecision, as the confidence interval around the effect size included 0, the null value. Evidence was downgraded an additional level due to inconsistency between studies, indicated by an I^2 value of 71%, suggesting substantial heterogeneity.
[b]Downgraded one level due to serious risk of bias. Evidence was downgraded an additional level due to imprecision, as the confidence interval around the effect size included 0 or 1.0, the null value.
[c]No data were available for this outcome.

Summary of findings 3. Vitamin D (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s)

Vitamin D (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s)

Patient or population: children under 5 years of age
Setting: any country
Intervention: oral vitamin D (higher dose: 400 to 2000 IU daily, or up to 300,000 IU bolus at enrolment) + micronutrient(s), including minerals such as calcium phosphate, multi-vitamin, or both
Comparison: oral vitamin D (lower dose: 200 to 2000 IU daily, or up to 90,000 IU bolus at enrolment) + micronutrient(s), including minerals such as calcium phosphate, multi-vitamin, or both

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with lower-dose vitamin D + micronutrient(s)	Risk with higher-dose vitamin D + micronutrient(s)				
Linear growth (length/height) Unit: cm Time frame: 3 months	Mean length in control group was **49.2 cm**	Mean length in intervention group was **0.6 cm longer** (3.33 shorter to 4.53 longer)	-	25 (1 RCT)	⊕⊕⊖⊖ **Low**[a]	No difference in linear growth was found between groups
Length/height-for-age z-score (L/HAZ)[b]	-	-	-	-	-	Not measured
Stunting[b]	-	-	-	-	-	Not measured
Adverse effect: hypercalciuria As defined by trialists Time frame: 3 months	**Study population**		**RR 1.00 (0.06 to 15.48)**	86 (1 RCT)	⊕⊕⊖⊖ **Low**[c]	There was no greater risk of increased calcium secretion in urine in groups receiving vitamin D
	23 per 1000	**23 per 1000** (1 to 360)				
Adverse effect: hypercalcaemia As defined by trialists	**Study population**		**RR 1.00 (0.90 to 1.11)**	126 (2 RCTs)	⊕⊕⊕⊖ **Moderate**[d]	There was no greater risk of increased calcium concen-
	145 per 1000	**298 per 1000**				

Time frame: 2.2 months (mean)		(268 to 331)				trations in blood in groups receiving vitamin D
Adverse effect: hyperphosphataemia[b]	-	-	-	-	-	Not measured
Adverse effect: kidney stones[b]	-	-	-	-	-	Not measured

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; RCT: randomised controlled trial; 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.

[a]Downgraded one level due to risk of bias and imprecision, as the 95% CI for the effect measure included the null value of 0. Evidence was downgraded an additional level due to indirectness as only one study conducted in Finland was included, restricting the population analysed.
[b]No data were available for this outcome.
[c]Downgraded one level due to risk of bias and imprecision, as the 95% CI for the effect measure included the null value of 1.0. Evidence was downgraded an additional level due to indirectness as only one study conducted in India was included, restricting the population analysed.
[d]Downgraded one level due to risk of bias and imprecision, as the 95% CI for the effect measure included the null value of 1.0.

BACKGROUND

Description of the condition

Linear growth faltering and stunting

Suboptimal health among children under five years of age remains a major global challenge (UNICEF, WHO, World Bank 2020; WHO 2016). Most of the 5.9 million deaths among children under five years of age in 2015 could be attributed to preventable causes with available treatment options, such as malnutrition (UNICEF, WHO, World Bank 2020).

Linear growth faltering, or failure to reach one's linear growth potential compared to normative standards (Leroy 2019; Perumal 2018), is associated with negative short- and long-term outcomes among children under five years of age. Linear growth faltering is a marker for poor health, reduced earnings, and lower cognitive capacity, as well as a direct factor in the causal pathway to biological states such as foetal growth restriction and shorter maternal height (Leroy 2019; Perumal 2018). A subset of children suffering from linear growth faltering may become stunted, which is defined as more than two standard deviations (SDs) below the World Health Organization (WHO) reference standard (length- or height-for-age z-score) (WHO 2006). The prevalence of stunting in a community offers a useful marker of well-being at the population level (Perumal 2018); however, it is not without limitations. Recent studies have suggested that the classical definition of stunting is based on an arbitrary cutoff and may fail to accurately represent the true proportion of children facing inadequate growth (Leroy 2019). Therefore, this review will use both linear growth faltering and stunting to better evaluate interventions.

Linear growth faltering and stunting have multiple causes, including cumulative poor nutrition in utero and postnatally (Dewey 2011). In addition, repeated infections, environmental enteropathy, and inadequate care have all been suggested as contributory to inadequate growth (Leroy 2019; Perumal 2018). A recent review of child stunting pinpointed growth faltering during childhood as both a causal mechanism for some poor outcomes and a non-causal indicator of other consequences (Leroy 2019). Linear growth faltering can lead to (1) cephalopelvic distortion leading to difficult birth, morbidity, and mortality; and (2) maternal short stature leading to smaller infants, who are more likely to die or not grow to optimal height (Ramakrishnan 1999). Linear growth faltering has additionally been shown to be associated with reduced earnings, lower school achievement and work capacity, reduced physical strength, chronic diseases, or poor cognition in adulthood (Black 2008; Dewey 2011; Haas 1996; Leroy 2019). Women stunted in childhood tend to bear stunted offspring, creating an intergenerational cycle of adverse physical, mental, and economic outcomes (Martorell 2012). A seminal study by Hoddinott et al followed a cohort of Guatemalan adults and, using instrumental variables, found that stunting played a causal role in adult economic productivity independent of childhood malnutrition and socioeconomic status. The mechanism behind this remains unknown, but it may be attributable to discrimination in schooling or when seeking employment. Although it is not generalisable to other populations, the analysis performed in this study remains important to support interventions to directly address inadequate childhood growth to improve economic disparities.

One risk factor for linear growth faltering of infants is maternal undernutrition; the intergenerational cycle of malnutrition is perpetuated by intrauterine growth restriction and restricted blood flow to the uterus, placenta, and foetus (Dewey 2011). Intrauterine growth restriction may lead to the infant being born premature (gestational age less than 32 weeks) and/or with low birth weight (birth weight less than 2.5 kg), both of which are risk factors for stunting (Danaei 2016). Another risk factor is recurrent infection (Caulfield 2006); as children age, their exposure to the environment increases, along with their risk of infection (Caulfield 2006). Stunting remains the most prevalent form of undernutrition among children under five years of age; 149 million suffer from stunting globally (WHO 2019). Global stunting decreased from 32.5% in 2000 to 21.9% in 2018 among children under five years of age (WHO 2019), but it remains a critical challenge in numerous geographical regions (De Onis 2012; De Onis 2013; Prendergast 2014). In India, for instance, 46 million children (nearly 40%) under five years of age are stunted, accounting for more than a third of the stunted children in the developing world (MoHFW 2019). The World Health Assembly aims to reduce stunting in children under five years of age by 40% between 2010 and 2025 (WHO 2012; WHO 2014a). Therefore, it is crucial to delineate modifiable causes of, and effective interventions against, stunting and linear growth faltering, including micronutrient supplementation.

Given the widely recognised burden of disease associated with childhood stunting in diverse populations (Black 2008; Black 2013; De Onis 2012; Prendergast 2014), many global research and policy efforts have sought to reduce growth faltering (Victora 2010; WHO 2014a). It has been estimated that improved understanding and scaling up of effective, evidence-informed, safe, and effective interventions can prevent stunting among 33.5 million children (Bhutta 2013; Huey 2016; WHO 2014a). In particular, investigators have explored vitamin D supplementation as an intervention to prevent and mitigate childhood stunting (Kumar 2011). Optimal vitamin D status, which is often assessed by measuring serum concentrations of calcifediol (i.e. 25(OH)D), allows calcium absorption and growth to support active vitamin D (i.e. calcitriol ($1,25\{OH\}_2D_3$)) (Holick 2010). Prolonged inadequate vitamin D status impairs transcriptional regulation of skeletal homeostasis and linear growth, which could result in stunting (Holick 2010).

Prior observational studies have provided evidence that stunting is associated with suboptimal vitamin D status among children (Walli 2017). Therefore, vitamin D supplementation as a potentially modifiable risk factor that can have an effect on linear growth requires further evaluation.

Description of the intervention

Vitamin D status

One billion people have suboptimal vitamin D status, according to global estimates (Holick 2010). Even in countries with sun exposure all year round, low vitamin D status is a global problem among all age groups (Palacios 2014). Consequences of low vitamin D include poor skeletal and extraskeletal health outcomes (Holick 2008a; Holick 2008b; Holick 2010).

Low circulating 25(OH)D serum concentration is widely regarded as the biomarker for vitamin D status (Heaney 2009), although cut-off values indicating deficiency and insufficiency are debated

(Holick 2011; Ross 2011). Between 30% and 50% of children in numerous countries in Africa, Asia, Europe, and North America (Holick 2010), including geographical areas with ample sunlight and heterogeneous economic resources, have 25(OH)D less than 50 nmol/L. In the context of vitamin D deficiency, infants and young children are considered a high-risk population, given that vitamin D intake is low during exclusive breastfeeding (Leroy 2014; Shrimpton 2001), and early life represents a critical period for linear growth and development of the immune system (Adkins 2004; Levy 2007). As further detailed in the next section, pleiotropic actions of vitamin D can impact skeletal, muscular, and immunological functions, all of which are related to optimal growth.

Vitamin D sources

Vitamin D can be acquired through consumption of a diet containing naturally vitamin D-rich and fortified foods, or vitamin D supplements, or through endogenous production via skin exposure to ultraviolet irradiation (Holick 2010). In this review, we focus on vitamin D supplementation, given that it overcomes the challenges of inadequate sunlight at some geographical latitudes, as well as minimal sun exposure based on individual lifestyle decisions and limited consumption of naturally vitamin D-rich or fortified foods (Holick 2010). Vitamin D supplements are available in two chemical forms (ergocalciferol (D2) and cholecalciferol (D3)), which differ in their side-chain structure (Holick 2010). Vitamins D2 and D3 have been observed to increase serum 25-hydroxyvitamin D (serum 25(OH)D), although at higher doses (50,000 IU), vitamin D2 appears less potent than equivalent doses of D3 in maintaining serum 25(OH)D levels (Holick 2010).

Vitamin D requirements

According to the WHO and the Food and Agriculture Organization (FAO), 200 international units (IU) of vitamin D is the daily recommended nutrient intake (RNI) among children under five years of age (WHO, FAO 2004). In the USA, the Institute of Medicine recommends that children between one and five years of age should consume a recommended dietary allowance of 600 IU per day, and have an estimated average requirement (EAR) of 400 IU per day (Institute of Medicine 2011). From birth to 12 months, it is recommended that children in the USA consume adequate intake (AI) of 400 IU per day (Institute of Medicine 2011).

No adverse effects occur at vitamin D intakes recommended by WHO and by FAO (WHO, FAO 2004). In the USA, the recommended upper limits of vitamin D consumption are based on age: 1000 IU from birth to six months, 1500 IU from six to 12 months, 2500 IU from one to three years, and 3000 IU from four to five years (Institute of Medicine 2011). Vitamin D toxicity has been observed in a few rare cases with long-term consumption of extreme pharmaceutical dosages (Barrueto 2005; Blank 1995; Holick 2011; Klontz 2007; Vieth 1999); it is caused primarily by excessive intestinal calcium or phosphate absorption and bone resorption (Holick 2010). Excess vitamin D may contribute to hypercalciuria, hypercalcaemia, hyperphosphataemia, and kidney stones (nephrolithiasis) (Holick 2010). Hypercalciuria, or high levels of calcium in the urine, is linked to the role of vitamin D in increasing intestinal calcium reabsorption and is defined differently across different age groups (Leslie 2020). In children over two years of age, hypercalciuria is defined as daily urinary excretion of more than 4 mg calcium per kg of body weight, or a 24-hour urinary calcium concentration less than 200 mg calcium per litre of urine (Leslie 2020). For children under two years, a random or spot urinary calcium-to-creatine ratio less than 0.2 mg calcium per mg creatine is considered normal (Leslie 2020). Hypercalcaemia is mainly caused by excess parathyroid hormone (PTH), which can be induced by high vitamin D intake, and is defined as high levels of calcium in blood; it can be classified as mild (10.5 to 11.9 mg/dL), moderate (12.0 to 13.9 mg/dL), or a hypercalcaemic crisis (14.0 to 16.0 mg/dL) (Sadiq 2020). Hyperphosphataemia indicates plasma phosphate greater than 7 mg/dL in children and can be induced by the role of vitamin D in increasing intestinal phosphate absorption (Goyal 2020). Kidney stones, detected via ultrasound, are calcium crystal concretions (composed primarily of calcium oxalate or calcium phosphate) travelling from the kidney through the genitourinary system. Kidney stones can occur in the setting of hypercalciuria (Nojaba 2020).

Metabolism of vitamin D

Evidence from mechanistic and dose-response studies suggests that increasing intake of vitamin D (via consumption (supplementation, dietary intake) or cutaneous synthesis) improves serum 25(OH)D concentration (Holick 2010; Holick 2011). After it enters the body, vitamin D is stored in fat or is metabolised by the liver (Holick 2010; Holick 2011). A 25-hydroxylase (CYP27B1) in the liver converts vitamin D to 25(OH)D, which is the major circulating form (Holick 2010; Holick 2011).

Available data from dose-response studies show that vitamin D supplementation increases serum 25(OH)D concentration, regardless of age (Heaney 2003; Holick 2008b; Holick 2010; Institute of Medicine 2011). A non-linear response of 25(OH)D to vitamin D has been observed in murine and human models (Institute of Medicine 2011). Dosages greater than or equal to 1000 IU daily have resulted in more gradual responses (e.g. 0.95 nmol/L to 1.4 nmol/L for every 100 IU; Smith 2009), and dosages below 1000 IU daily have achieved steeper responses (e.g. approximately 2.0 nmol/L for every 40 IU; Cashman 2008; Cashman 2009; Institute of Medicine 2011). Moreover, studies including young children with stunting have confirmed that vitamin D supplementation increases 25(OH)D (Kumar 2011). Widely ranging vitamin D supplementation dosages across studies have included daily physiological doses (200 IU to 400 IU; Alizadeh Taheri 2014; Fort 2016), as well as pharmacological doses (50,000 IU at birth; Moodley 2015), and even a single dose of 100,000 IU (Gupta 2016). In summary, preliminary data highlight the need for assessment of potential beneficial effects of vitamin D supplementation on stunting among children.

How the intervention might work

Cells of kidney, immune system, bone, and epithelium, and of other tissues in the body, use 1-OHase (CYP27R1) to metabolise 25(OH)D to the biologically active steroid hormone $1,25(OH)_2D$ (Bikle 2014; Christakos 2016; Holick 2010). In its hormonally active form, vitamin D plays pleiotropic roles in the human body, promoting skeletal health, muscle development and growth, and immune function.

$1,25(OH)_2D$ functions through genomic and non-genomic mechanisms (Bikle 2014; Christakos 2016; Holick 2010). First, genomic effects occur through binding of $1,25(OH)_2D$ to vitamin D receptor and retinoid X receptor, which results in a heterodimer complex that regulates gene activity (Bikle 2014; Christakos 2016; Holick 2010). At least 100 to 1250 target genes of vitamin D are known (Adams 2010; Holick 2007; Hossein-Nezhad 2013; Ramagopalan 2010; Tarroni 2012). These are directly targeted by

vitamin D (via a vitamin D response element; e.g. 1,25$(OH)_2$D has been shown to bind to vitamin D response element in the calcium-sensing receptor gene and subsequently to modulate calcium-sensing receptor expression (Bikle 2014; Canaff 2002; Christakos 2016; Holick 2010)). Second, 'rapid' or non-genomic responses occur extracellularly via interaction with plasma membrane vitamin D receptor (VDR) (Bikle 2014; Christakos 2016; Holick 2010). Examples of these include stimulation of intestinal calcium absorption and inhibition of apoptosis in osteoblasts (Bikle 2014; Christakos 2016; Holick 2010). This nuclear receptor has been identified in nearly all human tissues and cells assessed (Bikle 2014; Christakos 2016; Holick 2010).

Skeletal homeostasis and linear growth

Vitamin D has well-established effects on skeletal health, including bone mineralization and maintenance (Holick 2010). Active vitamin D (1,25$(OH)_2$D) functions in conjunction with two other hormones (parathyroid hormone and calcitonin) to maintain endocrine control of calcium and phosphorus concentrations (Holick 2010). This tight regulation of calcium and phosphorus flux (extracellular (bones, blood), intracellular) is critical for development and maintenance of bones (Holick 2010), which impacts linear growth. Specific roles of active vitamin D include increasing intestinal calcium absorption (Christakos 2012), renal calcium reabsorption, and skeletal calcium resorption (in conjunction with parathyroid hormone) (Holick 2010).

Previous studies have demonstrated that vitamin D deficiency is associated with stunting (Holick 2010), including stunting among children (Holick 2006; Wacker 2013). Maternal vitamin D deficiency has been associated with greater risk of stunting among neonates and children (Finkelstein 2012; Toko 2016).

Possible negative effects on linear growth in children have been noted with higher-dose vitamin D supplementation. An early case series of nine infants consuming over 1500 units of vitamin D daily from cod liver oil sources were found to have lowered growth rates after six months of age compared to infants consuming 300 to 600 units of vitamin D daily (Jeans 1938). These findings have been raised as a matter to concern by the Dietary Reference Intakes Committees in their review of vitamin D in both 1997 and 2010 (Institute of Medicine 1997; Institute of Medicine 2011). However, a population-based cohort study conducted in 2011 (n = 10,060 singletons) found that supplementation with 2000 IU vitamin D per day during infancy was not associated with height at age 14 or 31 years, and was not associated with reduced height at any age studied (Hyppönen 2011).

Muscle development and growth

Vitamin D may influence muscle mass and function, as well as related indicators (weight-for-height (WFH) and -age (WFA)). Observational studies have corroborated the link between severe vitamin D deficiency (≤ 8 ng/mL) and poor muscle health among individuals age 10 to 65 years (Plotnikoff 2003). As an example, among infants with HIV exposure and no infection, low 25(OH)D concentration (< 10 ng/mL or ~ 25 nmol/L) was associated with a higher incidence of wasting (hazard ratio 1.71, 95% confidence interval (CI) 1.20 to 2.43; Sudfeld 2015).

Previous studies have identified mechanisms that link vitamin D with myopathy (Bischoff-Ferrari 2012). In vitro studies have assessed human muscle tissues and isolated VDR (Bischoff-Ferrari 2004; Bischoff-Ferrari 2012; Ceglia 2010; Simpson 1985), which facilitate genomic and non-genomic effects (Haussler 1998; McDonnell 1987; Norman 2004; Vazquez 1998). Furthermore, murine models have demonstrated that deletion of VDR (via gene knockout) resulted in impaired skeletal muscle growth and muscle-related gene expression (Bouillon 2008; Endo 2003). Mice without VDR had smaller muscle fibres in all striated muscles (Endo 2003).

Why it is important to do this review

Linear growth retardation (including stunting) continues to affect many children worldwide (WHO 2018), and global stunting remains a critical and complex challenge in numerous geographical regions (De Onis 2013; Prendergast 2014; UNICEF, WHO, World Bank 2020). This is reflected in the World Health Assembly nutrition target to reduce stunting by 40% among children under five years of age by 2025, and Sustainable Development Goal 2.2 to reduce the prevalence of stunting and wasting in children under five years of age by 2025, highlighting the global importance of addressing this issue (United Nations 2015; WHO 2012; WHO 2014a). Although stunting among children under five years of age has decreased from 39.7% (in 1990) to 21.3% (in 2019) (De Onis 2012; Dewey 2020), the World Health Assembly nutrition target will not be achieved at this current trajectory (De Onis 2013).

Linear growth is considered an important overall indicator of child development (De Onis 2016). Critically, children with stunting often show minimal (if any) catch-up growth in later life (Martorell 1994). However, nutritional interventions have been seen to allow catch-up growth among children (Martorell 1994), especially during key developmental windows (including between birth and five years) (Prentice 2013). Vitamin D is already a known beneficial intervention for prevention of rickets in the same early, crucial childhood years, and despite conclusive evidence, the drive to reduce growth retardation is an important one with a plethora of potential beneficial effects.

The systematic method of our review is intended to achieve comprehensive assessment of current evidence on effects of vitamin D supplementation on growth faltering and other health outcomes among children. This approach facilitates consideration of other modulating factors, particularly in subgroup analyses. Given the multi-factorial origin of stunting, which needs further elucidation (Stewart 2013), accounting for other factors is important. Aside from nutritional factors that affect stunting, potential influences include repeated infections, poor sanitation, household environmental contamination, mycotoxin exposure, the gut, and associated enteropathy (Casanovas 2013; Owino 2016; Semba 2016; Stewart 2013; Waterlow 1994).

Separately, an estimated one billion people have suboptimal vitamin D status (Holick 2007), which is linked to numerous skeletal and extraskeletal outcomes (Holick 2010). Given the relative ease of administration, widespread availability, and ongoing acceptability, the benefits of supplementation for growth in the first five years of life should be explored. Despite the multitude of studies that have focused on vitamin D supplementation and clinical health indicators (Ferguson 2014; Jagannath 2010), particularly among adults (Avenell 2014; Bjelakovic 2014a; Palacios 2019; Straube 2015), evidence regarding growth and stunting among children under five years of age remains unclear. Thus, it is necessary to draw overall conclusions from currently available evidence regarding

how vitamin D supplementation impacts the growth of children under five years of age.

OBJECTIVES

To assess effects of oral vitamin D supplementation on linear growth and other health outcomes among infants and children under five years of age.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs. Quasi-RCTs included studies that did not involve a treatment regimen assignment with simple randomisation but systematically utilised another aspect of the study design (e.g. alternating assignments based on sequential study enrolment, medical record number). Cluster-randomised and cross-over trials were also eligible for inclusion.

Types of participants

Infants and children under five years of age who lived in any country, healthy and apparently non-vitamin D-deficient, as well as with diagnosed vitamin D deficiency, rickets, or other underlying health conditions (as defined by trialists). We included studies of children under five years of age and study participants who were both under and over five years of age (e.g. birth to 10 years) if study authors reported stratified outcomes; this review reports extracted results among children under five years of age. We included studies of vitamin D supplementation directly among infants and children under five years of age only. We excluded studies that provided vitamin D supplementation to mothers only and not to their offspring.

Types of interventions

Studies assessing effects of oral vitamin D supplementation, with or without micronutrients, compared to no intervention, placebo, a lower dose of vitamin D, or micronutrients alone in children under five years of age. Comparisons between intervention and comparator groups are described below (and in Table 1).

Interventions

Oral vitamin D (cholecalciferol D_3, ergocalciferol D_2, calcitriol) supplementation (Table 1). We included any form of oral consumption of vitamin D (such as capsules, tablets, soft gels, liquids, sprays/mists, and powders) and excluded alternative administration of vitamin D (e.g. intravenous injection, food fortification, dietary intake of vitamin D-rich foods). We documented key differences across interventions (including treatment dosage, duration, and frequency) during data extraction. For studies assessing effects of higher versus lower doses of vitamin D, we considered the higher dose as the intervention arm (see Differences between protocol and review). Studies with micronutrient supplementation plus vitamin D as the intervention were included if the comparator arm involved the same micronutrients without vitamin D, or provided a lower dose of vitamin D as the reference group.

Comparators

Study participants who received placebo, no intervention, or a lower dose of vitamin D (Table 1). Additionally, for studies with micronutrient supplementation plus vitamin D as the intervention, we included comparisons that involved the same micronutrients without vitamin D or with a lower dose of vitamin D as the reference group.

Types of outcome measures

Primary outcomes

1. Linear growth (reported continuously in centimetres)
2. Length/height-for-age (L/HAZ; reported continuously as WHO z-score; WHO 2006)
3. Stunting (reported as a categorical outcome; defined as L/HAZ more than 2 SDs below the reference WHO standard; WHO 2006)
4. Adverse effects relevant to excessive vitamin D (reported as categorical outcomes)
   a. Hypercalciuria (high urinary calcium levels, defined by trialists)
   b. Hypercalcaemia (high serum calcium levels, defined by trialists)
   c. Hyperphosphataemia (high plasma phosphate levels, defined by trialists)
   d. Kidney stones (nephrolithiasis, defined by trialists)

Secondary outcomes

1. Gain in linear growth (reported continuously in centimetres)
2. Weight-for-age (WAZ; reported continuously as WHO z-score; WHO 2006)
3. Underweight (reported as a categorical outcome; defined as WAZ more than 2 SDs below the reference WHO standard; WHO 2006)
4. Weight-for-length/height (WL/HZ; reported continuously as WHO z-score; WHO 2006)
5. Wasting (reported as a categorical outcome; defined as WHZ (or WLZ) more than 2 SDs below the reference WHO standard; WHO 2006)
6. Vitamin D status (based on serum 25(OH)D concentration (nmol/L); reported as continuous outcomes, including change in vitamin D status, and categorical outcomes, according to current recommended cut-offs from the Institute of Medicine and the Endocrine Society (in the USA) (Holick 2011)). Usage of a wide spectrum of vitamin D assay instruments, including immunoassays (e.g. radioimmunoassays) and chromatographic methods (e.g. liquid chromatography-tandem mass spectrometry)
7. Rickets (defined by trialists)

Search methods for identification of studies

Electronic searches

In March 2018, we searched the international and regional electronic databases and trial registers listed below. We updated the search in December 2019. We made some adjustments to our electronic search strategy post publication of our protocol (Yu 2017). Please see Differences between protocol and review.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 12), in the Cochrane Library, which includes the Cochrane Developmental, Psychosocial and Learning Problems Specialised Register (searched 11 December 2019).
2. PubMed National Library of Medicine (www.ncbi.nlm.nih.gov/pubmed; searched 11 December 2019).
3. Embase Ovid (1980 to 11 December 2019).
4. CINAHL EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1982 to 11 December 2019).
5. CABI (Centre for Agriculture and Biosciences International): CAB Abstracts and Global Health Web of Science (1973 to 11 December 2019).
6. Web of Science Core Collection Clarivate (searched 11 December 2019).
7. *Cochrane Database of Systematic Reviews* (CDSR; 2019, Issue 12), part of the Cochrane Library (searched 11 December 2019).
8. DARE (Database of Abstracts of Reviews of Effects, Centre for Reviews and Dissemination; www.crd.york.ac.uk/CRDWeb; searched 11 December 2019).
9. IBECS (ibecs.isciii.es; searched 11 December 2019).
10. LILACS (Latin American and Caribbean Health Sciences Literature; lilacs.bvsalud.org/en; searched 11 December 2019).
11. PAHO (Pan American Health Library; iris.paho.org; searched 11 December 2019).
12. WHOLIS (WHO Library; dosei.who.int; searched 11 December 2019).
13. SciELO (Scientific Electronic Library Online; www.scielo.br; searched 11 December 2019).
14. WPRIM (Western Pacific Region Index Medicus; www.wprim.org; searched 11 December 2019).
15. IndMED (Indian Medical Journals; indmed.nic.in; searched 14 March 2018; IndMED was not available at this URL after 2018, and the database could not be located).
16. WHO ICTRP (World Health Organization International Clinical Trials Registry Platform; apps.who.int/trialsearch; searched 14 March 2018).
17. Epistemonikos (www.epistemonikos.org; searched 11 December 2019).
18. Scopus Elsevier (searched 11 December 2019).
19. EUCTR (European Union Clinical Trials registry; www.clinicaltrialsregister.eu/ctr-search/search; searched 11 December 2019).

The search strategies for each database are provided in Appendix 1. We did not limit the searches by publication year, language, country, or region.

Searching other resources

We searched the reference lists of relevant publications (including trials, reviews, meta-analyses, reports) identified through our electronic searches, and we considered any potentially eligible trials included in these reference lists. Additionally, we attempted to obtain information on relevant ongoing and unpublished trials by contacting other entities such as the WHO Nutrition Section (www.who.int/nutrition/en), the United Nations Children's Fund (UNICEF; www.unicef.org), Nutrition International (formerly Micronutrient Initiative; www.nutritionintl.org), the International Micronutrient Malnutrition Prevention and Control Programme (IMMPaCt; www.immpact.org) from the US Centers for Disease Control and Prevention (CDC), and the Vitamin D Workshop Group (vitamindworkshop.org).

Data collection and analysis

We performed this review in accordance with the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020a). When possible, we used the methods described in our published protocol (Yu 2017). Unused methods may be found in Table 2.

Selection of studies

We modified the data extraction form on Covidence for use during screening of studies for this review. Using Covidence systematic review software (Covidence 2020), five review authors (SLH, AS, NA, RA, EAY) independently screened studies identified by the searches. Initially, they considered the title and abstract of each record to decide whether they met inclusion and exclusion criteria of this review (Criteria for considering studies for this review), and they selected 'No' for those that were irrelevant. For records that were not excluded, SLH, AS, and NA reviewed the full-text reports for eligibility. We contacted study authors if clarifications were necessary, or if full-text reports were not available (Dealing with missing data). SLH, AS, NA, EAY, and RA resolved discrepancies through discussion and, if necessary, through consultation with a sixth review author (SM).

We present the selection process in a PRISMA diagram (Moher 2009).

Data extraction and management

Three review authors (SLH, NA, AS) independently extracted data from eligible full-text studies using customised forms in Covidence that were piloted on a sample of studies and modified accordingly before full data extraction was undertaken (Covidence 2020). If any data were unclear, or if data included children over five years of age, we attempted to contact the study authors to ask them to provide further details or to share age-stratified data. SLH and NA extracted the data and entered them into Covidence; they then imported the data into Review Manager 5 (RevMan 5) (Review Manager 2014). SLH checked the data for accuracy.

SLH, NA, and AS resolved disagreements through discussion or through consultation with a fourth review author (SM). For this review, we aggregated study design details and findings from any duplicate or companion documents, as well as from multiple publications on a single study.

During data extraction, we recorded information regarding study design, setting, objectives and primary outcomes of the study, years the study was conducted, participants (inclusion and exclusion criteria), study methods (method of ascertaining vitamin D concentration and trial design), assessment of risk of bias, intervention information, and outcomes (see list in 'Study information' below). We recorded additional details beyond what we previously specified in our protocol (Yu 2017) (see Differences between protocol and review).

Study information

1. Identification
   a. Sponsorship
   b. Country
   c. Setting
   d. Study authors' contact details
   e. Study objectives
   f. Primary outcomes measured
   g. Year(s) of trial
2. Trial methods
   a. Trial design (RCT or quasi-RCT)
   b. Vitamin D concentration quantification method
3. Participants
   a. Inclusion criteria
   b. Exclusion criteria
   c. Group differences
   d. Baseline characteristics
4. Intervention
   a. Vitamin D content in IU
   b. Formulation
   c. Vitamin D type
   d. Frequency of dosage
   e. Duration of administration
   f. Other micronutrient content
   g. N (number) per group (in analysis)
   h. Vitamin D brand/company
5. Comparator
   a. None, placebo, other micronutrients, dosage of vitamin D
6. Outcomes
   a. Primary and secondary outcomes (as outlined under Types of outcome measures)

Assessment of risk of bias in included studies

SLH, AS, and NA independently assessed the risk of bias in each included study using the certainty assessment form in Covidence (Covidence 2020), which follows Cochrane's domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). These domains are sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessors; incomplete outcome data; selective reporting bias; and other sources of bias, which we measured as whether or not the sample size was calculated, and if calculated, met at randomisation and at endpoint of the study. We categorised each domain as low, high, or unclear risk of bias, depending on the sufficiency of information to characterise the risk of bias. Disagreements were resolved by discussion. Specific assessments by domain can be found in Appendix 2.

We detail our findings in the 'Risk of bias' tables and present a narrative summary of our findings in the Risk of bias in included studies section. We also present the findings graphically.

Measures of treatment effect

Continuous outcomes

When possible, we extracted means and standard deviations (SDs) for outcome data. When studies reported means and standard errors (SEs) or means and 95% confidence intervals (CIs), we extracted these values and used the calculator in RevMan 5 (Review Manager 2014) to back-calculate the SD using methods from the *Cochrane Handbook for Sytematic Reviews of Interventions* (Li 2020). This step was not included in our original protocol (Yu 2017) (see Differences between protocol and review). Some studies reported medians and interquartile ranges (IQRs) or medians and ranges, or means without variance estimates such as SDs, SEs, or 95% CIs for specific outcomes. When studies reported medians and IQRs, and the sample size per group was large (n ≥ 30), we entered the reported median as the mean in RevMan 5 (Review Manager 2014), and we treated the IQR as approximately 1.35 × SD. If the sample size was < 30, we omitted these data from the analysis. When studies reported ranges as a measure of variance, we omitted these data from the analysis per guidelines provided in the *Cochrane Handbook for Systematic Reviews of Intervention* (Li 2020). When a study reported only the means and no variance estimates, we omitted these data from the analysis.

We reported continuous outcomes as mean differences (MDs) with corresponding 95% CIs (Deeks 2020). Specifically, these included primary (linear growth, HAZ, or LAZ) and secondary (WAZ, WHZ, serum 25(OH)D concentration) outcomes. If trials used different scales to measure the same continuous outcome across studies, we used standardised mean differences (SMDs) with 95% CIs, when possible (Deeks 2020).

Categorical outcomes

For categorical outcomes, when possible, we presented data as measures of association (risk, rate, odds ratio with corresponding 95% CI; Deeks 2020). These included primary (stunting, adverse effects (hypercalciuria, hypercalcaemia, hyperphosphataemia)) and secondary (vitamin D status, rickets) outcomes. For dichotomous outcomes, we calculated risk ratios (RRs) for the probability of an event happening. In studies where each arm had zero events for a particular outcome that was rare (e.g. rickets), we used risk differences (RDs) to perform the meta-analysis (Higgins 2020b). To analyse dichotomous rickets outcomes, we summarised each study's number of participants who experienced at least one event (i.e. signs of rickets, which may have included multiple signs per participant; participants were not counted twice) as events, as a proportion of the total number of participants per group (Li 2020) (see Differences between protocol and review). For categorical vitamin D outcomes (severe serum vitamin D deficiency defined by trialists as <25 to <30 nmol/L, serum vitamin D deficiency defined as <50 nmol/L (Holick 2011), and serum vitamin D insufficiency defined as <75 nmol/L (Holick 2011), we present these outcomes as the proportion of participants achieving above these cut-offs, specifically ≥25 to ≥30 nmol/L, ≥50 nmol/L, or ≥75 nmol/L. For these outcomes, we combined both studies which presented participants developing severe deficiency, deficiency, or insufficiency, and those achieving vitamin D status above these cut-offs, by converting these outcomes in the former to the proportion of participants above the cut-offs to include them in analysis.

Unit of analysis issues

For each study included in this review, we documented the unit of randomisation during data extraction. The unit of randomisation included individual participants. We also considered whether

individuals had undergone more than one intervention, as in a cross-over trial, and whether a trial reported multiple observations for the same outcome(s), including repeated measurements or recurring events.

We included two cross-over trials, Rodd 2011 and Lava 2011, neither of which assessed any outcomes within the scope of this review. We did not identify any cluster-randomised trials. For methods to deal with cluster-randomised trials should we find any in future updates of this review, please see Table 2.

Studies with more than two treatment groups

For multi-arm studies, we included only the directly relevant arms (e.g. for one particular study, we excluded arms with only intramuscular injection of vitamin D but included arms administering oral vitamin D and oral placebo or control).

When studies included more than two intervention groups, we combined groups to perform a single pair-wise comparison. Specifically, we combined all relevant experimental groups into one group, and all relevant control intervention groups into a second group. Thus, for studies that compared dichotomous outcomes among multiple vitamin D arms and one placebo or no intervention arm, we combined the vitamin D arms into one vitamin D group by summing each arm's number of participants and number of events into one vitamin D group, which we then compared against the original placebo group. For studies that compared dichotomous outcomes among at least three varying dosages of vitamin D, we compared the lowest dose (control) of vitamin D to the combined higher-dosage arms of vitamin D, again by summing each arm's number of participants and number of events into one 'higher-dosage vitamin D' group (Higgins 2020b). For studies that compared continuous outcomes among multiple vitamin D arms and one placebo or no intervention arm, we combined the vitamin D arms into one group using formulae for combining groups available in RevMan 5 (Higgins 2020b; Review Manager 2014). For studies that compared continuous outcomes among at least three varying dosages of vitamin D, we compared the lowest dose (control) of vitamin D arm to the combined higher-dosage arms of vitamin D. We based our approach to meta-analysis on information provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020b).

These methods were not described in our protocol (Yu 2017), but we have added them based on the studies identified and examined; see Differences between protocol and review for more details.

Dealing with missing data

As necessary, we contacted study authors via email to ask them to share further information. If no response was received after one week, we emailed again; if again no response was received, we did not contact the authors again.

We did not impute any missing data, except we calculated SDs from IQRs when the sample size was greater than 30 per group (see Measures of treatment effect > Continuous data), and we used the calculator in RevMan 5 to convert means with 95% CIs and means with SEs into means with SDs (Review Manager 2014).

From each included study, we documented the missingness of key data and study participant information (including loss to follow-up) in 'Risk of bias' tables. Examples of unreported data include means and SDs of study participant subgroups. We recorded attrition as part of the 'Risk of bias' assessment. Loss to follow-up data included additional information regarding attrition and treatment adherence, or data on study participants who did not complete the trial or follow the protocol.

We considered all outcomes based on the intention-to-treat approach, when possible. In summarising across studies, for every outcome, the denominator represented the total number of study participants randomised to a treatment regimen (minus any participants with missing outcomes).

Assessment of heterogeneity

We quantified statistical heterogeneity across studies by using forest plots, Chi^2 (significance of α (alpha) = 0.10) testing, I^2 (≥ 75%) statistics, and Tau^2 values (Deeks 2020). We also considered critical differences between study designs (including study population characteristics) and risk of bias. In the event that we observed substantial heterogeneity, we considered performing prespecified subgroup analyses to gain a better understanding of the differences (Subgroup analysis and investigation of heterogeneity). For outcomes with substantial heterogeneity (according to our assessments), we did not report a pooled estimate.

Assessment of reporting biases

For each study, we checked for existence of study protocols or trial registrations published before or after reports of the study were published. We also checked that outcomes described in the methods or protocols, when available, were reported in published studies. In addition, we visually examined funnel plots for our primary outcomes to assess for bias due to missing results. We summarised these findings per each study in the Risk of bias in included studies section.

Data synthesis

Among comparable studies in this review (including similar outcomes and populations), we conducted a meta-analysis to estimate summary measures across studies. Specifically, these included studies with outcomes reported on the same scale (or as values that could be converted or standardised). For each outcome of interest, we considered reporting both continuous and categorical values across studies; we converted data to either continuous or categorical values to facilitate comparability, as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020).

We conducted meta-analysis via RevMan 5 (Review Manager 2014), and we utilised the inverse variance method. Per our protocol (Yu 2017), we conducted random-effects meta-analyses for outcomes with two or more studies to account for differences across study designs (including intervention dosages, durations, and frequencies, as well as study populations) (Deeks 2020). We also anticipated heterogeneity of reported time points (by reporting endpoint data, change from baseline data, etc.). For analyses including only one study, we used a fixed-effect model, as there is no inter-study heterogeneity (see Differences between protocol and review). In the event that we identified too few studies or study data could not be pooled, we provided a narrative description of trial results.

Summary of findings

For each primary outcome, two review authors (SLH and NA) used the GRADE approach to rate the certainty of evidence as high, moderate, low, or very low, according to the presence of the following factors: within-study risk of bias and limitations due to study design; directness of evidence; assessment of heterogeneity between studies; precision of effect estimates; and risk of publication bias (GRADEpro GDT 2020; Guyatt 2011). We assigned a grade of high certainty to evidence from RCTs and decreased this grade by one level for each factor present, up to a maximum of three levels. In the event of disagreement, we consulted an additional review author (SM or JPP, or both), who facilitated consensus through discussion. We present the grades of evidence for primary outcomes in a GRADE 'Summary of findings' table per each comparison.

We created 'Summary of findings' tables using GRADEpro GDT 2020 and Review Manager 2014 for our main comparisons when data were available: vitamin D versus placebo or no intervention (Summary of findings 1); vitamin D (higher dose) versus vitamin D (lower dose) (Summary of findings 2); and higher-dose vitamin D plus micronutrient(s) versus micronutrient(s) with lower-dose vitamin D (Summary of findings 3). We reported the following outcomes in each table, assessed at the end of the supplementation period, irrespective of whether or not there were data: linear growth; height-for-age z-score; stunting; hypercalciuria; hypercalcaemia; hyperphosphataemia; and kidney stones. For each primary outcome, we provide the anticipated absolute or relative effect and an evidence certainty rating assessed through the GRADE approach (Guyatt 2011); a rationale for the GRADE certainty rating is provided in the table footnotes. The tables also provide information on study population, setting, outcome measurements, and timing of measurement, as well as the numbers of studies and participants included.

Subgroup analysis and investigation of heterogeneity

We did not conduct our preplanned subgroup analyses because we did not find enough studies meeting the required number (more than three) for comparison by outcome (Yu 2017).

Sensitivity analysis

We did not conduct our preplanned sensitivity analyses because we did not find enough studies meeting the required number (more than 10) for comparison by outcome (Yu 2017).

RESULTS

Description of studies

Please see Characteristics of included studies, Characteristics of excluded studies, Characteristics of ongoing studies, and Characteristics of studies awaiting classification tables.

Results of the search

We found a total of 17,044 records (16,986 from electronic searches and 58 from other sources). After removing 5790 duplicates, we screened the remaining 11,254 unique records by title and abstract. We deemed 10,910 records to be irrelevant during screening and retrieved the full texts of the remaining 344 records for assessing eligibility.

We categorised 37 studies (80 reports) as 'Excluded'.

We identified 40 studies that included children within our age range but grouped their results with the results of children who were older than we had specified. We contacted the authors of each of these studies to request that they share age-stratified data. The authors of five studies shared age-stratified data; therefore we included these studies in the review (Rianthavorn 2013 Sánchez-Armendáriz 2018; Tang 2019; Thacher 2014; Trilok-Kumar 2011).

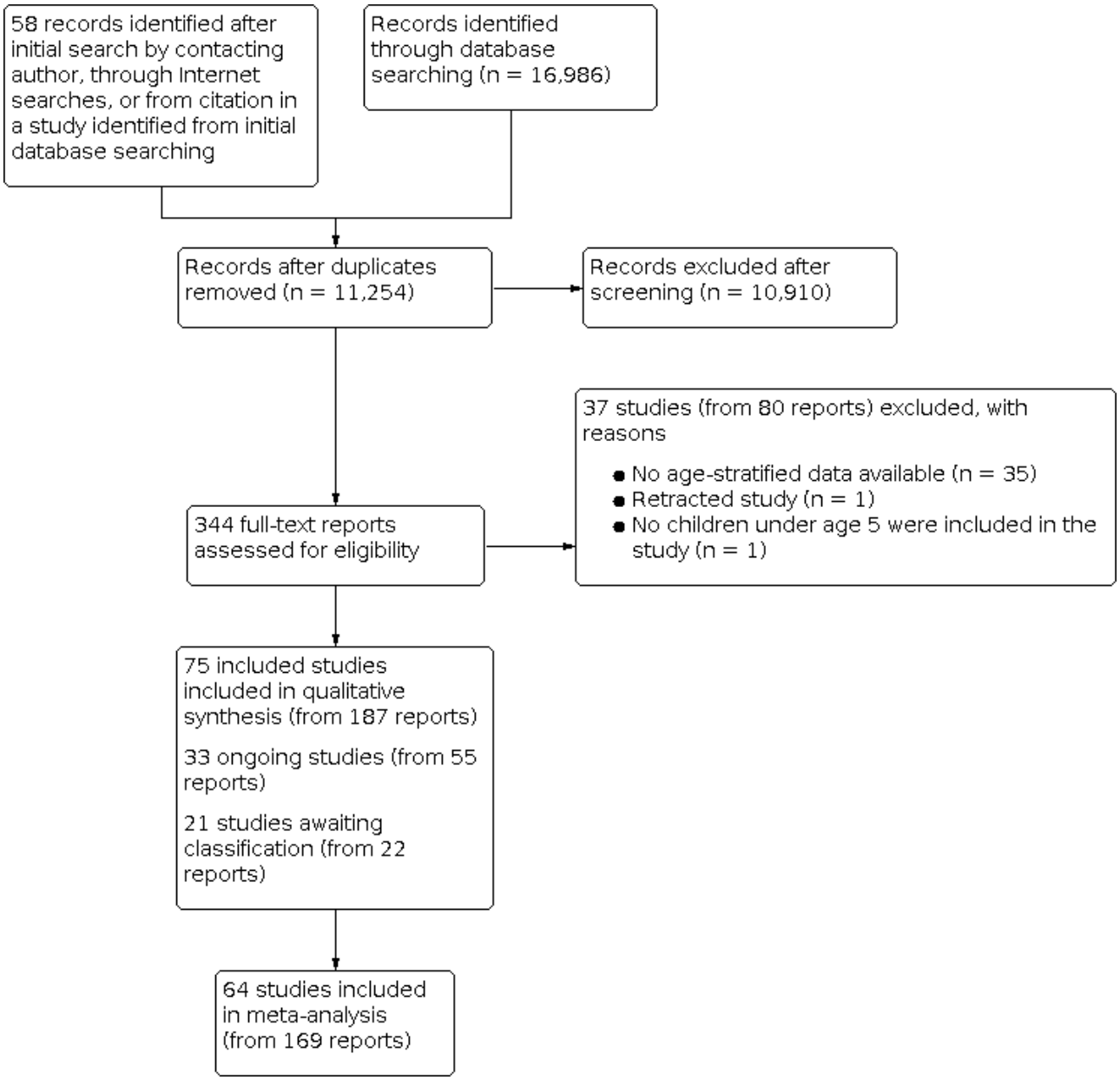
In total, 75 studies (187 total reports) met our inclusion criteria (Criteria for considering studies for this review). Of these, 64 studies (169 reports) reported on our prespecified outcomes and were included in meta-analyses. The remaining 11 studies did not report on any of our prespecified outcomes and therefore were not included in quantitative meta-analysis (Alam 2011; Aly 2019; Choudhary 2012; Kislal 2008; Lava 2011; Manaseki Holland 2010; Pehlivan 2003; Rodd 2011; Saad 2015; Sarhan 2019; Singh 2019).

We categorised 33 additional studies (55 reports) as 'Ongoing' because their trial registration status indicated that recruitment was currently ongoing, or because trial recruitment was complete and study author(s) indicated that a manuscript(s) from the trial would be published in the coming months.

We categorised an additional 21 studies (22 reports) as 'Awaiting classification' because the trial registration indicated that the trial recruitment status was complete but no current or upcoming manuscript or meeting abstract could be found, or because the status of the trial was unknown. We also categorised studies that did not provide enough information to assess eligibility as 'Awaiting classification', specifically if the age group was not specified (Bantz 2015; Behnamfar 2011), or if the study design was unclear and the full-text report could not be obtained (Hagag 2020; Özkan 2000). When we could identify contact information, we contacted the authors of all studies awaiting classification to request more information, and we kept the study categorised as 'Awaiting classification' if these attempts were unsuccessful.

We present the study selection procedure in a PRISMA diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

In total, we included in this review 75 studies (from 187 reports) with 12,122 participants. We summarise the key characteristics of these studies below. The Characteristics of included studies tables provide detailed information about the included trials in relation to the criteria prespecified in our protocol (Yu 2017). The earliest study was published in 1959 (Willi 1959), and the latest study was published in 2019 (Sarhan 2019).

Study design

Most included studies (70 studies) were parallel-group, randomised controlled trials (RCTs). Four additional studies were quasi-randomised controlled trials (Ala-Houhala 1985; Holst-Gemeiner 1978; Lagomarsino 1996; Willi 1959).

Two studies used a cross-over design (Lava 2011; Rodd 2011), neither of which assessed any outcomes within the scope of this review. We did not find any cluster-randomised trials.

Location/Setting

Most studies were conducted in India (14 studies), followed by the USA (10 studies), Canada (seven studies), and Finland (five studies). Four studies each took place in Egypt, Iran, and Turkey; three studies each were included from China and Germany; and two studies each were included from Afghanistan, Australia, Italy, Mexico, and Switzerland. The remaining studies reported on populations in Algeria, Austria, Bangladesh, Chile, Japan, Libya, London, Nigeria, Pakistan, Spain, and Thailand. Only six studies reported on children living at latitudes between the Tropics of Cancer (Northern Tropic) and Capricorn (Southern Tropic), and 67 studies reported on children living in latitudes outside the Tropic

of Cancer or Capricorn. Two studies had multiple study sites falling both between and outside of the Northern and Southern Tropics.

A majority of studies (65 studies) were conducted in hospitals, primary care practices, or clinics, or had a point of contact in a hospital; four were run out of institutional settings (Ducharme 2019; Jensen 2016; Rao 2016; Ziegler 2014), and three reported catchment areas in cities or in areas around a hospital (Feliciano 1994; Manaseki-Holland 2012; Specker 1992). Three studies did not report the exact setting (Rianthavorn 2013; Shajari 2009; Tomimoto 2018).

Participants

Collectively, participants at birth and up to five years of age were included. Eleven studies were conducted among both infants and children under five years of age, and nine additional studies were conducted among children older than one year. A majority of studies (55 studies) were conducted in infants younger than one year old. Four of the 55 infant studies followed up on the same participants after an extended follow-up period without vitamin D supplementation in a subsequent report.

Baseline health status included being healthy; being preterm or (very) low birth weight, or both; having rickets; having severe acute malnutrition; having infectious diseases such as acute or recurrent otitis media, acute diarrhoea, bronchiolitis, pneumonia, or upper or lower respiratory tract infection; having non-communicable diseases or disorders including asthma, chronic kidney disease, or chronic heart failure; or having autoimmune diseases such as juvenile idiopathic arthritis or atopic dermatitis.

Participant characteristics organised across the included studies are found in Table 3.

Interventions

Study interventions involved oral vitamin D supplementation in the form of vitamin D_3 (53 studies) or vitamin D_2 (seven studies), or did not specify the type of vitamin D involved (12 studies). Two studies involved both vitamin D_3 and vitamin D_2 (Gallo 2013a; Gordon 2008), and one study involved D_2 and calcitriol ($1,25(OH)_2D_3$) (Chan 1978). We grouped studies by intervention into four comparisons: (1) those that compared vitamin D to placebo or no intervention; (2) those that compared a higher dose of vitamin D to a lower dose of vitamin D; (3) those that compared a micronutrient intervention plus vitamin D to the same micronutrient intervention without vitamin D; and (4) those that compared a micronutrient intervention plus a higher dose of vitamin D to the same micronutrient intervention with a lower dose of vitamin D) (Table 1). Please see Differences between protocol and review regarding our rationale for grouping the analysis by each of the following four comparisons.

Comparison 1: vitamin D versus placebo or no intervention

Thirty-one studies compared vitamin D to placebo or no intervention, with a total of 7327 participants. Daily dosages of vitamin D ranged from 200 IU in Ponnapakkam 2010 to 2000 IU in Tang 2019. Bolus or pharmacological doses ranged from 40,000 IU in Rianthavorn 2013 to 300,000 IU in Singh 2019, which was usually given once, at enrolment - Jensen 2016; Manaseki Holland 2010; Moodley 2015; Somnath 2017 - or every few weeks - Rianthavorn 2013; Saleem 2018 - or months - Manaseki-Holland 2012; Singh 2019. The duration of follow-up ranged from 60 hours in Chan 1978 to 20 months in Singh 2019.

Comparison 2: vitamin D (higher dose) versus vitamin D (lower dose)

Thirty-four studies compared regimens of higher versus lower doses of vitamin D, with a total of 4027 participants. Daily dosages of the higher dose of vitamin D ranged from 200 IU in Specker 1992 to 6000 IU in Willi 1959, compared to lower doses of vitamin D of 100 IU in Specker 1992 up to 1000 IU in Morawa 1963. Nine studies investigated the effects of administering bolus or pharmacological doses, ranging from 50,000 IU in Huynh 2017; Shajari 2009; and Shakiba 2010 to 600,000 IU in Harnot 2017; Lagomarsino 1996; and Mittal 2014, compared to a daily lower-dose vitamin D supplementation in Holst-Gemeiner 1978; Huynh 2017; Mittal 2014; and Zeghoud 1994 or smaller bolus doses in Harnot 2017; Mittal 2014; and Zeghoud 1994. One study administered two bolus doses of 600,000 IU at months 1 and 5 of follow-up (Lagomarsino 1996). Duration of administration ranged from 5 to 10 minutes in an acceptability study - Lava 2011 - to 24 months in Rosendahl 2018. One study did not report the duration of follow-up (Pehlivan 2003). Finally, one study examining four vitamin D intervention groups with higher or lower doses of vitamin D included micronutrient supplementation (minerals, calcium, and phosphorus) in two of the four groups; therefore data from the two arms *not* containing calcium and phosphorus were included in this comparison (Backström 1999b).

Comparison 3: vitamin D + micronutrient(s) versus micronutrient(s) alone

One study was included in this comparison (Thacher 2014). This study investigated effects of 50,000 IU vitamin D_2 plus calcium against a placebo and calcium, given every month, for six months, among 53 participants.

Comparison 4: vitamin D (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s)

Nine studies, with a total of 649 participants, investigated micronutrient(s) content plus vitamin D versus the same micronutrient(s) content with or without a lower dose of vitamin D (Alizadeh 2006; Alizadeh Taheri 2014; Backström 1999b; Evans 1989; Gordon 2008; Mathur 2016; Mittal 2018; Rao 2016; Tergestina 2016). Six studies compared daily vitamin D supplementation, ranging between 400 IU in Alizadeh Taheri 2014 and 2000 IU in Evans 1989 to a daily lower dose of vitamin D, ranging between 200 IU in Alizadeh Taheri 2014 and 2000 IU in Gordon 2008. Daily supplementation of 4000 IU in Rao 2016 or 2000 IU in Gordon 2008 was compared to weekly supplementation of 30,000 IU in Rao 2016 or 50,00 IU in Gordon 2008, respectively. A bolus dose (300,000 IU) was compared to 90,000 IU, both given once, at enrolment (Mittal 2018). Duration of follow-up ranged from 51 days in Tergestina 2016 to 9 months in Rao 2016. Finally, one study examining four vitamin D groups with higher or lower doses of vitamin D included calcium and phosphorus supplementation in two of the four arms; therefore data from the two groups containing calcium and phosphorus supplementation were included in this comparison (Backström 1999b). Micronutrients administered in these studies mainly included minerals such as calcium (all studies), phosphorus (Alizadeh 2006; Alizadeh Taheri 2014; Backström 1999b; Mathur 2016; Tergestina 2016), and/or a multi-vitamin (Mathur 2016; Tergestina 2016).

Outcomes

Primary outcomes

Thirty-one studies included a primary outcome. Of these, 14 evaluated linear growth (Anderson-Berry 2017; Backström 1999a; Backström 1999b; Chandy 2016; Gallo 2013b; Greer 1981; Greer 1989; Holmlund-Suila 2012; Huynh 2017; Lagomarsino 1996; Natarajan 2014; Siafarikas 2011; Singh 2018a; Trilok-Kumar 2011). Three reported on height-for-age z-scores (HAZ) (Gallo 2013a; Gallo 2013b; Trilok-Kumar 2011), and one reported on stunting (Trilok-Kumar 2011). We found 29 studies reporting adverse effects (hypercalciuria, hypercalcaemia, hyperphosphataemia, and/or kidney stones).

Linear growth

Linear growth (length) was measured using infantometers or infant length boards (Greer 1981; Greer 1989; Chandy 2016; Singh 2018a), wall-mounted stadiometer (Thacher 2014), clinical charts (Backström 1999a; Backström 1999b), or standardised calibrated equipment (Siafarikas 2011), in centimetres; several studies did not specify what type of equipment was used to measure length (Anderson-Berry 2017; Holmlund-Suila 2012; Huynh 2017; Lagomarsino 1996; Natarajan 2014).

Length/height-for-age and stunting

Height-for-age was measured using the WHO Child Growth Standards, with stunting defined as HAZ less than 2 standard deviations (SDs) below the WHO reference standard (WHO 2006). Linear growth for calculation of HAZ was measured using infantometers or infant length boards (Gallo 2013b; Trilok-Kumar 2011), or it was not described (Gallo 2013a).

Adverse effects

Hypercalciuria

Hypercalciuria was measured using the urinary calcium-to-creatinine ratio. Urinary calcium was assayed by Beckman Coulter assay (Bozkurt 2017; Gallo 2013b; Natarajan 2014), photometric assay (Holmlund-Suila 2012), or DiasSorin Auto Analyzer (Mittal 2018); colorimetrically using o-cresol phthalein complexone (Pointe Scientific) (Shajari 2009), chemiluminescence (VitrosEci) (Singh 2018a), complexometric method with ethylenediaminetetraacetic acid (calcium), and the kinetic Jaffé reaction (creatinine) (Evans 1989); or by clinical chemistry analyser (Harnot 2017), urine spot (Tergestina 2016), or standard assays without further detail (Siafarikas 2011; Zeghoud 1994). Two studies did not specify which assay was used (Ducharme 2019; Gallo 2013a). Studies defined hypercalciuria as urinary calcium-to-creatinine ratio greater than 2.2 mmol/mmol (Holmlund-Suila 2012); greater than 1.25 mmol/mmol (for one-to-two-year-olds) or > 1 mmol/mmol (for two-to-five-year-olds) (Ducharme 2019; Jensen 2016; Mittal 2018); > 0.8 mg/mg (Natarajan 2014); > 1.35 mg/mg (Tergestina 2016); > 0.21 mmol/mmol (Shajari 2009); or > 0.86, 0.6, and 0.4 for children < 7 months old, 7 to 18 months old, and 19 months to 6 years old, respectively (Harnot 2017); or did not define hypercalciuria (Bozkurt 2017; Gallo 2013a; Gallo 2013b; Siafarikas 2011; Singh 2018a).

Hypercalcaemia

Hypercalcaemia was measured using total serum calcium. Total serum calcium was assayed by the Beckman Coulter assay (Anderson-Berry 2017; Hanson 2011; Huynh 2017; Natarajan 2014), randox (Chandy 2016), atomic absorption spectroscopy (Chan 1978), a multi-channel analyser (Roche Diagnostics) (Gordon 2008), Dimension RxL Max clinical chemistry analyser (Harnot 2017), photometric assays (Holmlund-Suila 2012), DiasSorin Auto Analyzer (Mittal 2018), flex gas analysers (Rosendahl 2018), spectrophotometric methods (Tergestina 2016), 'standard methods' without further detail (Siafarikas 2011; Zeghoud 1994), or ethylene glycol tetra-acetic acid titration (Robinson 1981), or colorimetrically using o-cresol phthalein complexone (Pointe Scientific) (Ziegler 2014). Six studies did not report the assay or method used (Aglipay 2017; Ducharme 2019; Gallo 2013a; Hibbs 2018; Mittal 2014; Shakiba 2010). Studies defined hypercalcaemia as total serum calcium > 10.5 mg/dL (Chan 1978; Chandy 2016), > 10.7 mg/dL (Hibbs 2018), > 10.8 mg/dL (Gupta 2016; Mittal 2014; Mittal 2018; Tergestina 2016), or > 11.2 mg/dL (Zeghoud 1994), or did not define hypercalcaemia (Aglipay 2017; Anderson-Berry 2017; Gallo 2013b; Gordon 2008; Hanson 2011; Holmlund-Suila 2012; Huynh 2017; Natarajan 2014; Robinson 1981; Rosendahl 2018; Siafarikas 2011; Shakiba 2010; Ziegler 2014).

Hyperphosphataemia

Hyperphosphataemia was measured using serum phosphorus. Methods for hyperphosphataemia were done using "standard assays" (Siafarikas 2011), or it was indicated that they were carried out at the study's clinical chemistry laboratory and otherwise not detailed (Aglipay 2017; Hibbs 2018). Only one study defined hyperphosphataemia as serum phosphorus > 9.5 mg/dL (3.07 mmol/L) (Hibbs 2018).

Kidney stones

Kidney stones were assessed using renal ultrasonography (Abdel-Hady 2019; Singh 2018a), or methods were not reported (Natarajan 2014).

Secondary outcomes

Gain in length

Gain in length was reported by three studies (Feliciano 1994; Mathur 2016; Ziegler 2014). Length was assessed using an infantometer (Mathur 2016), or standardised methods were used (Ziegler 2014). In one study, the method of measurement was not described (Feliciano 1994).

Weight-for-age and weight-for-height/length

Four studies reported on weight-for-age and weight-for-height/length (Gallo 2013a; Gallo 2013b; Saleem 2018; Trilok-Kumar 2011). Weight-for-age z-score (WAZ) and weight-for-height/length z-scores (WHZs) were measured using the WHO Child Growth standards (WHO 2006). Weight was measured using infant weighing scales (Gallo 2013b; Saleem 2018; Trilok-Kumar 2011); in one study, the method of measurement was not reported (Gallo 2013a). Height/length was measured using a wall-mounted stadiometer or infant length board (Gallo 2013b; Saleem 2018; Trilok-Kumar 2011). Recumbent length was measured among participants under two years of age, and standing height was measured when the child was over two years of age. One study reported on both underweight and wasting (Trilok-Kumar 2011).

Serum 25(OH)D concentration

Fifty-nine studies reported on vitamin D status (continuously or categorically in terms of deficiency or insufficiency versus sufficiency). Vitamin D status was measured using chemiluminescence protein-binding assay via the Cobase analyser kit with Elecsys Vitamin D Total Assay (Roche Diagnostics Ltd.) or automated immunoassay (IDS-iSYS, Immunodiagnostic System Ltd.) (CLPBA) (Gallo 2013a; Holmlund-Suila 2012; Manaseki-Holland 2012; Mittal 2018; Natarajan 2014; Ponnapakkam 2010; Rosendahl 2018; Rueter 2019); competitive protein-binding assay (CPBA) (Aglipay 2017; Ala-Houhala 1985; Greer 1981; Mathur 2016; Robinson 1981; Specker 1992; Stögmann 1985; Zeghoud 1994); electro-chemiluminescent assay (EIA) (Alizadeh Taheri 2014; Fort 2016; Gallo 2013b; Harnot 2017; Sánchez-Armendáriz 2018; Somnath 2017); liquid chromatography with tandem mass spectrometry (LC-MS/MS) (Anderson-Berry 2017; Bozkurt 2017; Ducharme 2019; Gallo 2013a; Gallo 2013b; Huynh 2017; Jensen 2016; Moodley 2015; Saleem 2018; Thacher 2014); high-performance liquid chromatography (HPLC) (Atas 2013; Backström 1999a; Backström 1999b; Greer 1989; Tang 2019); enzyme-linked immunoabsorbent assay (ELISA) (Abdel-Hady 2019); immunoassay (Hibbs 2018); radioimmunoassay (RIA) (Chan 1978; Chandy 2016; Evans 1989; Gallo 2013b; Gupta 2016; Hanson 2011; Holst-Gemeiner 1978; Mittal 2014; Shedeed 2012; Siafarikas 2011; Trilok-Kumar 2011; Ziegler 2014); and chemiluminescent assay (CLIA) (Gordon 2008; Marchisio 2013; Principi 2013; Rao 2016; Rianthavorn 2013; Shakiba 2010; Singh 2018a; Tergestina 2016). As shown, Gallo 2013a evaluated vitamin D concentration using two assays (CLPBA and LC-MS/MS), and Gallo 2013b evaluated vitamin D concentration using three different assays (EIA, RIA, and LC-MS/MS). One study did not report the vitamin D assay method used (Tomimoto 2018).

Rickets

Fourteen studies reported on rickets (Ala-Houhala 1985; Alizadeh 2006; Chandy 2016; Greer 1981; Huynh 2017; Mittal 2014; Mittal 2018; Morawa 1963; Ponnapakkam 2010; Robinson 1981; Siafarikas 2011; Specker 1992; Thacher 2014; Willi 1959).

We observed variation across 15 studies in the trial definitions of 'rickets', which was one of our secondary outcomes. Definitions of rickets as a dichotomous outcome across these studies included biochemical concentrations (measured by serum calcium, phosphorus, magnesium, and alkaline phosphatase; thresholds unspecified) (Ala-Houhala 1985); wide fontanelles, not defined (Huynh 2017), or defined as > 3 × 3 cm (Alizadeh 2006); craniotabes score, using a size-based scale (Morawa 1963), or the rate of craniotabes, undefined (Huynh 2017); X-ray changes, defined as fractures in the left-hand radiograph (Alizadeh 2006), or presentation of florid changes (Morawa 1963); clinical signs, defined as a combination of rachitic rosary, craniotabes, or widened wrists (Greer 1981); radiological scores > 0 (Mittal 2014; Mittal 2018); widened epiphyses or limb deformities, undefined (Huynh 2017); combinations of signs, such as elevated alkaline phosphatase and evidence of X-ray changes (Ponnapakkam 2010), or concavity and fraying of bone, widening of epiphyses (Specker 1992); radiological evidence, not defined (Robinson 1981); and clinical signs, including appearing translucent, pale, flushed, or showing failure (translated from German; Willi 1959). Two studies also reported symptoms of rickets as a continuous outcome, including mean radiographic score (Thacher 2014), median radiographic score (Evans 1989), and median anterior fontanelle size (Chandy 2016); these studies did not share the same control group (Chandy 2016 used placebo, and Evans 1989 and Thacher 2014 used a lower dose of vitamin D).

Missing data

We contacted study authors for additional information on included studies, as needed; most requests involved author sharing of age-stratified data to include only children under five years of age in the results. We also asked study authors to send us a full-text publication citation, if existing, of any meeting abstracts that we found, or to share unpublished data that could be incorporated into our analysis, if relevant.

In summary, we obtained a positive response (i.e. study authors shared specific information, published or unpublished data, or results) for nine studies (Aglipay 2017; Ponnapakkam 2010; Rianthavorn 2013; Rueter 2019; Sánchez-Armendáriz 2018; Tang 2019; Thacher 2014; Trilok-Kumar 2011; Ziegler 2014).

Funding sources

Studies were funded by a variety of sources, namely, non-profit funding. Two studies reported provision of the drug by the manufacturer, along with non-profit funding (Gallo 2013a; Huynh 2017). Two studies reported for-profit funding (Rodd 2011; Tomimoto 2018). Two studies were categorised as mixed funding (non-profit and for-profit funding) (Chan 1978; Greer 1981). Five studies specifically reported no funding (Bozkurt 2017; Choudhary 2012; Lava 2011; Mittal 2018; Sarhan 2019), and 26 studies did not disclose funding sources. The remaining studies were funded by non-profit sources. Information on specific funding sources may be found in the Characteristics of included studies tables.

Excluded studies

We excluded 37 studies (80 reports) for the following reasons: for 35 studies, no stratified data were available for population age group (which included children over five years of age), after contact with the study author; one study was retracted (Saad 2018); and one study's author indicated that no children under age five years were included in the study (Swangtrakul 2020). We considered conducting a sensitivity analysis including the studies from which we were unable to obtain age-stratified data using a threshold of children under the age of five years constituting ≥ 80% of the study population, based on descriptive statistics presented for the whole population; however, no study appeared to meet this criterion, or studies did not present variance estimates, limiting our inference. As such, these studies have not been included in the review meta-analyses. Further details may be found in the Characteristics of excluded studies tables.

Reasons for negative responses from study authors included not enough time to re-analyse the data; most children were ineligible (over five years of age); data were unavailable; or no response was received to our follow-up email after an initial positive response (see Characteristics of excluded studies).

Ongoing studies

We identified 33 ongoing studies (from 55 reports). These studies were registrations for trials for which no full-text publication was identified, recruitment was currently ongoing, or trial recruitment was complete and study author(s) indicated that a manuscript(s) from a trial would be published in the coming months. We present a

brief overview of these studies below. Further details may be found in the Characteristics of ongoing studies.

Study design

Ongoing studies included 32 parallel-group RCTs and one cross-over RCT (RBR-4r6p5v).

Location/Setting

The studies are being conducted in India (nine studies), Canada (six studies), USA (three studies), Chile (two studies), and Poland (two studies), and one study a piece is being conducted in Australia, Brazil, China, France, Indonesia, Iran, Israel, Japan, Saudi Arabia, and Spain. An additional study is being conducted across three countries: Austria, Canada, and Chile.

Settings include hospitals (10 studies), intensive care units (two studies), clinics (one study), and a university medical centre (one study), or the setting has not been reported (19 studies).

Participants

Studies included or aimed to include infants and children. Studies among infants (12 studies) included healthy (5 studies), small-for-gestational-age (1 study), preterm (5 studies), and low birth weight (2 studies) populations (with some overlap present). Studies among children (12 studies) included populations that were healthy (5 studies), or had asthma (1 study), atopic dermatitis (1 study), epilepsy (1 study), chronic kidney disease (1 study), Crohn's disease (1 study), or vitamin D deficiency plus low energy fracture (1 study). Several studies among children included only children over five age years of age (seven studies). Studies among both infants and children (nine studies) included populations that were healthy (two studies), or had rickets (two studies), cyanotic congenital heart disease (one study), vitamin D deficiency (two studies), lower respiratory tract infection (one study), or chronic heart disease requiring surgery (one study). Of these, five studies included children over the age of five years.

Interventions

Please see Differences between protocol and review regarding our rationale for grouping the analysis by each of the following four comparisons.

Comparison 1: vitamin D versus placebo or no intervention

Sixteen studies examined vitamin D versus placebo or no intervention. Doses ranged from 400 IU in ACTRN12614000334606/NCT02112734; CTRI/2013/04/003566; CTRI/2015/08/006132; UMIN000034864; and NCT01363167 to 100,000 IU in NCT03365687. Duration ranged from six weeks in NCT01996423 to one year in ACTRN12616000659404; and Galdo 2018, with one study not reporting the duration of follow-up (CTRI/2017/12/010827).

Comparison 2: vitamin D (high dose) versus vitamin D (low dose)

An additional 16 studies examined a high dose of vitamin D versus a lower dose of vitamin D. As a note, one study examined two different dosages of vitamin D versus placebo; therefore it is applicable to both comparison 1 and comparison 2 (NCT02046577). Doses ranged from 400 IU in NCT02563015 to 150,000 IU in CTRI/2018/12/016760 in the higher-dose group, and from 400 IU in NCT02563015 to 4000 IU in CTRI/2018/12/016760 in the lower-dose group. Duration ranged from three weeks in CTRI/2018/04/013300 to three years in NCT02563015.

As a note, one additional study examined two interventions: 5600 IU vitamin D_3 versus 11,200 IU vitamin D_3, compared to placebo; as such, in a future version of this review, we may include this study in both comparison 1 and comparison 2 and analyse the study arms accordingly (comparison 1: 5600 IU D_3 versus placebo and 11,200 IU D_3 versus placebo; comparison 2: 5600 IU D_3 versus 11,200 IU D_3) (NCT02046577).

Comparison 3: vitamin D + micronutrient(s) versus micronutrient(s) alone

No studies are assessing this comparison.

Comparison 4: vitamin D (high dose) + micronutrient(s) versus vitamin D (low dose) + micronutrient(s)

One study was included in this comparison (IRCT20171030037093N4). This study investigated the effects of 300 IU vitamin D and an additional 400 IU vitamin D plus vitamin A, against 300 IU vitamin D and vitamin A, until 40 weeks' postmenstrual age.

Outcomes

Primary outcomes

Five studies listed "growth" (linear growth) in their protocol as an outcome (CTRI/2013/04/003566; CTRI/2015/08/006132; Galdo 2018; NCT03742310; NCT01363167). Eleven studies listed adverse effects (hypercalcaemia, hypercalciuria, and/or kidney stones) as outcomes of interest (CTRI/2017/11/010385; CTRI/2017/12/010827; CTRI/2018/12/016760; Galdo 2018; NCT03365687; NCT03536845; NCT03087149; NCT02452762; NCT01838447; NCT03742505; NCT01363167).

Secondary outcomes

Twenty-five studies listed examining mean 25(OH)D concentrations, or changes in and/or achieving sufficiency. Although nine ongoing studies included serum calcium, urinary calcium, serum phosphorus, the urinary calcium-to-creatinine ratio, or adverse events/effects, they did not specifically list measuring hypercalciuria, hypercalcaemia, hyperphosphataemia, or kidney stones specifically as adverse effects.

Missing data

We contacted the authors of the trial registrations for additional information, including asking the authors to confirm a full-text publication of any meeting abstracts found, or to share unpublished data that we could cite (see Characteristics of ongoing studies tables for details).

Funding sources

Fourteen studies were funded by non-profit entities; one study was funded by a non-profit organisation plus the company provided the drug; one study received no funding; and one study was funded by a for-profit entity. The remaining 16 studies did not disclose funding sources.

Studies awaiting classification

We categorised an additional 21 studies (22 reports) as 'Awaiting classification' if the trial registration indicated that the trial

recruitment status was complete but no current or upcoming manuscript or meeting abstract could be found, or if the status of the trial was unknown. We also categorised studies that did not provide enough information to assess eligibility as 'Awaiting classification', specifically, if the age group was not specified (Bantz 2015; Behnamfar 2011), or if the study design was unclear and the full-text report could not be obtained (Hagag 2020; Özkan 2000). When we could identify contact information, we contacted the authors of all studies awaiting classification to ask for more information, and we kept the study categorised as 'Awaiting classification' if these attempts were unsuccessful. See Characteristics of studies awaiting classification for more information.

Risk of bias in included studies

Below, we summarise the results of our 'Risk of bias' assessment. Further details can be found in the 'Risk of bias' tables, beneath the Characteristics of included studies tables. Figure 2 and Figure 3 provide graphical summaries of the 'Risk of bias' assessment.

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

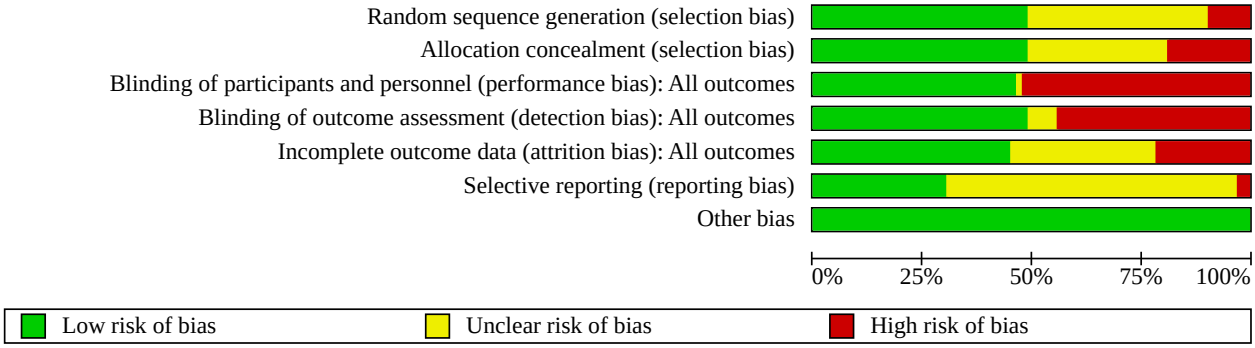


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

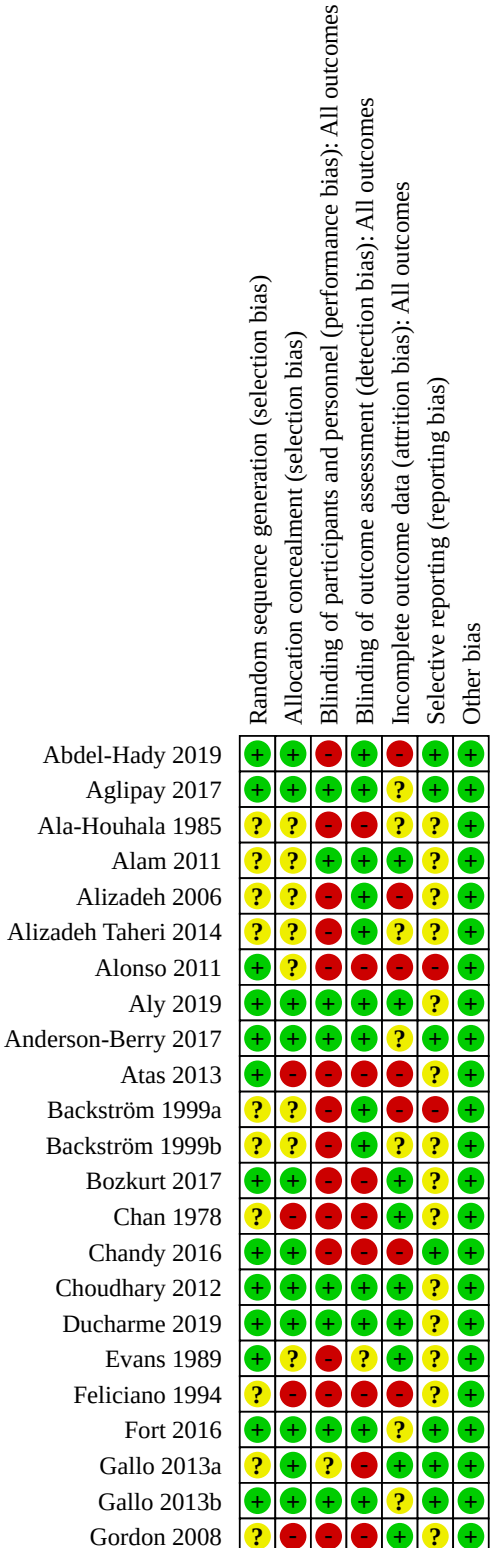


Figure 3. (Continued)

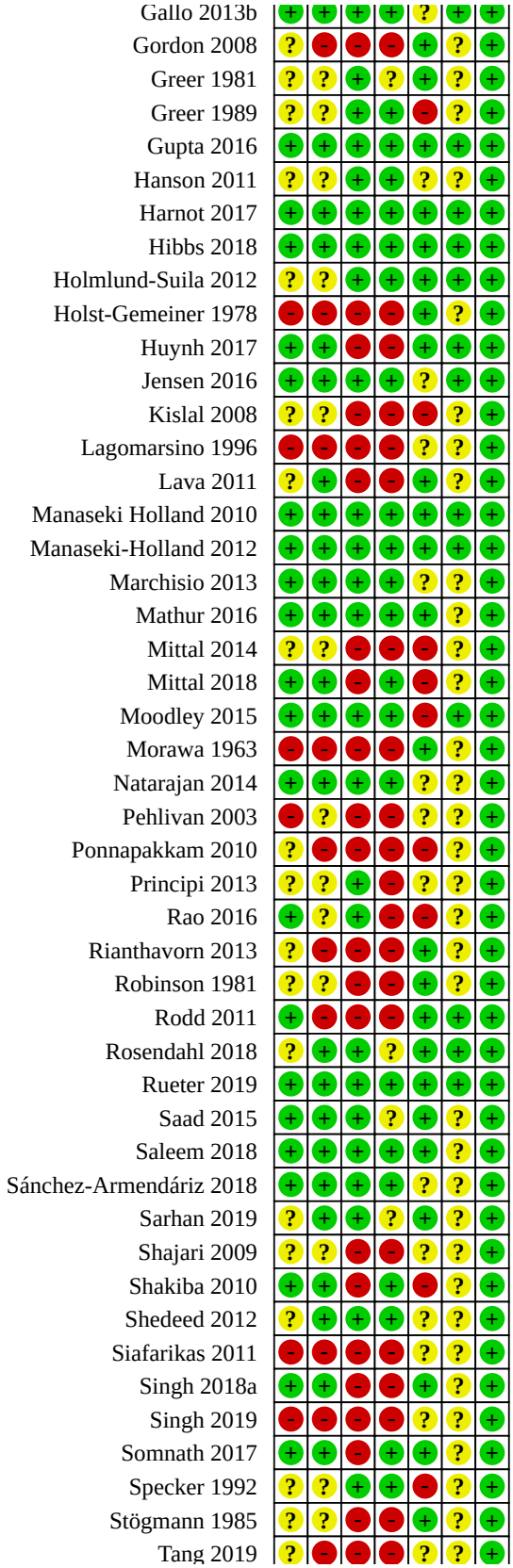
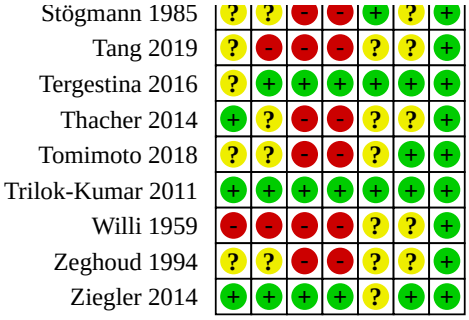


Figure 3. (Continued)



Allocation

Included studies were individually randomised or block-randomised controlled trials.

Sequence generation

We determined that 37 studies had adequate sequence generation and subsequently rated them at low risk of bias. Methods included computer-based random number generators, such as random number tables, or Statiscal Analysis Software (SAS) procedures (31 studies); websites such as www.randomization.com and www.randomizer.org (four studies: Gallo 2013a; Moodley 2015; Rodd 2011; Rueter 2019); and the low-tech technique of coin flips (two studies: Evans 1989; Thacher 2014). Seven studies reported inadequate methods of sequence generation due to employing alternating randomisation and therefore were rated at high risk of bias (Holst-Gemeiner 1978; Lagomarsino 1996; Morawa 1963; Pehlivan 2003; Siafarikas 2011; Singh 2019; Willi 1959). The remaining 31 studies reported that groups were randomly allocated but did not provide details on how the randomisation sequence was generated and therefore were rated at unclear risk of bias.

Allocation concealment

We judged 37 studies to have adequate allocation concealment and thus low risk of bias, 14 studies to have inadequate methods of allocation concealment and therefore high risk of bias, and 24 studies to have unclear methods of allocation concealment and unclear risk of bias. The 14 studies with inadequate allocation concealment included studies in which allocation concealment was not described and the varying dosages/frequencies would indicate the allocation given (Atas 2013; Feliciano 1994; Gordon 2008; Holst-Gemeiner 1978; Lagomarsino 1996; Ponnapakkam 2010; Rianthavorn 2013; Rodd 2011; Singh 2019; Tang 2019; Willi 1959); one study in which the types of interventions would indicate allocation, which included two study arms that were administered intramuscular vitamin D (Morawa 1963); one study in which parents were directly told the allocation (Chan 1978); and one study that used odd- and even-numbered envelopes to allocate the intervention (Siafarikas 2011). The 24 studies with unclear risk of bias generally did not describe their allocation concealment procedures in enough detail to allow a judgement on their risk of selection bias.

Blinding

Twenty-four studies were described as 'double-blind' or appeared so, three studies were described as 'single-blind' (Lava 2011; Principi 2013; Rao 2016), and 12 studies were specifically not blinded (i.e. 'open label') (Alonso 2011; Huynh 2017; Mittal 2014; Singh 2018a; Singh 2019; Somnath 2017; Stögmann 1985; Tang 2019; Thacher 2014; Tomimoto 2018; Willi 1959; Zeghoud 1994). Thirty-seven studies had partial or non-described blinding. One study was triple-blind (Ducharme 2019).

Blinding of participants and staff (performance bias)

Many studies did not describe blinding, or were blinded only to staff and not parents, leading us to judge 39 studies as having high risk of performance bias. We judged 35 studies to be at low risk of bias as they either were double-blind or were blinded to staff with likely blinding to parents of participants (even if not stated explicitly). We considered one study, Gallo 2013a, to have unclear risk of performance bias due to lack of description of blinding, but because of adequate allocation concealment, participants and staff were likely blinded.

Blinding of outcome assessors (detection bias)

We judged 33 studies to be at high risk of detection bias due to lack of description and the subjective nature of outcomes. We rated 37 studies at low risk of detection bias due to explicit mention of blinding to outcome assessors or mention of double-blinding. We judged five studies to be at unclear risk of detection bias due to lack of a specific description but likely blinded due to the mention of a "double-blind" study design (Evans 1989; Greer 1981; Rosendahl 2018; Saad 2015; Sarhan 2019).

Incomplete outcome data

We judged 16 studies to be at high risk of attrition bias, 34 at low risk of attrition bias, and 25 at unclear risk of attrition bias. Reasons for high risk of attrition bias included lack of reporting on the number of participants at randomisation compared to endpoint (Alizadeh 2006); high loss to follow-up (Chandy 2016; Greer 1989; Mittal 2014); participants lost to follow-up not examined for differences from those who were included (Alonso 2011; Feliciano 1994; Ponnapakkam 2010); reasons for loss to follow-up not given, not compared by arm, or both (Alizadeh 2006; Atas 2013; Feliciano 1994; Greer 1989; Kislal 2008; Mittal 2018; Moodley 2015; Ponnapakkam 2010); outcomes reported at an intermediate study time point but not at the end of full follow-up (Abdel-Hady 2019); or use of complete case or per-protocol analysis instead of intent-to-treat analysis (Backström 1999a; Chandy 2016; Greer 1989; Kislal 2008; Mittal 2018; Moodley 2015; Ponnapakkam 2010; Rao 2016; Shakiba 2010; Specker 1992). Reasons for low risk of bias included indistinguishable interventions/comparators; all

randomised participants completing follow-up or no missing data; reasons for missing data not related to the outcome (e.g. moving away); missing data balanced across groups and similar reasons; small proportion of missing data; and intention-to-treat analysis conducted, including all participants randomised. We assigned a judgement of unclear risk of bias when insufficient information was available to reach a judgement of high or low risk of bias.

Selective reporting

We considered most studies (50 studies) to be at unclear risk of reporting bias, as no study protocols or trial registration identifiers were reported (see Risk of bias in included studies), or a trial registration was found online but appeared to have been published after the study was completed. We judged two studies to be at high risk of bias because the methods sections mentioned measuring growth (Alonso 2011), or referred to specific biochemical parameters (Backström 1999a), but these measures were not reported in the results section; in addition, neither study had a published protocol or trial registration.

We judged 23 studies to be at low risk of bias because they had a protocol pre-registered on a trial registry, or because they cited a published study protocol that proposed measuring the outcomes presented in the published study (Aglipay 2017; Rosendahl 2018).

Also, for each comparison, we visually inspected funnel plots to assess for bias due to missing results in our primary outcomes; we did not observe bias due to missing results.

Other potential sources of bias

We did not observe any other potential sources of bias in these studies and therefore rated all studies at low risk of bias on this domain.

Effects of interventions

See: **Summary of findings 1** Vitamin D versus placebo or no intervention; **Summary of findings 2** Vitamin D (higher dose) versus vitamin D (lower dose); **Summary of findings 3** Vitamin D (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s)

Please see Differences between protocol and review regarding our rationale for grouping the analysis by each of the following four comparisons.

Please see Table 4 for the results of sensitivity analyses conducted with fixed-effect models for outcomes including at least two studies in the comparison.

Comparison 1: vitamin D versus placebo or no intervention

Primary outcomes

Please see Summary of findings 1. All outcomes were measured at the end of the intervention, with average time frames ranging from 6 to 7.5 months.

Linear growth

There is little to no difference between vitamin D and placebo or no intervention in linear growth (mean difference (MD) 0.66 cm, 95% confidence interval (CI) -0.37 to 1.68; 3 studies, 240 participants; I^2 = 49%; tau^2 = 0.41; random-effects model; Analysis 1.1; low-certainty evidence). The results were similar with a fixed-effect model (Table 4).

Length/height-for-age (L/HAZ)

Compared to placebo or no intervention, vitamin D may improve length/height-for-age z-score (L/HAZ) scores (MD 0.11, 95% CI 0.001 to 0.22; 1 study, 1258 participants; fixed-effect model; Analysis 1.2; moderate-certainty evidence).

Stunting

Some evidence suggests that, compared to placebo or no intervention, vitamin D has little to no effect on stunting (risk ratio (RR) 0.90, 95% CI 0.80 to 1.01; 1 study, 1247 participants; fixed-effect model; Analysis 1.3; moderate-certainty evidence).

Adverse effects

Hypercalciuria

Insufficient evidence suggests that, compared to placebo or no intervention, vitamin D has an effect on the incidence of hypercalciuria (RR 2.03, 95% CI 0.28 to 14.67; 2 studies, 68 participants; I^2 = 0%; tau^2 = 0.0; random-effects model; Analysis 1.4; moderate-certainty evidence). The results were similar with a fixed-effect model (Table 4).

Hypercalcaemia

Compared to placebo or no intervention, we are uncertain whether vitamin D supplementation has an effect on the incidence of hypercalcaemia, as the certainty of the evidence was very low (RR 0.82, 95% CI 0.35 to 1.90; 2 studies, 367 participants; I^2 = 48%; tau^2 = 0.18; random-effects model; Analysis 1.5). The results were similar with a fixed-effect model (Table 4).

No study included in this comparison measured the following primary outcomes: hyperphosphataemia and kidney stones.

Secondary outcomes

Weight-for-age (WAZ)

Insufficient evidence suggests that, compared to placebo or no intervention, vitamin D has an effect on mean WAZ scores (MD 0.09, 95% CI −0.02 to 0.20; 1 study, 1273 participants; fixed-effect model; Analysis 1.6).

Underweight

Insufficient evidence suggests that, compared to placebo or no intervention, vitamin D has an effect on differences in the proportion of underweight children between groups (RR 0.94, 95% CI 0.80 to 1.11; 1 study, 1282 participants; fixed-effect model; Analysis 1.7).

Weight-for-length/height (WL/HZ)

Insufficient evidence suggests that, compared to placebo or no intervention, vitamin D has an effect on WL/HZ score between intervention arms (MD 0.65, 95% CI −0.67 to 1.97; 2 studies, 1442 participants; I^2 = 93%; tau^2 = 0.84; random-effects model; Analysis 1.8). The results were similar with a fixed-effect model (Table 4).

Wasting

Insufficient evidence suggests that, compared to placebo or no intervention, vitamin D has an effect on differences in the

proportion of wasted children between groups (RR 1.25, 95% CI 0.82 to 1.91; 1 study, 1282 participants; fixed-effect model; Analysis 1.9)

Vitamin D status

Continuous 25(OH)D concentration (nmol/L)

Across 21 studies, children receiving vitamin D had higher serum 25(OH)D concentrations than children receiving placebo or no intervention (MD 30.91 nmol/L, 95% CI 21.82 to 40.00; 21 studies, 2202 participants; I^2 = 95%; tau^2 = 385.1; random-effects model; Analysis 1.10). The results were similar with a fixed-effect model (Table 4). We explored possible reasons for the high heterogeneity observed across studies, including analysis of studies examining physiological doses of vitamin D only; infants only; and children only (Table 5). We found that limiting the included studies to physiological doses of vitamin D and studies done in infants did not decrease inter-study heterogeneity (I^2 = 95% for both analyses), but analysing only children over one year of age decreased inter-study heterogeneity to I^2 = 87%.

Change in 25(OH)D concentration

Compared to placebo or no intervention, vitamin D resulted in a larger change in vitamin D concentration (MD 28.36 nmol/L, 95% CI 10.41 to 46.32; 3 studies, 495 participants; I^2 = 88%; tau^2 = 0.01; random-effects model; Analysis 1.11). The results were similar with a fixed-effect model (Table 4).

25(OH)D ≥ 50 nmol/L

Groups receiving vitamin D were 88% more likely to have vitamin D status ≥ 50 nmol/L (RR 1.88, 95% CI 1.63 to 2.17; 6 studies, 982 participants; I^2 = 20%; tau^2 = 0.01; random-effects model; Analysis 1.12) than groups receiving placebo or no intervention. The results were similar with a fixed-effect model (Table 4).

25(OH)D ≥ 75 nmol/L

Insufficient evidence suggests that, compared to placebo or no intervention, vitamin D has an effect on achieving vitamin D status above 75 nmol/L (RR 5.75, 95% CI 0.49 to 67.59; 2 studies, 138 participants; I^2 = 91%; tau^2 = 2.90; random-effects model; Analysis 1.13). With a fixed-effect model, vitamin D had an effect on achieving vitamin D status above 75 nmol/L (Table 4).

25(OH)D < 25 to 30 nmol/L

In three studies, children in the vitamin D groups had 74% lower risk of severe vitamin D deficiency than those given placebo or no intervention (RR 0.26, 95% CI 0.19 to 0.36; 3 studies, 836 participants; I^2 = 0%; tau^2 = 0; random-effects model; Analysis 1.14). The results were similar with a fixed-effect model (Table 4).

Rickets

Insufficient evidence suggests that, compared to placebo or no intervention, vitamin D has an effect on anterior fontanelle maximum diameter (MD -0.20 cm, 95% CI -0.61 to 0.21; 1 study, 101 participants; fixed-effect model; Analysis 1.15).

No study included in this comparison assessed the secondary outcome of gain in linear growth.

Comparison 2: vitamin D (higher dose) versus vitamin D (lower dose)

Primary outcomes

Please see Summary of findings 2. All outcomes were measured at completion of the intervention, with average time frames ranging from 3.9 to 8.6 months.

Linear growth

Data show little to no difference between higher doses of vitamin D and lower doses of vitamin D on linear growth, although we are uncertain about the result (MD -1.00 cm, 95% CI -2.22 to 0.21; 5 studies, 283 participants; I^2 = 71%; tau^2 = 1.22; random-effects model; Analysis 2.1). With a fixed-effect model, higher doses of vitamin D resulted in less linear growth than lower doses of vitamin D, although we are uncertain about the result (Table 4).

Length/height-for-age (L/HAZ)

Insufficient evidence suggests that, compared to a lower dose of vitamin D, a higher dose of vitamin D has an effect on L/HAZ (MD 0.40 z-score, 95% CI -0.06 to 0.86; 2 studies, 105 participants; I^2 = 0%; tau^2 = 0; random-effects model; Analysis 2.2; low-certainty evidence). The results were similar with a fixed-effect model (Table 4).

Adverse effects

Hypercalciuria

Insufficient evidence suggests that, compared to a lower dose of vitamin D, a higher dose of vitamin D has an effect on the incidence of hypercalciuria (RR 1.16, 95% CI 1.00 to 1.35; 6 studies, 554 participants; I^2 = 0%; tau^2 = 0; random-effects model; Analysis 2.3; low-certainty evidence). The results were similar with a fixed-effect model (Table 4).

Hypercalcaemia

Insufficient evidence suggests that, compared to a lower dose of vitamin D, a higher dose of vitamin D has an effect on the incidence of hypercalcaemia (RR 1.39, 95% CI 0.89 to 2.18; 5 studies, 986 participants; I^2 = 0%; tau^2 = 0; random-effects model; Analysis 2.4; low-certainty evidence). The results were similar with a fixed-effect model (Table 4).

No studies included in this comparison evaluated the primary outcome of stunting or had quantifiable data for the primary outcome of kidney stones or phosphataemia.

Secondary outcomes

Gain in linear growth

Insufficient evidence suggests that, compared to a lower dose of vitamin D, a higher dose of vitamin D has an effect on change in linear growth (MD -0.01 cm, 95% CI -0.02 to 0.00; 3 studies, 378 participants; I^2 = 0%; tau^2 = 0; random-effects model; Analysis 2.5). The results were similar with a fixed-effect model (Table 4).

Weight-for-age (WAZ)

Insufficient evidence suggests that, compared to a lower dose of vitamin D, a higher dose of vitamin D has an effect on WAZ scores (MD 0.07, 95% CI -0.44 to 0.58; 2 studies, 103 participants; I^2 = 0%; tau^2 = 0; random-effects model; Analysis 2.6). The results were similar with a fixed-effect model (Table 4).

Weight-for-length/height (WL/HZ)

Insufficient evidence suggests that, compared to a lower dose of vitamin D, a higher dose of vitamin D has an effect on WL/HZ scores (MD -0.18, 95% CI -0.74 to 0.37; 1 study, 53 participants; fixed-effect model; Analysis 2.7).

Vitamin D status

Continuous 25(OH)D concentration (nmol/L)

Overall, compared to a lower dose of vitamin D, a higher dose of vitamin D increased vitamin D status (MD 16.13 nmol/L, 95% CI 7.11 to 25.15; 20 studies, 2765 participants; I^2 = 96%; tau^2 = 333.1; random-effects model; Analysis 2.8). The results were similar with a fixed-effect model (Table 4). We explored possible reasons for the high heterogeneity observed across studies, including analysis of studies examining physiological doses of vitamin D only; infants only; and preterm infants only (Table 6). We found that only the sensitivity analysis including preterm infants only decreased inter-study heterogeneity to I^2 = 89%.

Change in 25(OH)D concentration

Insufficient evidence suggests that, compared to a lower dose of vitamin D, a higher dose of vitamin D has an effect on change in vitamin D status (MD 4.12 nmol/L, 95% CI -5.82 to 14.07; 3 studies, 142 participants; I^2 = 46%; tau^2 = 37.3; random-effects model; Analysis 2.9). The results were similar with a fixed-effect model (Table 4).

25(OH)D ≥ 50 nmol/L

Twelve studies comparing higher-dose vitamin D to lower-dose vitamin D found no association between higher-dose vitamin D and attaining serum 25(OH)D concentrations ≥ 50 nmol/L (RR 1.04, 95% CI 1.00 to 1.08; 12 studies, 1735 participants; I^2 = 42%; tau^2 = 0; random-effects model; Analysis 2.10). The results were similar with a fixed-effect model (Table 4).

25(OH)D ≥ 75 nmol/L

Compared to the lower-dose vitamin D group, those in the higher-dose vitamin D group had 31% increased probability of reaching vitamin D sufficiency (RR 1.31, 95% CI 1.19 to 1.45; 6 studies, 1172 participants; I^2 = 38%; tau^2 = 0.01; random-effects model; Analysis 2.11). The results were similar with a fixed-effect model (Table 4).

25(OH)D < 25 to 30 nmol/L

Insufficient evidence suggests that, compared to a lower dose of vitamin D, a higher dose of vitamin D has an effect on the risk of severe vitamin D deficiency (RR 0.14, 95% CI 0.02 to 1.35; 1 study, 142 participants; fixed-effect model; Analysis 2.12).

Rickets

Compared to the lower-dose vitamin D group, those in the higher-dose vitamin D group had 36% lower risk of signs of rickets (RR 0.64, 95% CI 0.46 to 0.90; 4 studies, 212 participants; I^2 = 0%; tau^2 = 0; random-effects model; Analysis 2.13). The results were similar with a fixed-effect model (Table 4).

Comparison 3: vitamin D + micronutrient(s) versus micronutrient(s) alone

Primary outcomes

The study included in this comparison, Thacher 2014, did not assess any primary outcomes (linear growth, length/height-for-age, stunting, adverse effects (hypercalciuria, hypercalcaemia, hyperphosphataemia, kidney stones)).

Secondary outcomes

Vitamin D status

Continuous *25(OH)D* concentration (nmol/L)

Some evidence suggests that, compared to micronutrients alone, vitamin D + micronutrients increase vitamin D concentrations (MD 18.90 nmol/L, 95% CI 8.53 to 29.27; 1 study, 50 participants; fixed-effect model; Analysis 3.1).

Rickets

Insufficient evidence suggests that, compared to micronutrients alone, vitamin D + micronutrients has an effect on mean radiographic scores (MD -0.94 radiographic score, 95% CI -2.10 to 0.22; 1 study, 53 participants; fixed-effect model; Analysis 3.2).

Thacher 2014 did not assess any other secondary outcomes in this comparison (gain in linear growth, weight-for-age, underweight, weight-for-length/height, wasting).

Comparison 4: vitamin D (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s)

Primary outcomes

Please see Summary of findings 3. All outcomes were measured at completion of the intervention, with average time frames ranging from 2.2 to 3 months.

Linear growth

Insufficient evidence suggests that compared to lower-dose vitamin D + micronutrients, higher-dose vitamin D + micronutrients may result in little to no difference on linear growth (MD 0.60 cm, 95% CI -3.33 to 4.53; 1 study, 25 participants; fixed-effect model; Analysis 4.1; low-certainty evidence).

Adverse effects

Hypercalciuria

Insufficient evidence suggests that compared to lower-dose vitamin D + micronutrients, higher-dose vitamin D + micronutrients may result in little to no difference in the incidence of hypercalciuria (RR 1.00, 95% CI 0.06 to 15.48; 1 study, 86 participants; fixed-effect model; Analysis 4.2; low-certainty evidence).

Hypercalcaemia

Compared to lower-dose vitamin D + micronutrients, higher-dose vitamin D + micronutrients probably results in little to no effect on the incidence of hypercalcaemia (RR 1.00, 95% CI 0.90 to 1.11; 2 studies, 126 participants; I^2 = 0%; tau^2 = 0; random-effects model; Analysis 4.3; moderate-certainty evidence). The results were similar with a fixed-effect model (Table 4).

No study included in this comparison assessed the following primary outcomes: length/height-for-age; stunting; hyperphosphataemia; kidney stones.

Secondary outcomes

Gain in linear growth

Some evidence suggests that, compared to lower-dose vitamin D + micronutrients, higher-dose vitamin D + micronutrients is associated with greater gain in linear growth (MD 0.73 cm, 95% CI 0.12 to 1.34; 1 study, 50 participants; fixed-effect model; Analysis 4.4).

Vitamin D status

Continuous 25(OH)D concentration (nmol/L)

Insufficient evidence suggests that, compared to lower-dose vitamin D + micronutrients, higher-dose vitamin D + micronutrients has an effect on vitamin D status (MD 27.94 nmol/L, 95% CI -2.75 to 58.63; 5 studies, 325 participants; I^2 = 96%; tau^2 = 1163.79; random-effects model; Analysis 4.5. However, with a fixed-effect model, children receiving higher-dose vitamin D + micronutrients had higher serum 25(OH)D concentrations than children receiving lower-dose vitamin D + micronutrients (Table 4).

Change in 25(OH)D concentration

Some evidence suggests that, compared to lower-dose vitamin D + micronutrients, higher-dose vitamin D + micronutrients is associated with greater change in vitamin D concentration (MD 7.19 nmol/L, 95% CI 2.97 to 11.41; 1 study, 30 participants; fixed-effect model; Analysis 4.6).

25(OH)D ≥ 50 nmol/L

Insufficient evidence suggests that, compared to lower-dose vitamin D + micronutrients, higher-dose vitamin D + micronutrients has an effect on achieving vitamin D sufficiency (RR 1.34, 95% CI 0.76 to 2.35; 3 studies, 225 participants; I^2 = 92%; tau^2 = 0.23; random-effects model; Analysis 4.7). The results were similar with a fixed-effect model.

Rickets

Insufficient evidence suggests that, compared to lower-dose vitamin D + micronutrients, higher-dose vitamin D + micronutrients has an effect on signs of rickets (RR 1.23, 95% CI 0.24 to 6.30; 2 studies, 153 participants; I^2 = 0%; tau^2 = 0; random-effects model; Analysis 4.8). The results were similar with a fixed-effect model (Table 4).

No study included in this comparison assessed the following secondary outcomes: weight-for-age, underweight, weight-for-length/height, wasting.

DISCUSSION

This systematic review evaluated the effects of oral vitamin D supplementation on linear growth, anthropometric z-scores, stunting, adverse effects, vitamin D status, and rickets.

Summary of main results

In total, we included 75 studies (from 187 reports), 31 of which discussed at least one of our primary outcomes in this review.

For linear growth, vitamin D compared to placebo (3 randomised controlled trials (RCTs), 240 participants; low-certainty evidence); higher-dose vitamin D compared to lower-dose vitamin D (5 RCTs, 283 participants; very low-certainty evidence); and vitamin D (higher dose) plus micronutrients compared to vitamin D (lower dose) plus micronutrients (1 RCT, 25 participants; moderate-certainty evidence) were not associated with any differences in mean length/height (cm) between groups.

Mean length/height-for-age z-scores were slightly higher in groups receiving vitamin D compared to those given placebo (1 RCT, 1258 participants; moderate-certainty evidence) but were not different between groups in the higher-dose versus lower-dose vitamin D comparison (2 RCTs, 105 participants; low-certainty evidence).

Prevalence of stunting was not different in the vitamin D versus placebo groups (1 RCT, 1247 participants; moderate-certainty evidence). However, in the original study, Trilok-Kumar 2011 reported an adjusted risk ratio (RR), which showed that children in the vitamin D group had a 27% lower risk of stunting (95% confidence interval (CI) 5% to 43%) compared to children in the placebo group. The adjusted RR accounted for all characteristics associated with missing data, including sex, quintiles of socioeconomic status, quintiles of exposure to sunlight, season, socioeconomic status, housing materials, material possessions, and breastfeeding. Stunting was not reported by studies included in the other comparisons.

Adverse effects of oral vitamin D reported by studies included hypercalciuria, hypercalcaemia, hyperphosphataemia, and kidney stones. We found no evidence of differences in the risk of hypercalciuria or hypercalcaemia across the four comparisons. All trials measuring hyperphosphataemia or kidney stones, or both, reported no occurrences.

Overall completeness and applicability of evidence

In this review, we sought to determine the effects of oral vitamin D supplementation on our primary outcomes of linear growth, length/height-for-age, stunting, and adverse effects in children from birth to five years of age, as determined by randomised and quasi-randomised controlled trials. We aimed to systematically review the evidence that already exists for oral vitamin D supplementation and linear growth, and to compare oral vitamin D supplementation against placebo, no intervention, and a lower dose of vitamin D intervention, with or without micronutrients.

A major limitation that we encountered while conducting this review is that we were able to synthesise very few studies for the primary outcomes of interest per each comparison. For example, in total, we identified 14 studies that evaluated linear growth, three that evaluated length/height-for-age (L/HAZ), and one that evaluated stunting. Studies measuring linear growth were analysed across Comparison 1 (three studies), Comparison 2 (five studies), and Comparison 4 (one study), showing the limited number of studies available for inclusion in a meta-analysis. In contrast, Comparison 1 and Comparison 2 each included more than 20 studies that analysed vitamin D status. These findings highlight the need to study in future trials the primary outcomes of interest - linear growth, L/HAZ, and stunting.

All of these studies measured linear growth at the end of the supplementation period in infants (either preterm or term). The

only studies (three studies) evaluating linear growth, L/HAZ, or stunting in children between one and five years of age were performed after a longer follow-up period among infants who were previously supplemented but did not receive vitamin D supplementation during that time (Gallo 2013b; Greer 1981; Trilok-Kumar 2011). This represents a major gap in evidence for the effects of oral vitamin D supplementation on linear growth at the end of the supplementation period in children specifically between one and five years of age. In comparisons including more than one study, evidence was rated as low or very low certainty. No comparisons were judged to have high-certainty evidence, demonstrating the need for further research. Measurable effects on linear growth, L/HAZ, and stunting may be observed only after a long period of supplementation and follow-up and among large cohorts. Twenty-eight studies reported on adverse effects of vitamin D supplementation, including hypercalciuria, hypercalcaemia, hyperphosphataemia, and kidney stones, and overall found no greater risk of incidence in the vitamin D groups. Studies in these comparisons involved mainly infants, with two studies reporting on children only, and three studies reporting on both infants and children, with a range of health issues at baseline (preterm, very low birth weight, asthma or upper respiratory tract infection, rickets).

Heterogeneity of studies across outcomes was an issue in the current evidence base. Across the 75 studies included in this review, participants ranged in baseline health status, which included being healthy; being vitamin D deficient; being preterm or of low birth weight, or both; having rickets; having infectious diseases such as acute or recurrent otitis media, acute diarrhoea, bronchiolitis, pneumonia, or upper or lower respiratory tract infection; or having non-communicable diseases or disorders, including asthma, dermatitis, chronic kidney disease, juvenile idiopathic arthritis, or chronic heart failure. The included studies were conducted as early as 1959, which presented challenges in 'Risk of bias' assessments and data extraction due to reporting standards changing over time, such as lack of study design or randomisation sequence generation details or reasons for loss-to-follow-up. Oral vitamin D supplementation doses were variable in range, quantity, frequency, and duration across studies. Often studies did not meet their target sample size, if calculated, raising the likelihood of low power to detect an effect in individual studies. There were not enough studies per any one comparison or primary outcome to investigate potential subgroup differences in terms of participant characteristics or intervention administration. The heterogeneity in intervention doses and durations as well as population characteristics, coupled with small sample sizes that were often underpowered at the analysis stage, and lack of reporting of full measurements of outcomes (i.e. not including variance estimates) for estimates of effect in many studies limited our ability to conduct a full meta-analysis of all available evidence identified by the literature search. Further, trials that may have been included but were not eligible due to lack of age-stratified data represent a gap in the evidence that could not be analysed in this review (see Characteristics of excluded studies tables).

A majority of studies were performed outside of the Tropic of Cancer and the Tropic of Capricorn, where populations are considered to be at higher susceptibility to vitamin D deficiency. However, among the studies conducted completely or partially between these latitudes (i.e. thought to be at lower risk for vitamin D deficiency due to more abundant sunshine), most studies reported baseline deficiency in vitamin D, either < 50 nmol/L (Rianthavorn 2013; Somnath 2017; Singh 2019; Thacher 2014), or < 75 nmol/L (Tergestina 2016), or they did not report baseline vitamin D status (Feliciano 1994; Specker 1992), showing the need for further investigation in these areas.

Quality of the evidence

In this review, we included 75 studies, 64 of which reported quantifiable data on our primary or secondary outcomes, or both. Our primary outcomes were measured by studies in three of our four comparisons, and secondary outcomes were measured by all studies across all four comparisons. We made efforts to contact study authors to request additional data. The certainty of evidence varied between high and very low across outcomes in each comparison.

Our primary outcomes included linear growth, length/height-for-age z-score (L/HAZ), stunting, and adverse effects (hypercalciuria, hypercalcaemia, hyperphosphataemia, and kidney stones). Among all studies measuring at least one primary outcome across all comparisons (31 studies), 53% lacked caregiver or investigator blinding, and 35% lacked (or lacked a description of) blinding of outcome assessors, and 29% were open-label or included no description of blinding. In studies with no intervention as the comparator (one study), blinding was not possible. Lack of blinding is unlikely to have impacted the results, all of which were measured objectively by study personnel; however, lack of blinding of caregivers could potentially have raised the risk for differential attrition. Over 50% of studies were considered to have unclear or high risk of attrition bias due to high loss to follow-up, differential by study arm, or overall, in particular when reasons for loss to follow-up were not detailed and intention-to-treat analysis was not carried out. Most studies had low risk of selection bias regarding sequence generation and allocation concealment.

We evaluated the certainty of evidence using the GRADE method (GRADEpro GDT 2020); our findings are shown in the 'Summary of findings' tables (Summary of findings 1; Summary of findings 2; Summary of findings 3) for our primary outcomes linear growth, L/HAZ, stunting, hypercalciuria, and hypercalcaemia. We planned to conduct a GRADE assessment for hyperphosphataemia and kidney stones, but no data were available for analysis of those outcomes; in three studies reporting on hyperphosphataemia, and in one study reporting on kidney stones, the outcome did not occur.

The certainty of evidence across Comparisons 1, 2, and 4, respectively, as assessed by GRADE, was low, very low, and low for linear growth; moderate and low for L/HAZ (Comparisons 1 and 2 only); moderate for stunting (Comparison 1 only); moderate, low, and low for hypercalciuria; and very low, low, and moderate for hypercalcaemia. Overall, the majority of reasons for downgrading the evidence included moderate to high heterogeneity, imprecision about the estimate, and serious risk of bias.

Potential biases in the review process

We believe that potential biases were minimal in the creation of this review. We conducted a systematic assessment of studies by having at least two reviewers evaluate each potential study at every stage (literature searches, screening of titles and abstracts, screening of full-text reports, extraction of data, and performance of 'Risk of bias' assessments, and GRADE assessments). We

searched 17 electronic databases and two trial registries to be as comprehensive as possible in examining all available evidence. However, we were not able to assess for publication bias using funnel plots due to lack of studies for comparison, thereby preventing us from drawing conclusions on publication bias of the included studies (Table 2; Differences between protocol and review).

Agreements and disagreements with other studies or reviews

Below, we compare the results of previous reviews assessing effects of oral vitamin D supplementation on health outcomes in children.

A previous umbrella (i.e. overview) review of systematic reviews and meta-analyses examined observational associations between circulating vitamin D concentrations and clinical outcomes, and randomised controlled trials (RCTs) assessing vitamin D supplementation and health outcomes. This umbrella review analysed some outcomes similar to those discussed in this review among neonates, infants, and children, including (birth) length and bone mineral density (Theodoratou 2014). No conclusion was reached regarding effects of vitamin D on neonatal and infant growth (i.e. birth length) and bone mineral density (in lumbar spine) in children, and a substantial effect was unlikely for bone mineral density in general, specifically in the forearm, or in the hip in children. However, it seems that these results are pooled from both reviews of observational studies and RCTs, limiting comparability with our study, which analysed only RCTs.

A previous Cochrane Review assessed effects of vitamin D supplementation for improving bone mineral density in children and adolescents age 1 month up to 20 years (Winzenberg 2011). This review graded available evidence between moderate and high certainty and reported no improvements in total body, hip bone, lumbar spine, and forearm bone mineral density from baseline after one to two years of follow-up. This is similar to the findings of our review, which analysed six studies reporting on bone mineral density (total, forearm shaft, tibia, distal forearm, lumbar spine) as a secondary outcome and found no differences between any comparisons at the end of the supplementation period or at long-term follow-up. As a note, this review found an effect of vitamin D supplementation on bone mineral density among children who were deficient in vitamin D, but not among children with replete vitamin D levels; however, given that there are no deficiency cutoff recommendations for vitamin D for linear growth, we did not examine effects by deficiency status.

Another Cochrane Review analysed effects of vitamin D supplementation on asthma among both children and adults (Martineau 2016). This review found that vitamin D supplementation had a positive effect on asthma outcomes, such as reduced risk of asthma exacerbation (high-certainty evidence), but we did not find any effect of vitamin D supplementation on asthma. However, it is difficult to compare our findings, as only three studies in our review analysed asthma in association with vitamin D, one of which was terminated early and included only children. Another non-Cochrane review assessing higher-dose vitamin D supplementation among children and adolescents age 5 to 18 years for asthma found a reduction in asthma exacerbation with vitamin D ≥ 500 IU per day compared to control (Pojsupap 2015).

A previous Cochrane Review analysed effects of vitamin D supplementation for prevention of nutritional rickets in children born at full term (Lerch 2007). Based on data from four studies, specifically among term-born children, review authors concluded that it was reasonable to offer vitamin D as a preventive measure to groups at high risk, such as infants and toddlers, and those from settings such as Africa, Asia, or the Middle East. In our review, vitamin D compared to placebo or no intervention did not result in any differences in signs of rickets at endpoint, but higher-dose vitamin D compared to lower-dose vitamin D showed reduced risk of rickets signs at endpoint; these studies were conducted in Finland, Germany, India, Australia, London, and Switzerland, and most participants were infants. Our results are consistent with the findings of the 2007 review and provide some support for potentially updating this review with trials published since 2007.

Finally, a systematic review analysed the response of serum 25[OH]D concentration to vitamin D supplementation among children and adolescents (age 3 to 17 years) and adults and found that, overall, vitamin D intervention groups obtained a higher serum vitamin D concentration than controls, with an obvious dose-response effect among low-, moderate-, and higher-dose groups (Mo 2019). These findings are consistent with our results, which showed higher vitamin D in intervention groups across all three comparisons (vitamin D versus placebo or no intervention, higher-dose vitamin D versus lower-dose vitamin D, and vitamin D plus multiple micronutrients versus micronutrients only), although the populations studied were slightly non-overlapping in terms of age group.

A previous Cochrane Review analysed effects of vitamin D among children under five years of age but on outcomes not covered in this review. That review examined the effects of oral vitamin D on preventing infection and, overall, found no evidence of effects of vitamin D supplementation on death, incidence of pneumonia, or diarrhoea, among a limited number of studies with low-certainty evidence (Yakoob 2016).

AUTHORS' CONCLUSIONS

Implications for practice

The studies included in this review were performed in populations that were healthy or had preexisting conditions. Evidence suggests that oral vitamin D supplementation may result in little to no difference in linear growth, stunting, hypercalciuria, or hypercalcaemia. However, vitamin D supplementation probably leads to a slight increase in length-for-age z-score compared to placebo, based on one study in low birth weight infants between birth and six months of age, which found a 0.11 unit increase in length/height-for-age z-score (L/HAZ). For context, this will be equivalent to 0.22 cm and 0.27 cm for males and females, respectively, based on a standard deviation (SD) of 2.04 cm for males and 2.42 cm for females for the reference population (for six months of age) for World Health Organization (WHO) Growth Standards (WHO 2006). For linear growth, there are no recommendations for the dose of vitamin D supplementation. To determine if any dose is efficacious in impacting linear growth, a majority of trials in this review examined a range of physiological doses, while some involved pharmacological doses. Current evidence does not support the recommendation of vitamin D supplementation for linear growth.

Implications for research

This review highlights the need for randomised controlled trials (RCTs) to evaluate effects of oral vitamin D supplementation on linear growth among children under five years of age, given the few studies available for data synthesis. Larger, well-designed, rigorous RCTs of longer durations, carried out in populations stratified by age, and in cohorts of varying health status, with complete, high-certainty reporting regarding all methodological aspects, are highly recommended. Further, future research should consider dose-response trials that address infant- and child-specific serum vitamin D concentrations, and should be appropriately powered to address all clinical outcomes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abdel-Hady 2019

Study characteristics	
Methods	**Study design:** randomised controlled trial
	Study grouping: parallel group
	Funding: undisclosed
	Country: Egypt

Abdel-Hady 2019 *(Continued)*

	Study period: September 2014 to August 2016
Participants	**Included criteria:** prematurity with gestational age 28 weeks and < 37 weeks, postnatal age > 72 hours, and presence of clinical and haematological signs suggestive of late-onset sepsis, ascertained by a scoring system containing 11 clinical and haematological domains including skin colour, capillary refill, tone, feeding intolerance, hepatomegaly, apnoea, bradycardia, metabolic acidosis, thrombocytopenia, leukocytosis, and shift to left. Total score is 25 points. Infants with a score < 5 were considered normal, with a score of 5 to 10 were suspected to have sepsis, and score > 10 were considered clinically septic **Excluded criteria:** major congenital anomalies, chromosomal anomalies, known inborn errors of metabolism, immunodeficiency disorders **Group differences:** average total vitamin D daily intake (feeding along with supplementation) was significantly greater in the 800 IU group (Table Supplement, Supplemental Digital Content; links.lww.com/MPG/B551) **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (400 IU D_3): 34.2 ± 16.5 2. Intervention group (800 IU D_3): 41.1 ± 19.0
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: not stated 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: until discharge from NICU (40 weeks' PMA) 5. *N per group (in analysis)*: 21 6. *Brand/company*: not reported 800 IU D_3 1. *Vitamin D content and type*: 800 IU D_3 2. *Formulation*: not stated 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: until discharge from NICU (40 weeks' PMA) 5. *N per group (in analysis)*: 23 6. *Brand/company*: not reported

Outcomes	**Primary**
	
	1. Adverse effect: kidney stones
	
	Secondary
	
	1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)
	2. Serum 25(OH)D < 50 nmol/L
	   a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis
	3. Serum 25(OH)D < 75 nmol/L
	   a. **Notes:** converted to vitamin D sufficiency ≥ 75 nmol/L for meta-analysis
	
	Measurement
	
	1. Kidney stones: renal ultrasonography
	   a. **Notes:** no events in either arm; data did not contribute to meta-analysis
	2. Serum 25(OH)D (nmol/L): enzyme-linked immunoabsorbent assay (ELISA) (Calbiotech, Spring Valley, CA, USA)

Abdel-Hady 2019 *(Continued)*

	Time points: baseline, 1 week, discharge from neonatal intensive care unit (40 weeks' PMA)
Notes	Sample size calculated as n = 50, but this was met only at randomisation and not during analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "infants with [late onset sepsis] were randomized using computer-generated stratified randomization codes" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "the allocation sequence was concealed by using sealed opaque envelopes that contained the serial number and the group to which a subject would be enrolled" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "double blind... Clinicians and primary caregivers were masked to the intervention... Antibiotic therapy and supportive care were continued according to managing physician who was not aware of the group assignment... After each parental consent, an envelope would be opened by the principle [sic] investigator and group assignment would be established" Judgement comment: caregivers were blinded; although indicated to be double-blind, the principal investigator was aware of group allocation and may have been biased toward a particular outcome, which could increase the risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "clinicians and primary caregivers were masked to the intervention... Antibiotic therapy and supportive care were continued according to managing physician, who was not aware of the group assignment" Judgement comment: outcome assessors blinded; outcome measurements not subjective and unlikely to be influenced
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: low loss to follow-up (reasons given: mortality, discontinued intervention; flow diagram in Figure Supplement) similar in both arms; intent-to-treat analysis not performed
Selective reporting (reporting bias)	Low risk	Judgement comment: study was registered at ClinicalTrials.gov (ID: NCT02273843) prospectively; reported in text; prespecified outcomes and reported outcomes consistent
Other bias	Low risk	Judgement comment: no other risks observed

Aglipay 2017

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Canadian Institutes of Health Research Institute of Human Development, Child and Youth Health and Nutrition, Metabolism and Diabetes, and the Thrasher Research Fund

Aglipay 2017 *(Continued)*

	Country: Canada **Study period:** winter months between 13 September 2011 and 30 June 2015
Participants	**Included criteria:** healthy children age 1 to 5 years **Excluded criteria:** gestational age under 32 weeks, chronic illness (other than asthma) **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (400 IU D_3): 89.6 ± 30.7 2. Intervention group (2000 IU D_3): 92.1 ± 29.2
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 to 8 months 5. *N per group (in analysis)*: 350 6. *Brand/company*: Kids Ddrops 2000 IU D_3 1. *Vitamin D content and type*: 2000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 to 8 months 5. *N per group (in analysis)*: 349 6. *Brand/company*: Kids Ddrops
Outcomes	**Primary** 1. Adverse effect: hypercalcaemia 2. Adverse effect: hyperphosphataemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D insufficiency: < 75 nmol/L a. **Notes:** converted to vitamin D sufficiency ≥ 75 nmol/L for meta-analysis **Measurement** 1. Hypercalcaemia (serum calcium): assay not reported a. Definition: not reported b. **Notes:** no events in either arm; data did not contribute to meta-analysis 2. Hyperphosphataemia (serum phosphorus): assay not reported a. Definition: not reported b. **Notes:** no events in either arm; data did not contribute to meta-analysis 3. Serum 25(OH)D (nmol/L): Roche Elecsys Vitamin D total assay (Roche Diagnostics Ltd., Basel, Switzerland) a. **Notes:** data presented as mean (95% CI), which we converted to standard deviation **Time points:** enrolment, 4 to 8 months
Notes	Sample size calculated and met

Aglipay 2017 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the randomization sequence was generated using a computer-based random-number generator by the SickKids research pharmacy" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "the research pharmacy prepared the vitamin D formulations in sealed, serially numbered bottles identical in appearance and weight to maintain allocation concealment" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "study personnel, parents, attending physicians, laboratory personnel, investigators, and data analysts were all blinded to group allocation throughout the study period" Judgement comment: all personnel and participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "study personnel, parents, attending physicians, laboratory personnel, investigators, and data analysts were all blinded to group allocation throughout the study period" Judgement comment: all personnel and participants blinded; outcome measurements not subjective and unlikely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "complete case analysis was performed for all primary and secondary outcomes in which only cases with available data were analyzed... all analyses were conducted using the intention-to-treat principle" Judgement comment: complete case analysis violates the intention-to-treat principle and leads to bias unless data were missing at random, but study authors do not examine missingness. Few participants were lost to follow-up (reasons not described), while 31 and 24 participants discontinued the intervention per arm, possibly increasing the risk of attrition bias
Selective reporting (reporting bias)	Low risk	Quote: "the primary outcome was the number of all-cause laboratory-confirmed viral upper respiratory tract infections per child. Secondary outcomes included time to first laboratory-confirmed, total parent-reported, laboratory-confirmed influenza, and [non-influenza] upper respiratory tract infections and serum 25-hydroxyvitamin D levels. Other secondary outcomes not presented in this article included asthma exacerbations among children with asthma, physician-diagnosed otitis media and pneumonia, emergency department visits, and hospitalizations. Trial procedures have been described in detail elsewhere (see Supplement 1)" Quote (from 2011 protocol): "the primary analysis will be a comparison of laboratory-confirmed upper respiratory tract infection rate (per child) between study groups using a Poisson regression model. Secondary analyses will include a comparison of vitamin D serum levels, asthma exascerbations [sic] and the frequency of respiratory syncitial [sic] virus, adenovirus and influenza viruses between arms. Furthermore, a cost effectiveness analysis on the effect of wintertime vitamin D supplementation of preschoolers will be undertaken using the net benefit regression approach" Judgement comment: prespecified protocol in supplemental content; describes outcomes measured and reported on; study registered prospectively at ClinicalTrials.gov (ID: NCT01419262) and reported in text

Aglipay 2017 *(Continued)*

Other bias	Low risk	Judgement comment: no other risks observed

Ala-Houhala 1985

Study characteristics	
Methods	**Study design:** quasi-randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Piltti grant from the Foundation of Pediatric Research, the National Board of Health, and the Academy of Finland **Country:** Finland **Study period:** winter 1981
Participants	**Included criteria:** healthy, term, breastfed infants and their mothers **Excluded criteria:** mother-infant pairs that failed to complete breastfeeding **Maternal pretreatment:** "during pregnancy the mothers had vitamin D supplementation of 0-500 IU/day: one-half of the mothers had no supplementation during pregnancy; one-fourth of the mothers received 500 IU/day vitamin D during middle pregnancy; and one-fourth of mothers, 500 IU/day vitamin D during one entire pregnancy" (quote). However, study authors do not specify which group each of the infants' mothers fell into (winter or summer, Group 2 or 3) **Baseline vitamin D status (mean ± standard error, nmol/L)** 1. Control group (400 IU D_3 (winter)): 14.4 ± 2.2 2. Control group (400 IU D_3 (summer)): 35.0 ± 5.2 3. Intervention group (1000 IU D_3 (winter)): 23.2 ± 4.6 4. Intervention group (1000 IU D_3 (summer)): 31.2 ± 3.5
Interventions	**Intervention characteristics** 400 IU D_2 (winter) 1. *Vitamin D content and type*: 400 IU D_2 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 20 weeks 5. *N per group (in analysis)*: 15 6. *Brand/company*: Leiras, Turku, Finland 400 IU D_2 (summer) 1. *Vitamin D content and type*: 400 IU D_2 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 20 weeks 5. *N per group (in analysis)*: 16 6. *Brand/company*: Leiras, Turku, Finland 1000 IU D_2 (winter) 1. *Vitamin D content and type*: 1000 IU D_2 2. *Formulation*: not reported

Ala-Houhala 1985 *(Continued)*

3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 20 weeks
5. *N per group (in analysis)*: 15
6. *Brand/company*: Leiras, Turku, Finland

1000 IU D_2 (summer)

1. *Vitamin D content and type*: 1000 IU D_2
2. *Formulation*: not reported
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 20 weeks
5. *N per group (in analysis)*: 14
6. *Brand/company*: Leiras, Turku, Finland

Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Rickets **Measurement** 1. Serum 25(OH)D (nmol/L): competitive protein-binding assay (CPBA) a. **Notes:** these values are estimated from graphs, Figures 2, 3, and 5 (Ala-Houhala 1985). Values with standard deviations were reported in abstract b. **Notes**: data were not included in meta-analysis due to reported values as mean ± standard error, with fewer than 30 participants per group, limiting conversion of standard error to standard deviation 2. Rickets: clinical or biochemical indicators a. **Notes:** no events in either arm; data did not contribute to meta-analysis **Time points:** birth, 8 weeks of age, 20 weeks of age
Notes	No sample size calculation; study may be underpowered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "they were randomly allocated to three groups with different supplementation protocols of vitamin D" Judgement comment: study authors state that they randomly allocated the interventions but did not describe the random sequence generation method
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. However, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias)	Unclear risk	Judgement comment: no loss to follow-up

Ala-Houhala 1985 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified. Outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Alam 2011

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Bangladesh **Study period:** not reported
Participants	**Included criteria:** children age 6 to 36 months with acute diarrhoea attending the International Centre for Diarrhoeal Disease Research, Bangladesh Hospital **Excluded criteria:** not specified **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 1000 IU D_3 + milk suji 1. *Vitamin D content and type*: 1000 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 5 days 5. *N per group (in analysis)*: 27 6. *Brand/company*: not reported Milk suji 1. *Vitamin D content and type*: none 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 5 days 5. *N per group (in analysis)*: 26 6. *Brand/company*: not reported 1000 IU D_3 + L-isoleucine + milk suji 1. *Vitamin D content and type*: 1000 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 5 days 5. *N per group (in analysis)*: 26 6. *Brand/company*: not reported L-isoleucine + milk suji

Alam 2011 *(Continued)*

1. *Vitamin D content and type*: none
2. *Formulation*: not reported
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 5 days
5. *N per group (in analysis)*: 28
6. *Brand/company*: not reported

Outcomes	None within scope of this review
Notes	Meeting abstracts available only; milk suji: mixture of milk and rice powder (70 kcal/100 mL)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: not described (meeting abstract)
Allocation concealment (selection bias)	Unclear risk	Judgement comment: not described (meeting abstract)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind" Judgement comment: double-blind but not further detailed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind" Judgement comment: double-blind but not further detailed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: no loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified; outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Alizadeh 2006

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Iran **Study period:** May 2001 to May 2002
Participants	**Included criteria:** gestational age < 38 weeks, birth weight < 2000 g **Excluded criteria:** use of specific medications interacting with vitamin D metabolism (e.g. anticonvulsants, diuretics, corticosteroids) in mother, diabetes mellitus in mother, previous intrauterine growth

Alizadeh 2006 *(Continued)*

	restriction or small for gestational age, long-term use of furosemide in infant, having nothing by mouth for longer than 2 weeks **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 400 IU 1. *Vitamin D content and type*: 400 IU vitamin D 2. *Formulation*: enteral 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: "from time they tolerated full enteral nutrition until they gained a normal term birth weight (3000-3500 g)" (quote): mean of 46.6 days (minimum = 35, maximum = 56) 5. *Other micronutrient content*: infants breast fed: 90 to 120 mg/kg/d calcium gluconate, phosphate supplement (55 to 75 mg/kg/d); infants not breastfed: premature formula Prenon enriched in calcium and phosphate 6. *N per group (in analysis)*: 32 7. *Brand/company*: not reported 1000 IU 1. *Vitamin D content and type*: 1000 IU vitamin D 2. *Formulation*: enteral 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: "from time they tolerated full enteral nutrition until they gained a normal term birth weight (3000-3500 g)" (quote): mean of 47.4 (minimum = 40, maximum = 56) 5. *Other micronutrient content*: infants breastfed: 90 to 120 mg/kg/d calcium gluconate, phosphate supplement (55 to 75 mg/kg/d); infants not breastfed: premature formula Prenon enriched in calcium and phosphate 6. *N per group (in analysis)*: 36 7. *Brand/company*: not reported
Outcomes	**Secondary** 1. Rickets **Measurement** 1. Rickets: wide fontanelles, X-ray findings **Time points:** birth, 9 weeks
Notes	Sample size calculated and met

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "within 2 weeks of birth, eligible infants randomly divided in two groups by block randomization of two, to receive a vitamin D 400 IU/d (group A) and 1000 IU/d (group B)" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described

Alizadeh 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding of participants and/or personnel not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "physical examination and x-ray analysis were made blind by expert pediatricians" Judgement comment: blinding of X-ray analysis was done; other outcomes not specified to have been assessed by blinded personnel, but outcome measurements not subjective and unlikely to be influenced
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: the number of participants randomised and completing follow-up not specified. No analysis or reasons given for loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial protocol or clinical trial registration identified. Outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Alizadeh Taheri 2014

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Iran **Study period:** May 2010 to May 2012
Participants	**Included criteria:** gestational age 37 weeks, birth weight 2000 g **Excluded criteria:** taking specific medications interacting with vitamin D metabolism (e.g. anticonvulsants, diuretics, corticosteroids) in mother, diabetes mellitus in mother, previous intrauterine growth restricted or small-for-gestational-age baby, long-term use of furosemide in infant, NPO (non per oral) > 2 weeks **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (200 IU D_3): 80.3 ± 24.5 2. Intervention group (400 IU D_3): 79.2 ± 26.2
Interventions	**Intervention characteristics** 200 IU 1. *Vitamin D content and type*: 200 IU vitamin D 2. *Formulation*: enteral 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 to 8 weeks

Alizadeh Taheri 2014 *(Continued)*

5. *Other micronutrient content*
   a. Infants tolerating breast milk (100%): calcium gluconate (90 to 120 mg/kg/d), and phosphate sandose supplement (55 to 75 mg/kg/d)
   b. Infants not breastfeeding: Prenon formula enriched in calcium and phosphate
6. *N per group (in analysis)*: 30
7. *Brand/company*: not reported

400 IU

1. *Vitamin D content and type*: 400 IU vitamin D
2. *Formulation*: enteral
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 6 to 8 weeks
5. *Other micronutrient content*
   a. Infants tolerating breast milk (96.7%): calcium gluconate (90 to 120 mg/kg/d) and phosphate sandose supplement (55 to 75 mg/kg/d)
   b. Infants not breastfeeding: Prenon formula enriched in calcium and phosphate
6. *N per group (in analysis)*: 30
7. *Brand/company*: not reported

Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Rickets **Measurement** 1. Serum 25(OH)D (nmol/L): enzyme-linked immunoabsorbent assay (ELISA) 2. Rickets: radiographic signs, including wide fontanelles, widening of wrist, Harrison groove, craniotabes, fraying, increased distance of metaphysis **Time points:** birth, 6 to 8 weeks of life
Notes	No sample size calculation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the newborns were randomly divided into two groups by block randomization of two, to receive a 200 IU/d vitamin D (Group 1) and 400 IU/d vitamin D (Group 2) since they tolerated full enteral nutrition" Judgement comment: study authors state that they randomly allocated interventions by block randomisation but did not describe the random sequence generation method used
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "physical examination and X-ray evaluation were made by blinded expert neonatalogists [sic]"

Alizadeh Taheri 2014 *(Continued)*

		Judgement comment: outcome assessors were blinded, which is appropriate for subjective outcomes from physical examination and X-ray evaluation; other outcomes were not specified to have been assessed by blinded personnel, but outcome measurements are not subjective and are unlikely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: no discussion of loss to follow-up or evidence of no loss to follow-up; unclear
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified; outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Alonso 2011

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Supported in part by grant from the Instituto de Salud Carlos III and by the Fundación Nutrición y Crecimiento **Country**: Spain **Study period:** February 2007 to February 2008
Participants	**Included criteria:** healthy term infants who were seen for a routine health visit in the first 15 days of life at 11 participating primary healthcare centres in a community of northern Spain **Excluded criteria:** chronic disease; use of medications known to affect vitamin D metabolism; refusal of parents to participate; prematurity; dark skin pigmentation; sunlight exclusion for cultural, religious, or other reasons; breastfeeding by vegetarian mothers. Thus, no child with risk factors for vitamin D deficiency was included in the study. During follow-up, additional exclusion criteria were long hospitalisation, refusal of parents, loss to follow-up, and non-compliance with prophylaxis or study visits **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 402 IU D_3 1. *Vitamin D content and type*: 402 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 12 months 5. *N per group (in analysis)*: 41 6. *Brand/company*: commercial preparation (not specified) Nothing 1. *Duration of administration (study time)*: 12 months 2. *N per group (in analysis)*: 47
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)

Alonso 2011 *(Continued)*

	Measurement 1. Serum 25(OH)D (nmol/L): electrochemiluminescent assay (EIA) (Roche Laboratory, Barcelona, Spain) **Time points:** 3, 6, 12 months of age
Notes	No sample size calculation and no indication of how many were screened for enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the principal investigator (AA) made the assignment by phone using a computer software, Epi Dat 3.1 (Xunta de Galicia, La Coruña. Spain, and Pan-American Health Organization, Washington, DC)" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the study was not blinded to parents and investigators" Judgement comment: not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the interventions' allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: blinding not done; outcomes measured not subjective in nature and less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: somewhat unbalanced loss to follow-up: 11 patients lost to follow up in group 1, 4 lost to follow-up in group 2. No analysis or reasons given for loss to follow-up
Selective reporting (reporting bias)	High risk	Judgement comment: no trial registration or protocol identified; outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Aly 2019

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Egypt **Study period:** January 2017 to December 2017
Participants	**Included criteria:** gestational age between 28 0/7 and 33 6/7 weeks, postnatal age 14 days at the time of enrolment, receiving enteral feed ≥ 100 mL/kg/d

Aly 2019 *(Continued)*

	Excluded criteria: congenital and chromosomal anomalies, diagnosed with necrotising enterocolitis (NEC) **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (400 IU D_3): 55.4 ± 22.8 2. Intervention group (800 IU D_3): 41.0 ± 29.3
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 weeks 5. *N per group (in analysis)*: 20 6. *Brand/company*: Vidrop, Ismailia, Egypt 800 IU D_3 1. *Vitamin D content and type*: 800 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 weeks 5. *N per group (in analysis)*: 20 6. *Brand/company*: Vidrop, Ismailia, Egypt
Outcomes	None within scope of review
Notes	Sample size calculated and met

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was done using a computerized program ((Statistical Package for the Social Sciences) SPSS)" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "the allocation sequence was concealed by using sealed opaque envelopes that contained the serial number and the group to which a subject would be enrolled" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "all care providers and laboratory personnel were blinded to the study group allocation" Judgement comment: all laboratory personnel and participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "laboratory personnel were blinded to the study group allocation" Judgement comment: all laboratory personnel and participants blinded
Incomplete outcome data (attrition bias)	Low risk	Judgement comment: no loss to follow-up reported

Aly 2019 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Judgement comment: study registered retrospectively at ClinicalTrials.gov (ID: NCT03793309), as reported in text. No prepublished protocol identified
Other bias	Low risk	Judgement comment: no other risks observed

Anderson-Berry 2017

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Supported in part by the Edna Ittner Pediatric Research Support Fund through the University of Nebraska Medical Center, and in part by a grant from the National Institute of Standards and Technology **Country:** USA **Study period:** not reported
Participants	**Included criteria:** parents age 19 or over, patients at 32 weeks' gestational age **Excluded criteria:** congenital anomalies, disorders of calcium metabolism, inborn error of metabolism, kidney disease, liver disease, use of steroids **Baseline vitamin D status (mean (interquartile range); nmol/L)** 1. Control group (400 IU D_3): 41.9 (23.9) 2. Intervention group (800 IU D_3): 42.9 (40.7)
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: enteral 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 8 weeks 5. *N per group (in analysis)*: 16 6. *Brand/company*: not reported 800 IU D_3 1. *Vitamin D content and type*: 800 IU D_3 2. *Formulation*: enteral 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 8 weeks 5. *N per group (in analysis)*: 16 6. *Brand/company*: not reported
Outcomes	**Primary** 1. Linear growth 2. Adverse effect: hypercalcaemia

Anderson-Berry 2017 *(Continued)*

Secondary

1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)
2. Change in serum 25(OH)D

Measurement

1. Length (cm): assay not reported
   a. **Notes:** data not included in meta-analysis due to reported values as mean ± interquartile range, with fewer than 30 participants per group, limiting conversion of interquartile range to standard deviation
2. Hypercalcaemia (serum calcium): Beckman Coulter assay
   a. Definition: not reported
   b. **Notes:** no events in either arm; data did not contribute to meta-analysis
3. Serum 25(OH)D (nmol/L): liquid chromatography with tandem mass spectroscopy (LC-MS/MS)
   a. **Notes:** reported in later publication (Anderson-Berry 2017 see Hanson 2017)

Time points: birth, 4 weeks, 8 weeks

Notes	Sample size calculated and met at final analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the study statistician generated a randomization sequence stratified by race (white and non-white) using SAS software and the study pharmacist randomized each infant" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "infants were randomized to receive either 400 IU or 800 IU of vitamin D3 enterally with the initiation of enteral feedings in addition to parenteral multivitamin injection while on parenteral nutrition and enteral vitamin D from breast milk and human milk fortifier or preterm formula. The study vitamin D was delivered in a brown oral syringe (to protect the product from light) and the product was identical in color, volume and smell regardless of dose... Formulations were prepared and dispensed by a research pharmacist who was independent of the study" Judgement comment: appropriate allocation concealment by a third party, although serial labelling was not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blinded... Investigators and neonatal intensive care unit staff were blinded to subject group assignment" Judgement comment: although indicated to be double-blind, participants were not specifically blinded. However, intervention was administered enterally, limiting the likelihood of caregivers distinguishing the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "investigators and neonatal intensive care unit staff were blinded to subject group assignment" Judgement comment: outcome assessors blinded; outcome measurements not subjective and unlikely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "thirty-two infants were enrolled in the study (16 per group) and were included in the final analysis" Judgement comment: although the diagram shows no loss to follow-up, when patients were discharged from the neonatal intensive care unit, they were dis-

Anderson-Berry 2017 *(Continued)*

		continued in the study. N=32 infants were randomised equally to the 2 arms and no loss to follow-up occurred according to Figure 1. Intention-to-treat analysis was used
Selective reporting (reporting bias)	Low risk	Judgement comment: study registered prospectively at ClinicalTrials.gov (ID: NCT01469650), as reported in text, and protocol published (Maguire 2014). Pre-specified outcomes consistent with those reported
Other bias	Low risk	Judgement comment: no other risks observed

Atas 2013

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Turkey **Study period:** June 2006 to May 2007
Participants	**Included criteria:** none **Excluded criteria:** prematurity, any natal or postnatal complications, metabolic disorders, dysmorphic features, formula feeding **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 200 IU D_3 1. *Vitamin D content and type*: 200 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 months 5. *N per group (in analysis)*: 75 6. *Brand/company*: Multitabs 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 months 5. *N per group (in analysis)*: 64 6. *Brand/company*: Multitabs

Outcomes	**Secondary**
	
	1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)
	2. Serum 25(OH)D < 50 nmol/L
	   a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis
	3. Serum 25(OH)D < 75 nmol/L
	   a. **Notes:** converted to vitamin D sufficiency ≥ 75 nmol/L for meta-analysis

Atas 2013 *(Continued)*

	Measurement 1. Serum 25(OH)D (nmol/L): high-performance liquid chromatography (HPLC) (Chromsystems Instruments Chemicals GmbH, Muchen, Germany) a. **Notes:** data not included in meta-analysis due to reported values as mean ± range, which we could not convert to standard deviation **Time points:** ~ 15 days of age; 4 months of age
Notes	Sample size calculation not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "one hundred and sixty-nine participants were randomly assigned with simple randomization procedures (computerized random numbers) to groups" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	High risk	Judgement comment: allocation concealment not described; given that both groups were given different amounts of the same intervention, allocation concealment is unlikely
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. However, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "82% ... thirty infants who did not complete the study were excluded with following reasons: (1) loss of follow-up, (2) formula-feeding, (3) improper vitamin D supplementation" Judgement comment: reasons for attrition include (1) loss to follow-up, (2) formula feeding, (3) improper vitamin D supplementation, but not given by arm; impossible to know if reasons were balanced. No attempt described to check if excluded participants differed in some way from included participants. Attrition led Group 1 to have 11 more participants than Group 2, which may increase the risk for attrition bias
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial protocol cited or found; outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Backström 1999a

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group

Backström 1999a *(Continued)*

	Funding: undisclosed **Country:** Finland **Study period:** May 1994 to January 1996
Participants	**Included criteria:** gestational age less than 33 weeks, appropriate weight for gestational age **Excluded criteria:** major congenital malformation, failure to supplement vitamin D **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (200 to 400 IU D_3): 29.8 ± 10.0 2. Intervention group (960 IU D_3): 29.2 ± 11.8
Interventions	**Intervention characteristics** 200-400 IU D_3 1. *Vitamin D content and type*: 200 to 400 IU D_3 from 0 to 3 months; 400 IU D_3 from 3 to 6 months 2. *Formulation*: enteral 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (in analysis)*: 6 to 19 (depending on outcome) 6. *Brand/company*: not reported 7. *Vitamin D per kg body weight per day*: 200 to 400 IU D_3 960 IU D_3 1. *Vitamin D content and type*: 960 IU D_3 from 0 to 3 months; 400 IU D_3 from 3 to 6 months 2. *Formulation*: enteral 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (in analysis)*: 6 to 16 (depending on outcome) 6. *Brand/company*: not reported
Outcomes	**Primary** 1. Linear growth **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Length (cm): clinical charts a. **Notes:** data not included in meta-analysis due to reported values as mean ± range, which we could not convert to standard deviation 2. Serum 25(OH)D (nmol/L): high-performance liquid chromatography (HPLC) **Time points:** birth; 6 weeks', 12 weeks', 3 and 6 months' corrected age
Notes	Sample size calculations were reported, but no outcomes contain the full sample size, suggesting loss to follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement

Backström 1999a *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "at hospital discharge all parents received written instructions on how to lower vitamin D dose according to the amount of formula used in order to maintain the constancy of the dose" Judgement comment: very likely parents were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the weight and length of the infants were obtained from clinical charts... The randomisation was concealed from those performing bone densitometry and determination of serum vitamin D metabolites" Judgement comment: outcome assessors blinded; outcome measurements not subjective and unlikely to be influenced
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: no discussion of loss to follow-up; does not specify if analysis was intention-to-treat or how missing data were handled. Few reported outcomes were based on entire sample
Selective reporting (reporting bias)	High risk	Judgement comment: no trial registration or protocol identified; outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Backström 1999b

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Finland **Study period:** August 1985 to May 1987
Participants	**Included criteria:** preterm infants with birth weight < 2000 g and gestational age < 37 weeks **Excluded criteria:** major congenital malformation **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 500 IU, CaP+ 1. *Vitamin D content and type*: 500 IU vitamin D 2. *Formulation*: enteral 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *Other micronutrient content*: calcium: 108 mg/kg/d; phosphorus: 53 mg/kg/d 6. *N per group (in analysis)*: 12

Backström 1999b *(Continued)*

7. *Brand/company*: not reported
8. **Note: included in Comparison 4**

1000 IU, CaP+

1. *Vitamin D content and type*: 1000 IU vitamin D
2. *Formulation*: enteral
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 3 months
5. *Other micronutrient content*: calcium: 108 mg/kg/d; phosphorus: 53 mg/kg/d
6. *N per group (in analysis)*: 13
7. *Brand/company*: not reported
8. **Note: included in Comparison 4**

500 IU, CaP-

1. *Vitamin D content and type*: 500 IU vitamin D
2. *Formulation*: enteral
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 3 months
5. *Other micronutrient content*: none
6. *N per group (in analysis)*: 22
7. *Brand/company*: not reported
8. **Note: included in Comparison 2**

1000 IU, CaP-

1. *Vitamin D content and type*: 1000 IU vitamin D
2. *Formulation*: enteral
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 3 months
5. *Other micronutrient content*: none
6. *N per group (in analysis)*: 23
7. *Brand/company*: not reported
8. **Note: included in Comparison 2**

Outcomes

Primary

1. Linear growth

Secondary

1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)

Measurement

1. Length (cm): clinical charts
2. Serum 25(OH)D (nmol/L): high-performance liquid chromatography (HPLC)

Time point: 3 months of age

Notes

Sample size calculation described; possibly done retrospectively

CaP+ included calcium and phosphorus; CaP- did not include calcium and phosphorus

Risk of bias

Bias	Authors' judgement	Support for judgement

Backström 1999b *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned to four groups" Judgement comment: randomisation sequence generation method not described
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the randomization was concealed from those performing measurements by bone densitometry and assaying the serum vitamin D metabolites. All scans and analyses were made by the same experienced laboratory technician in a blinded fashion" Judgement comment: outcome assessors blinded; outcome measurements not subjective and unlikely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "the original study group sizes were: 12 (500 IU, CaP+), 13 (1000 IU, CaP +), 22 (500 IU, CaP-), and 23 (1000 IU, CaP-)" Judgement comment: no loss to follow-up at the 3-month time point
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no published trial protocol or trial registration identified; outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Bozkurt 2017

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** no funding **Country:** Turkey **Study period:** January 2014 to March 2016
Participants	**Included criteria:** preterm infants with gestational age 24 to 32 weeks, admitted to neonatal intensive care unit, achieved ≥ 75% of total nutrition by enteral feedings at postnatal 2 weeks **Excluded criteria:** infants with perinatal asphyxia, major congenital or chromosomal anomalies, twin-twin transfusion syndrome, requirement of dopamine ≥ 15 µg/kg/min or > 1 inotrope, no expectation of survival in first 2 weeks, total parenteral nutrition not ceased by first 2 weeks **Group differences:** frequency of multiple births was higher in 400 IU group **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (400 IU D_3): 41.9 ± 16.5 2. Intervention group (800 IU D_3): 37.9 ± 14.7

Bozkurt 2017 *(Continued)*

3. Intervention group (1000 IU D_3): 42.9 ± 18.0

Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 to 12 weeks 5. *Other micronutrient content*: fortified human milk: 283 to 320 IU/d; enteral feeding: 288 to 300 IU/d (weighing 1.5 kg) 6. *N per group (in analysis)*: 40 7. *Brand/company*: Devit-3 Oral Drop, 50,000 IU D_3/15 mL, Deva Company, Turkey 800 IU D_3 1. *Vitamin D content and type*: 800 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 to 12 weeks 5. *Other micronutrient content*: fortified human milk: 283 to 320 IU/d; enteral feeding: 288 to 300 IU/d (weighing 1.5 kg) 6. *N per group (in analysis)*: 41 7. *Brand/company*: Devit-3 Oral Drop, 50,000 IU D_3/15 mL, Deva Company, Turkey 1000 IU D_3 1. *Vitamin D content and type*: 1000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 to 12 weeks 5. *Other micronutrient content*: fortified human milk: 283 to 320 IU/d; enteral feeding: 288 to 300 IU/d (weighing 1.5 kg) 6. *N per group (in analysis)*: 40 7. *Brand/company*: Devit-3 Oral Drop, 50,000 IU D_3/15 mL, Deva Company, Turkey
Outcomes	**Primary** 1. Adverse effect: hypercalciuria **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D < 50 nmol/L a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis 3. Serum 25(OH)D < 75 nmol/L a. **Notes:** converted to vitamin D sufficiency ≥ 75 nmol/L for meta-analysis **Measurement** 1. Hypercalciuria (urinary calcium/creatinine (mg/mg)): Beckman Coulter assay a. Definition: not reported 2. Serum 25(OH)D (nmol/L): liquid chromatography with tandem mass spectrometry (Waters Quattro Premier™ XE, Waters, Milford, MA, USA) **Time points:** birth, 36 weeks' postmenstrual age

Bozkurt 2017 *(Continued)*

Notes	Sample size calculation met

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization cards were generated using computer generated random number list and concealed in opaque, sequentially numbered, sealed envelopes" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "after parental consent, infants were randomly allocated to either of the 3 groups designating oral Vitamin D 3 dose of: 1) 400 IU/day; 2) 800 IU/ day; 3) 1000 IU/day by sealed opaque envelopes... The envelopes were opened and each infant was randomised just after achieving 75% of total nutrition as enteral feeding" Judgement comment: appropriate allocation concealment, although not specified if envelopes were sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. However, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "138 infants with gestational age of 24–32 completed weeks were randomized to one of the 3 vitamin D supplementation dose. After intervention 17 infants were excluded for the declared reasons in consort diagram, eventually 121 infants completed the study and a total of 40 infants in the 400 IU, 41 infants in the 800 IU, 40 infants in the 1000 IU groups were analyzed (Fig. 1)" Judgement comment: CONSORT diagram shows exact reasons for loss to follow-up per arm, and no infants were excluded from analysis; it appears it was intent-to-treat, although this was not specified
Selective reporting (reporting bias)	Unclear risk	Judgement comment: study registered retrospectively at ClinicalTrials.gov (ID: NCT02941185), as reported in text. No protocol identified
Other bias	Low risk	Judgement comment: no other risks observed

Chan 1978

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** non-profit and for-profit funding: grant from Ross Laboratories, Columbus, OH, USA; Maternal and Child Health Training Project No.174 and grant AM 14881 **Country:** USA

Chan 1978 *(Continued)*

	Study period: 24 November 1975 to 23 October 1976
Participants	**Included criteria:** gestation ≤ 37 weeks, appropriate for gestational age **Excluded criteria:** uncertain date of last menstrual period, 2 weeks or more was apparent between calculated and clinical measurements, family history of diabetes **Baseline vitamin D status:** unclear
Interventions	**Intervention characteristics** Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 60 hours 5. *N per group (in analysis)*: 8 6. *Brand/company*: not reported 400 IU D_2 1. *Vitamin D content and type*: 400 IU D_2 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 60 hours 5. *N per group (in analysis)*: 8 6. *Brand/company*: University of Wisconsin 20 IU 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) 1. *Vitamin D content and type*: 20 IU $1,25(OH)_2D_3$/kg body weight 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 60 hours 5. *N per group (in analysis)*: 8 6. *Brand/company*: University of Wisconsin 400 IU $1,25(OH)_2D_3$ 1. *Vitamin D content and type*: 400 IU $1,25(OH)_2D_3$ 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 60 hours 5. *N per group (in analysis)*: 8 6. *Brand/company*: University of Wisconsin
Outcomes	**Primary** 1. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Hypercalcaemia (serum calcium): atomic absorption spectroscopy (AAS) a. Definition: > 10.5 mg/dL b. **Notes:** no events in either arm; data did not contribute to meta-analysis

Chan 1978 *(Continued)*

	2. Serum 25(OH)D (nmol/L): competitive protein binding radio assay (CPBA) a. **Notes:** data presented in Figure 4 (Chan 1978), but not extractable **Time points:** 12 and 72 hours of age
Notes	Sample size was not calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the 32 infants were divided randomly and equally into one of four groups" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	High risk	Quote: "parents of infants given placebo were told that a placebo was used" Judgement comment: allocation not concealed from parents
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "parents of infants given placebo were told that a placebo was used" Judgement comment: parents of infants receiving placebo may be less likely to adhere to the allocated placebo and may increase vitamin D from other sources. Investigator blinding was not described; investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. However, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: no loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified; outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Chandy 2016

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Grants to study author from Department of Biotechnology, Government of India, and Indian Society for Bone and Mineral Research **Country:** India **Study period:** September 2012 to June 2014
Participants	**Included criteria:** all mothers giving birth in 2 maternity units of the institution who intended to continue exclusive breastfeeding through first 6 months and come to hospital of birth for immunisation

Chandy 2016 *(Continued)*

Excluded criteria: birth weight ≤ 2 kg, sick neonate admitted to intensive care unit, mother or infant on treatment with anticonvulsants or antitubercular drugs, mothers who had received any vitamin D other than the 10 µg present in calcium tablets

Pretreatment: all mothers instructed to give infants 15 minutes of traditional baby massage once per day, under the sun between 9 am and 4 pm

Baseline vitamin D status (median (interquartile range); nmol/L)

1. Control group (placebo): 20.0 (13.1 to 30.3)
2. Intervention group (400 IU D_3): 17.8 (10.3 to 28.3)

Interventions

Intervention characteristics

400 IU D_3

1. *Vitamin D content and type*: 400 IU D_3
2. *Formulation*: syrup
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 9 months
5. *N per group (in analysis)*: 47
6. *Brand/company*: not reported

Placebo

1. *Vitamin D content and type*: none
2. *Formulation*: syrup
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 9 months
5. *N per group (in analysis)*: 54
6. *Brand/company*: not reported

Outcomes

Primary

1. Linear growth
2. Adverse effect: hypercalcaemia

Secondary

1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)
2. Serum 25(OH)D > 50 nmol/L
3. Serum 25(OH)D < 25 nmol/L
4. Rickets

Measurement

1. Length (cm): infantometer (NeoCare)
   a. **Notes:** data presented as mean (interquartile range), which we converted to standard deviation
2. Hypercalcaemia (serum calcium): Randox
   a. Definition: > 2.62 mmol/L
3. Serum 25(OH)D (nmol/L): radioimmunoassay (RIA) (DiaSorin, Saluggia, Italy)
   a. **Notes:** data presented as mean (interquartile range), which we converted to standard deviation
4. Rickets: anterior fontanelle (cm) (test not specified)
   a. **Notes:** data presented as mean (interquartile range), which we converted to standard deviation

Time points: birth, 3.5 and 9 months of age

Chandy 2016 *(Continued)*

Notes	This study also included a maternal supplementation group, which we did not include here, because supplement was not given directly to infants. Sample size was calculated but was not met in the group receiving 400 IU/d

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "after maternal blood sample was collected for serum 25(OH)D 2–4 day after delivery, mother–infant pairs were randomly assigned at birth to one of three treatment regimens described below, to be followed for 9 months. Numbers were computer-generated and allocation was done by one research staff who supervised medication distribution. This staff member was not involved in data collection" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "allocation was done by one research staff who supervised medication distribution. This staff member was not involved in data collection" Judgement comment: allocation was done by a third party who was not involved in data collection, minimising risk of bias of knowing allocation sequence; however, further details (serial numbering, etc.) were not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Outcomes such as measuring anterior fontanelle may be subjective, increasing the risk of detection bias; however, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "of 230 recruited mother–infant pairs, 152 came for the 3.5 month visit (66% response rate). Those who came for follow-up did not differ from those who were absent, in maternal (socio-economic score, and body mass index and 25(OH)D 2–4 d after delivery) and infant (birth length, weight, head circumference, chest circumference and maximum anterior fontanelle diameter) characteristics (online Supplementary Table S1)... All analyses were done as per protocol" Judgement comment: reasons for high loss to follow-up (Figure 1) are not described; further analyses were done on those lost to follow-up, who were found to not be significantly different from those who completed follow-up. Per-protocol analyses suggest no intent-to-treat analysis
Selective reporting (reporting bias)	Low risk	Judgement comment: study registered prospectively with Clinical Trial Registry of India (CTRI, ctri.nic.in) (ID: CTRI/2012/09/002958). All prespecified outcomes reported; no prepublished protocol identified
Other bias	Low risk	Judgement comment: no other risks observed

Choudhary 2012

Study characteristics

Choudhary 2012 *(Continued)*

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** no funding **Country:** India **Study period:** not reported
Participants	**Included criteria:** age 2 to 60 months; clinical diagnosis of severe pneumonia; presenting to paediatric emergency department; severe pneumonia diagnosed as fever, cough, tachypnoea, crepitations; tachypnoea defined as respiratory rate ≥ 50/min in children 2 to 12 months and ≥ 40/min in children 1 to 5 years; pneumonia and chest indrawing or ≥ danger sign (inability to feed, lethargy, cyanosis) diagnosed as severe pneumonia **Excluded criteria:** severe wasting (weight for height < 3 standard deviations), chronic illness, previous history of vitamin D intake over last 4 weeks, known asthma **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 1000 IU D_3 1. *Vitamin D content and type*: 1000 IU D_3 2. *Formulation*: liquid 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 5 days 5. *N per group (in analysis)*: 100 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: nothing 2. *Formulation*: liquid 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 5 days 5. *N per group (in analysis)*: 100 6. *Brand/company*: not reported
Outcomes	None within scope of review
Notes	Sample size calculated and met

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was done according to computer generated random number table" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "both looked alike in terms of appearance, taste and color. The code key was opened only after the intervention, data collection, follow up and tabulation were completed" Quote: "allocation concealment was done by sealed envelope technique"

Choudhary 2012 *(Continued)*

		Judgement comment: appropriate allocation concealment; however, envelopes not specified as sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind" Judgement comment: double-blind but not further detailed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind" Judgement comment: double-blind but not further detailed; however, this study did not analyse any outcomes within the scope of this review
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "overall 173 (86.5%) children improved (vitamin D: 87; placebo: 86) and 23 (11.5%) remained in the same condition. Worsening occurred in 4 (2%) children only. Two children died, 1 each in vitamin D and placebo group. A total of 7 children could not complete the study as parents left against medical advice (Fig. 1). There was no difference between the two groups in the proportion of children who improved. A total of 191 children received all five doses of the drug" Judgement comment: all loss to follow-up reasons documented and equivalent across both arms of the trial; intent-to-treat analysis performed
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified; outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Ducharme 2019

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Two research bridge-funding grants (# 313322 and 142741) of the Canadian Institutes of Health Research (CIHR) **Country:** Canada **Study period:** September 2014 to July 2016
Participants	**Included criteria:** age 1 to 5 years, physician-diagnosed asthma based on clinical signs of airflow obstruction and reversibility, upper respiratory tract infection (URTI) reported by parents as the main asthma trigger; ≥ 4 URTIs in the preceding year, ≥1 exacerbation requiring rescue oral corticosteroids (OCS) in the preceding 6 months (or ≥ 2 in the past 12 months) confirmed by pharmacy or medical records or both **Excluded criteria:** intake of or intention to use > 400 IU/d of vitamin D supplement, extreme prematurity (< 28 weeks' gestation), high risk of vitamin D deficiency (e.g. vegan diet), condition(s) (e.g. rickets) or drug(s) altering calcium or vitamin D absorption or metabolism (e.g. antiepileptic, diuretic, antacid, antifungal), anticipated difficult follow-up **Group differences:** most baseline characteristics were similar between groups but some appeared slightly imbalanced, with a greater proportion of male participants, environmental tobacco exposure, use of combination therapy, more school days missed, fewer Caucasians, and lower vitamin D dietary intake in the intervention group compared to the placebo group (not statistically tested)

Ducharme 2019 *(Continued)*

	Baseline vitamin D status (n (%) < 75 nmol/L) 1. Control (placebo): 13 (54) 2. Intervention (100,000 IU): 15 (68)
Interventions	**Intervention characteristics** 100,000 IU D_3 1. *Vitamin D content and type*: 100,000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: enrolment, 3.5 months 4. *Duration of administration (study time)*: 7 months 5. *N per group (in analysis)*: 22 6. *Brand/company*: Euro-Pharm Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: enrolment, 3.5 months 4. *Duration of administration (study time)*: 7 months 5. *N per group (in analysis)*: 23 6. *Brand/company*: Euro-Pharm
Outcomes	**Primary** 1. Adverse effect: hypercalciuria 2. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Hypercalciuria (urinary calcium/creatinine ratio): assay not reported a. Definition: > 1.25 mmol/mmol (1 to 2 years of age) or > 1 mmol/mmol (2 to 5 years of age) 2. Hypercalcaemia (serum calcium): assay not reported a. Definition: not reported b. **Notes:** no events in either arm; data did not contribute to meta-analysis 3. Serum 25(OH)D (nmol/L): tandem mass spectrometry a. **Notes:** data not included in meta-analysis due to reported values as mean ± interquartile range, with fewer than 30 participants per group, limiting conversion of interquartile range to standard deviation **Time points:** enrolment; 3. 5, and 7 months
Notes	Sample size not calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated random numbers with variable permuted blocks" Judgement comment: sequence generation method adequate

Ducharme 2019 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "the Central Pharmacy (SJUHC) held the allocation codes, prepared the study supplements in sequentially coded syringes, and dispensed as per randomisation 2 mL of vitamin D 3 (100,000 IU of cholecalciferol) or identical placebo, administered by the nurse at baseline and 3.5 months" Judgement comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "triple-blind... At the end of follow up, parents, nurse, and physician independently guessed the child's group assignment" Judgement comment: data related to this statement were not reported; however, triple-blind indicates that participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "triple-blind... At the end of follow up, parents, nurse, and physician independently guessed the child's group assignment" Judgement comment: data related to this statement were not reported; however, triple-blind implies that outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "an intention-to-treat (ITT) analysis was carried out whereby all randomised children were included in the analysis, wherever possible" Judgement comment: minimal loss to follow-up; intention-to-treat analysis done
Selective reporting (reporting bias)	Unclear risk	Quote: "after premature trial cessation due partial funding enabling only a 2-year single-centre pilot trial, rather than an adequately powered multicentre study of 865 children, the primary outcome was modified post hoc to the overall change (Δ) from baseline in total serum 25OHD and at 3.5 and 7 months, similar to our previous pilot study [21]" Judgement comment: study was registered prospectively at ClinicalTrials.gov (ID: NCT02197702), as reported in text. Outcomes were changed following the start of the study; however this change was due to lack of funding - not to intervention or outcome
Other bias	Low risk	Judgement comment: no other risks observed

Evans 1989

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Medical Research of Canada Grant to Dr David Cole **Country:** Canada **Study period:** not reported
Participants	**Included criteria:** infants born at Grace Maternity Hospital (Halifax, Nova Scotia, Canada) who weighed < 1500 g at birth and survived to 72 hours of postnatal age **Excluded criteria:** major congenital anomaly, congenital infection, inherited metabolic disease **Pretreatment:** infants were entered into the study after informed consent was obtained, and were stratified according to size for gestational age at birth and requirement for mechanical ventilation.

Evans 1989 *(Continued)*

Three control infants received high doses of vitamin D at the discretion of the attending physician after 4-week wrist radiographs obtained for clinical indications were interpreted as showing moderate bone disease (scores of 4, 4, and 6, respectively). For these 3 infants, only data obtained up to the day of the switch were used in subsequent analyses. Control and experimental groups were well matched for known possible confounding variables. No significant difference was noted between the 2 groups with respect to gestational age; birth weight; mean daily weight gain; intake of calories, calcium, or phosphorus; number who were small for gestational age at birth, who required mechanical ventilation, or who had more than 30% of their total enteral intake from human milk or commercial soy formula (Isomil); or time (in days) to establishment of enteral feedings

Baseline vitamin D status: not reported

Interventions

Intervention characteristics

400 IU D_2

1. *Vitamin D content and type*: 400 IU D_2
2. *Formulation*: enteral
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 6 weeks
5. *Other micronutrient content*: calcium, 1.5 to 2 mEq/dL of intravenous administration of fluids, dextrose, and water, begun at 60 to 65 mL/kg/d
   a. Not mechanically ventilated: mother's milk or commercial formula
   b. Mechanically ventilated: continuous soy formula
6. *N per group (in analysis)*: 40
7. *Brand/company*: not reported

2000 IU D_2

1. *Vitamin D content and type*: 2000 IU D_2
2. *Formulation*: enteral
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 6 weeks
5. *Other micronutrient content*: calcium, 1.5 to 2 mEq/dL of intravenous administration of fluids, dextrose, and water, begun at 60 to 65 mL/kg/d
   a. Not mechanically ventilated: mother's milk or commercial formula
   b. Mechanically ventilated: continuous soy formula
6. *N per group (in analysis)*: 41
7. *Brand/company*: not reported

Outcomes

Primary

1. Adverse effect: hypercalciuria

Secondary

1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)
2. Rickets

Measurement

1. Hypercalciuria (urinary calcium-to-creatinine ratio, mmol/mmol): complexometric method with ethylenediaminetetraacetic acid and kinetic Jaffé reaction
   a. Definition: not reported
2. Serum 25(OH)D (nmol/L): competitive binding radioimmunoassay diagnostic kit (Nichols Institute, San Juan Capistrano, CA, USA)
   a. **Notes:** data not included in meta-analysis due to reported values as mean ± range, which we could not convert to standard deviation

Evans 1989 *(Continued)*

3. Rickets: radiographic scores (right wrist): anteroposterior or posteroanterior, standard step-wedge technique
   a. **Notes:** data values presented in Figure 1 (Evans 1989). Data not included in meta-analysis due to reported values only in median without variance

Time points: 72 hours' postnatal age, 6 weeks of age

Notes	Sample size stated but calculation not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the first of each pair of infants entered into a stratum was randomly assigned by a coin flip to receive a daily oral supplement of either 2000 IU vitamin D_2, begun by 72 hours of postnatal age (experimental group), or 400 IU vitamin D_2, begun once oral feedings were established according to standard nursery policy (control group). The second of each pair of infants entered into that stratum received the alternate treatment. Infants were removed from the study if they did not survive to 6 weeks of postnatal age or if they developed prolonged obstructive jaundice" Quote: "stratified according to size for gestational age at birth and requirement for mechanical ventilation" Judgement comment: infants were stratified, using low-tech coin flip - an appropriate randomisation method
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "assessments of each radiograph, done on three different occasions by the pediatric radiologist, who was unaware of study group assignments, previous radiographic assessment, and biochemical data, were used to assign the grade" Judgement comment: outcome assessors were blinded for radiograph assessment - a subjective outcome; other outcome measurements were not subjective and were unlikely to be at risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "of the remaining 89 eligible infants, 87 were enrolled after consent was obtained. One infant was inadvertently missed, and consent could not be obtained for one infant. Six enrolled infants did not complete the study, four because they died before 6 weeks of postnatal age (two in each study group) and two because of the development of severe obstructive jaundice (both in the experimental group). Of the 81 infants who completed the study, 40 were randomly assigned to the control group and 41 to the experimental group" Judgement comment: n = 3 control infants were excluded from final follow-up due to presence of bone disease. Because this outcome is related to the intervention, this loss to follow-up may introduce some bias (effect may have been underestimated), but only 3 infants were excluded, and therefore this is unlikely to impact the effect estimate

Evans 1989 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified; prespecified outcomes consistent with those reported
Other bias	Low risk	Judgement comment: no other risks observed

Feliciano 1994

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Funded in part by the Thrasher Research Fund, Salt Lake City, UT, USA; and the Perinatal Research Institute, Cincinnati, OH, USA **Country:** China **Study period:** fall (September and October 1986) and spring (March and April 1987)
Participants	**Included criteria:** gestational age 37 weeks or over, absence of gastrointestinal disease and congenital anomaly **Excluded criteria:** none specified **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 100 IU, North China, Spring born 1. *Vitamin D content and type*: 100 IU vitamin D 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 15 6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA 200 IU, North China, Spring born 1. *Vitamin D content and type*: 200 IU vitamin D 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 13 6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA 400 IU, North China, Spring born 1. *Vitamin D content and type*: 400 IU vitamin D 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 13 6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA 100 IU, North China, Fall born

Feliciano 1994 *(Continued)*

1. *Vitamin D content and type*: 100 IU vitamin D
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 6 months
5. *N per group (in analysis)*: 18
6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA

200 IU, North China, Fall born

1. *Vitamin D content and type*: 200 IU vitamin D
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 6 months
5. *N per group (in analysis)*: 15
6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA

400 IU, North China, Fall born

1. *Vitamin D content and type*: 400 IU vitamin D
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 6 months
5. *N per group (in analysis)*: 16
6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA

100 IU, South China, Spring born

1. *Vitamin D content and type*: 100 IU vitamin D
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 6 months
5. *N per group (in analysis)*: 15
6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA

200 IU, South China, Spring born

1. *Vitamin D content and type*: 200 IU vitamin D
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 6 months
5. *N per group (in analysis)*: 20
6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA

400 IU, South China, Spring born

1. *Vitamin D content and type*: 400 IU vitamin D
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 6 months
5. *N per group (in analysis)*: 20
6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA

100 IU, South China, Fall born

1. *Vitamin D content and type*: 100 IU vitamin D
2. *Formulation*: drops
3. *Frequency of dosage*: daily

Feliciano 1994 *(Continued)*

4. *Duration of administration (study time)*: 6 months
5. *N per group (in analysis)*: 22
6. *Brand/company*: Kremers-Urban Co, Milwaukee, WI, USA

200 IU, South China, Fall born

1. *Vitamin D content and type*: 200 IU vitamin D
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 6 months
5. *N per group (in analysis)*: 10
6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA

400 IU, South China, Fall born

1. *Vitamin D content and type*: 400 IU vitamin D
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 6 months
5. *N per group (in analysis)*: 23
6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA

Outcomes	**Secondary** 1. Linear growth: gain in length **Measurement** 1. Length (cm): equipment not reported **Time points:** birth, 6 months of age
Notes	Sample size not calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "at age 3-5 days, the infants were randomly assigned to receive either 100, 200, or 400 IU of vitamin D a day" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	High risk	Judgement comment: allocation concealment is not described; given that both groups were given different amounts of the same intervention, allocation concealment is unlikely
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. However, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias)	High risk	Quote: "eighty-two per-cent of the infants enrolled at birth completed the study (209/255)"

Feliciano 1994 *(Continued)*

All outcomes		Judgement comment: overall loss to follow-up (18%) is noted but not by group, and no reasons are described. Whether analysis was intent-to-treat, or if infants failing to complete the study were different from completers, is not addressed
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified; outcomes reported in methods and in results
Other bias	Low risk	Judgement comment: no other risks observed

Fort 2016

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. National Institutes of Health (Kaul Pediatric Research Institute Senior Investigator Award U10 HD34216) **Country**: USA **Study period:** June 2012 to October 2014
Participants	**Included criteria:** inborn infants with gestational age between 23 and 27 completed weeks admitted to neonatal intensive care unit at University of Alabama Hospital **Excluded criteria:** major congenital or chromosomal anomalies, moribund infant with low likelihood of survival as out-born infant **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: enteral 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 28 days 5. *Other micronutrient content*: 200 IU vitamin D from enteral feeding 6. *N per group (in analysis)*: 36 7. *Brand/company*: not reported 200 IU D_3 1. *Vitamin D content and type*: 200 IU D_3 2. *Formulation*: enteral 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 28 days 5. *Other micronutrient content*: 200 IU vitamin D from enteral feeding 6. *N per group (in analysis)*: 34 7. *Brand/company*: Enfamil D-Vi-Sol, Mead Johnson Company, Limited Liability Company (LLC), Evansville, IN, USA 800 IU D_3

Fort 2016 *(Continued)*

1. *Vitamin D content and type*: 800 IU D_3
2. *Formulation*: enteral
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 28 days
5. *Other micronutrient content*: 200 IU vitamin D from enteral feeding
6. *N per group (in analysis)*: 30
7. *Brand/company*: Enfamil D-Vi-Sol, Mead Johnson Company, LLC, Evansville, IN, USA

Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D < 50 nmol/L a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis **Measurement** 1. Serum 25(OH)D (nmol/L): enzyme-linked immunoabsorbent assay (Eagle Biosciences, Inc., Nashua, NH, USA) a. **Notes:** data from Figure 1 (Fort 2016). Data presented as mean (interquartile range), which we converted to standard deviation **Time points:** birth, postnatal day 28; followed up at 2 years of age in associated report (Fort 2016; see Salas 2018)
Notes	Sample size was calculated and met except for 800 IU group; study is powered to determine a difference of 50% in vitamin D concentrations on postnatal day 28

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "after consent, infants were randomly allocated by the research pharmacy staff using computer-generated stratified randomization codes to one of three groups" Judgement comment: appropriate sequence generation method, by third party
Allocation concealment (selection bias)	Low risk	Quote: "the medication was dispensed by a research pharmacist in an amber syringe to mask the caregivers" Judgement comment: appropriate allocation concealment; no description of sequentially labelled containers or envelopes; however, intervention administered by blinded study staff - not caregivers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind... The medication was dispensed by a research pharmacist in an amber syringe to mask the caregivers" Judgement comment: participants were blinded, and personnel appear to have been blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind... Clinical data were collected by a trained research coordinator" Judgement comment: outcome assessors appear to be blinded; outcome measurements are not subjective and are unlikely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "between June 2012 and October 2014, 100 infants with birth weights ranging from 360 g to 1290 g (mean 770 ± 215 g) were randomized to three vitamin D daily intake groups: 36 infants to the placebo group, 34 to the 200

Fort 2016 *(Continued)*

		IU/day, and 30 to the 800 IU/day. Of the 100 infants, 37 did not complete the study: 15 due to death, 12 developed necrotizing enterocolitis or spontaneous intestinal perforation, and 12 were not fed for more than 24 hours (Figure 1)" Judgement comment: from Figure 1, 37% of infants did not complete the study; reasons for discontinuing included those related to the outcome (death (n = 15), necrotising enterocolitis/consuming nothing by mouth/spontaneous intestinal perforation (n = 12)) or not (lack of feeding for longer than 24 hours (n = 12)). Numbers of those discontinuing the intervention were much higher (n = 17) in the 200 IU group and n = 9 in the 800 IU group, compared to n = 5 in the placebo group. Intention-to-treat analysis was performed. Children who did not complete the study were not compared with those who completed follow-up
Selective reporting (reporting bias)	Low risk	Judgement comment: study was registered prospectively at ClinicalTrials.gov (ID: NCT01600430), as reported in text; prespecified outcomes are consistent with those reported. No prepublished protocol was identified
Other bias	Low risk	Judgement comment: no other risks observed

Gallo 2013a

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** non-profit + provision of drug. Grant from the Canadian Foundation for Dietetic Research and the D Drops Company provided vitamin D supplements in kind; Canadian Foundation for Innovation **Country**: Canada **Study period:** May 2010 to September 2011
Participants	**Included criteria:** healthy, singleton, term infants born at appropriate size for gestational age as assessed according to the World Health Organization (WHO) Child Growth Charts (between 5th and 95th percentiles) to healthy, breastfeeding women (consuming > 80% of total feeds from breast milk) **Excluded criteria:** infants of mothers with history of gestational diabetes or hypertension in pregnancy, malabsorption syndromes (coeliac and Crohn's diseases), or taking medications that interfere with vitamin D metabolism (anticonvulsants and corticosteroids), and mothers taking ≥ 50 µg/d of vitamin D through supplementation **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (400 IU D_2): 68.3 ± 21.4 2. Intervention group (400 IU D_3): 69.5 ± 21.7
Interventions	**Intervention characteristics** 400 IU D_2 1. *Vitamin D content and type*: 400 IU D_2 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (in analysis)*: 24 6. *Brand/company*: Ddrops company

Gallo 2013a *(Continued)*

	7. **Note: for analysis, this group was considered the 'lower-dose' group** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (in analysis)*: 26 6. *Brand/company*: Ddrops Company 7. **Note: for analysis, this group was considered the 'higher-dose' group**
Outcomes	**Primary** 1. Length/height-for-age z-score (L/HAZ) **Secondary** 1. Weight-for-age z-score (WAZ) 2. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 3. Change in 25(OH)D 4. Serum 25(OH)D ≥ 50 nmol/L 5. Serum 25(OH)D ≥ 75 nmol/L **Measurement** 1. Length (cm): infant length boards 2. Weight (kg): equipment not reported 3. Z-score: World Health Organization Child Growth Standards (WHO 2006) a. **Notes:** data presented as mean (standard error), which we converted to standard deviation 4. Serum 25(OH)D (nmol/L): (1) automated chemiluminescent immunoassay system (Liaison, DiaSorin, Saluggia, Italy) and (2) liquid chromatography–mass spectrometry (Warnex Bioanalytical Services, Laval, Quebec, Canada) **Time points:** 1 and 4 months of age
Notes	Calculated sample size was attained at randomisation but not at primary analysis, and primary analysis does not include all who were randomised. Did not meet sample size in D_2 group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "infants were randomly assigned to receive a 10-mg/d oral dose of either D_2 or D_3 in a 1:1 ratio stratified by sex" Judgement comment: study authors state that they randomly allocated interventions but do not describe the random sequence generation method used
Allocation concealment (selection bias)	Low risk	Quote: "there were no differences in appearance and both products were tasteless and odorless. These products are oil based (coconut and palm) and dosages were delivered in 1-drop volumes (0.03 mL) using a standardized Eurodropper" Judgement comment: appropriate allocation concealment; no description of sequentially labelled envelopes
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement comment: given concealed allocation, participants were likely blinded. If blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering addition-

Gallo 2013a *(Continued)*

All outcomes		al vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. However, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "the intent-to-treat principle was applied for all outcomes" Judgement comment: Figure 1 gives those lost to follow-up but not reasons for loss to follow-up. Intention-to-treat analysis is done but does not include those lost to follow-up. However, loss to follow-up is minimal (Figure 1)
Selective reporting (reporting bias)	Low risk	Judgement comment: study was registered retrospectively at ClinicalTrials.gov (ID: NCT01190137), as reported in text; prespecified outcomes are consistent with those reported. No prepublished protocol was identified
Other bias	Low risk	Judgement comment: no other risks observed

Gallo 2013b

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Canadian Institutes for Health Research, Nutricia Research Foundation, and Canadian Foundation for Innovation, and in-kind support from Euro-Pharm International Canada Inc. for provision of the supplements. Fonds de la Recherche en Santé du Québec provided personal funding for the doctoral student (Ms Gallo), and Canada Research Chairs provided a salary award to Dr Weiler **Country:** Canada **Study period:** May 2007 to August 2010
Participants	**Included criteria:** healthy, term, singleton, appropriate size for gestational age, breastfeeding (consuming 80% of total milk volume) **Excluded criteria:** infants of mothers with gestational diabetes, hypertension in pregnancy, chronic alcohol use, or malabsorption syndrome **Group differences:** maternal and infant baseline characteristics were similar among groups except for mother's race (P = 0.03); thus, race was included as a covariate in all analyses. There were no differences in attrition rates, referring centres, or reported adherence across treatment groups **Baseline vitamin D status (mean (95% confidence interval); nmol/L)** 1. Control group (400 IU D_2): 55.6 (45.0 to 61.8) 2. Intervention group (800 IU D_3): 52.3 (45.7 to 63.0) 3. Intervention group (1200 IU D_3): 64.0 (54.5 to 72.6) 4. Intervention group (1600 IU D_3): 63.6 (52.1 to 77.0)
Interventions	**Intervention characteristics** 400 IU D_3

Gallo 2013b *(Continued)*

1. *Vitamin D content and type*: 400 IU D_3
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 11 months
5. *N per group (in analysis)*: 29
6. *Brand/company*: Euro-Pharm International Canada Inc.

800 IU D_3

1. *Vitamin D content and type*: 800 IU D_3
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 11 months
5. *N per group (in analysis)*: 32
6. *Brand/company*: Euro-Pharm International Canada Inc.

1200 D_3

1. *Vitamin D content and type*: 1200 IU D_3
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 11 months
5. *N per group (in analysis)*: 27
6. *Brand/company*: Euro-Pharm International Canada Inc.

1600 IU D_3

1. *Vitamin D content and type*: 1600 IU D_3
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 11 months
5. *N per group (in analysis)*: 13
6. *Brand/company*: Euro-Pharm International Canada Inc.

Outcomes

Primary

1. Length/height-for-age z-score (L/HAZ)
   a. **Notes:** reported in associated report (Gallo 2013b; see Hazel 2017 and Wicklow 2017)
2. Adverse effect: hypercalciuria
3. Adverse effect: hypercalcaemia

Secondary

1. Weight-for-age z-score (WAZ)
   a. **Notes:** reported in associated report (Gallo 2013b; see Hazel 2017 and Wicklow 2017)
2. Weight-for-length/height (WL/HZ)
   a. **Notes:** reported in associated report (Gallo 2013b; see Hazel 2017 and Wicklow 2017)
3. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)
   a. Data from Figure 3 (Gallo 2013b)
   b. **Notes:** data presented as mean (95% CI), which we converted to standard deviation
4. Serum 25(OH)D ≥ 75 nmol/L
   a. Data from Figure 2(A) (Gallo 2013b)
   b. **Notes:** data presented as mean (95% CI), which we converted to standard deviation
5. Serum 25(OH)D ≥ 50 nmol/L
   a. Data from Figure 2(B) (Gallo 2013b)
   b. **Notes:** data presented as mean (95% CI), which we converted to standard deviation

Gallo 2013b *(Continued)*

Measurement

1. Length (cm): infant length boards
2. Hypercalciuria (urinary calcium-to-creatinine ratio): Beckman Coulter assay
   a. Definition: not reported; identified as 'suspected' hypercalciuria
3. Hypercalcaemia (serum calcium): assay not reported
   a. Definition: not reported; identified as 'suspected' hypercalcaemia
4. Weight (kg): infant scale (Model SB 32000; Mettler Toledo Inc., Toledo, OH, USA)
5. Z-score: World Health Organization Child Growth Standards (WHO 2006)
6. Serum 25(OH)D (nmol/L):
   a. Enzyme immunoassay (Octeia, Immunodiagnostic Systems Inc., Gaithersburg, MD, USA)
   b. Radioimmunoassay (DiaSorin Inc., Saluggia, Italy)
   c. Liquid chromatography with tandem mass spectroscopy (LC-MS/MS), Model API-4000, ABSciex, Ontario, Canada, or Triple Stage Quadrupole (TSQ)-Vantage LC-MS/MS instrument (ThermoScientific, Waltham, MA, USA)
   d. **Notes:** data presented as mean (95% confidence interval), which we converted to standard deviation

Time points: 1, 3, 6, 9, and 12 months of age; followed up at 3 years of age

Notes	Sample size calculated and met at randomisation for groups randomised to 400 IU, 800 IU, and 1200 IU vitamin D. Group randomised to 1600 IU vitamin D per day did not meet the target sample size at randomisation. Participants in this group received 1600 IU vitamin D per day until age 12 months (n = 6), until age 6 months (n = 4), or until age 9 months (n = 6) before investigators re-assigned these participants to the 400 IU per day group, thereafter receiving 400 IU per day. Children in the 1600 IU group were not included in statistical models owing to discontinuation of the intervention (see Gallo 2013b for details)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "following enrollment into the study and baseline measurements, the infants were randomly assigned to 1 of the 4 groups in a 1:1:1:1 allocation ratio. Randomization was stratified by sex in equal blocks of 4. The randomization list was generated using http://www.randomization.com and blinded supplement codes. The codes were revealed only after the statistical analysis was complete" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "supplements containing 400, 800, 1200, or 1600 IU of vitamin D 3 were formulated by Europharm International Canada Inc and administered in 2-mL/day volume using a standardized dropper; all had similar taste, smell, and appearance. Supplements were provided in precoded bottles of 60-mL volume" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "parents and researchers were blinded to treatment dosage" Judgement comment: participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the codes were revealed only after the statistical analysis was complete" Judgement comment: outcome assessors were blinded

Gallo 2013b *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "careful comparisons of participants with missing and fully observed data were consistent with data missing at random. The mixed-model analysis of variance estimates the effect size based on available data (Figure 1 and Figure 2), and participants with missing data are not dropped, mitigating the need for imputation" Judgement comment: similar proportions of loss to follow-up across study groups; reasons for dropouts not given explicitly, only "lost to follow-up", and "insufficient blood". Analysis done by intention-to-treat
Selective reporting (reporting bias)	Low risk	Judgement comment: study was registered prospectively at ClinicalTrials.gov (ID: NCT00381914), as reported in text; prespecified outcomes are consistent with those reported. No study protocol was identified
Other bias	Low risk	Judgement comment: no other risks observed

Gordon 2008

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Grants from Allen Foundation and McCarthy Family Foundation; National Institutes of Health Grant MO1-RR-2172 to Children's Hospital Boston General Clinical Research Center; and Project T71 MC00009 Maternal and Child Health Bureau, Human Resources and Services Administration **Country:** USA **Study period:** October 2005 to June 2007
Participants	**Included criteria:** age 8 to 24 months, enrolled from Children's Hospital Boston Primary Care Center, vitamin D deficient 50 nmol/L **Excluded criteria:** chronic disease (e.g. asthma, seizure disorder, sickle cell disease), use of oral glucocorticoid over previous 3 months, other therapy known to affect vitamin D metabolism **Baseline vitamin D status (mean; nmol/L)** 1. Control group (2000 IU D_2): 39.2 2. Control group (2000 IU D_3): 34.2 3. Intervention group (50,000 IU D_3): 34.4
Interventions	**Intervention characteristics** 2000 IU D_2 1. *Vitamin D content and type*: 2000 IU D_2 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 weeks 5. *Other micronutrient content*: 50 mg/kg/d elemental calcium 6. *N per group (in analysis)*: 12 7. *Brand/company*: Sanofi-Synthelabo Inc. (Bridgewater, NJ, USA) 50,000 IU D_2

Gordon 2008 *(Continued)*

1. *Vitamin D content and type*: 50,000 IU D_2
2. *Formulation*: drops
3. *Frequency of dosage*: weekly
4. *Duration of administration (study time)*: 6 weeks
5. *Other micronutrient content*: 50 mg/kg/d elemental calcium
6. *N per group (in analysis)*: 14
7. *Brand/company*: Sanofi-Synthelabo Inc. (Bridgewater, NJ, USA)

2000 IU D_3

1. *Vitamin D content and type*: 2000 IU D_3
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 6 weeks
5. *Other micronutrient content*: 50 mg/kg/d elemental calcium
6. *N per group (in analysis)*: 14
7. *Brand/company*: Biotics Research Corp (Rosenberg, TX, USA)

Outcomes

Primary

1. Adverse effect: hypercalcaemia

Secondary

1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)
2. Serum 25(OH)D < 50 nmol/L
   a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis
3. Change in 25(OH)D

Measurement

1. Hypercalcaemia (mild): multi-channel analyser
   a. Definition: not reported
2. Serum 25(OH)D (nmol/L): DiaSorin chemiluminescent assay (DiaSorin, Stillwater, MN, USA)
   a. **Notes:** data from Figure 1 (Gordon 2008). Inter-group difference data not included in meta-analysis due to reported values only in mean without variance; change data from Figure 1 (Gordon 2008): mean and 95% confidence interval from repeated-measures regression analysis of log-transformed concentration measures

Time points: enrolment, 6 weeks

Notes

Sample size calculated but not met

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients identified to have hypovitaminosis D were randomly assigned to one treatment protocol. The randomization list was stratified by age at screening (9 or 18 months) and blocked in randomly permuted sequences of 3 or 6, ensuring that no treatment would be disproportionately represented in any season or age group" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	High risk	Quote: "the vitamin D_2 preparation (200 IU per drop or 0.025 ml) was manufactured by Sanofi-Synthelabo Inc. (Bridgewater, NJ), and doses were provided as 10 drops or 0.25 ml daily for the 2,000 IU dose and 6.25 ml weekly for the

Gordon 2008 *(Continued)*

		50,000 IU dose; for each vitamin D 2 dose, the suspension was administered via a provided dropper onto the tongue" Judgement comment: given that both groups were given different amounts of the same intervention, allocation concealment is unlikely
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. However, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "we conducted an intention-to-treat analysis, attributing the assigned treatment to all randomized subjects regardless of compliance" Judgement comment: low loss-to-follow-up; intention-to-treat analysis performed
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified; outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Greer 1981

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** for-profit and non-profit: Grant from Ross Laboratories and National Institute of Child Health and Human Development **Country:** USA **Study period:** summer 1979 and November 1979
Participants	**Included criteria:** healthy, term, exclusively breastfed infants **Excluded criteria:** none specified **Pretreatment:** no differences in baseline infant bone mineral content, biochemical measurements, maternal intake, and breast milk minerals **Baseline vitamin D status (mean ± standard error; nmol/L)** 1. Control group (placebo): 50.6 ± 9.6 2. Intervention group (400 IU D_3): 72.5 ± 8.1
Interventions	**Intervention characteristics** Placebo 1. *Vitamin D content and type*: none

Greer 1981 *(Continued)*

2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 12 weeks
5. *N per group (in analysis)*: 9
6. *Brand/company*: not reported

400 IU D_2

1. *Vitamin D content and type*: 400 IU D_2
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 12 weeks
5. *N per group (in analysis)*: 9
6. *Brand/company*: Drisdol (Winthrop-Breon Laboratories, New York City, NY, USA)

Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): competitive protein-binding assay following preparative chromatography, after the method of Haddad and Chyu a. **Notes:** data from Figure 2 (Greer 1981) **Time points:** birth, 12 weeks of age; followed up at 1 year of age
Notes	Sample size not calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "eighteen healthy, term, exclusively breast-fed infants were divided randomly into two groups" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "neither mothers nor investigators knew whether vitamin D or placebo was given to the infants... After 12 weeks, the study was unblinded to the investigators. At six months, the study was unblinded to the mothers of the study infants, at which time all infants were allowed solid foods and the placebo group was given a daily vitamin D supplement of 400 IU" Judgement comment: mothers were blinded until age 6 months (reported in Greer 1982); investigators were unblinded at 12 weeks (end of study)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind fashion; after 12 weeks, the study was unblinded to the investigators" Judgement comment: outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "at 9 months, six of 13 (46%) infants remaining in the study from the placebo and supplemented groups were still breast-feeding. At one year, three infants were still breast-feeding, and ten infants were receiving cow milk. An additional 12 term, healthy, exclusively formula-fed infants from the same private practice served as a comparison group for bone mineral content only"

Greer 1981 *(Continued)*

		Judgement comment: no loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified; all outcomes in methods reported in results
Other bias	Low risk	Judgement comment: no other risks observed

Greer 1989

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. US Department of Agriculture grant **Country:** USA **Study period:** October 1985 to January 1987
Participants	**Included criteria:** breastfed, term; mothers must plan to exclusively breastfeed until 6 months **Excluded criteria:** none specified **Group differences:** birth length was significantly lower in the formula group compared with the human milk groups; gestational age of formula group was lower than that of the group receiving no vitamin D **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (placebo): 58.7 ± 19.1 2. Intervention group (400 IU D_3): 60.0 ± 11.8
Interventions	**Intervention characteristics** 400 IU D_2 1. *Vitamin D content and type*: 400 IU D_2 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 22 6. *Brand/company*: Drisdol (Winthrop-Breon Laboratories, New York City, NY, USA) Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 24 6. *Brand/company*: not reported
Outcomes	**Primary** 1. Linear growth

Greer 1989 *(Continued)*

Secondary

1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)

Measurement

1. Length (cm): length board
2. Serum 25(OH)D (nmol/L): direct ultraviolet detection after high-performance liquid chromatography (HPLC)

Time points: birth, 6 months of age

Notes	Sample size calculated and met

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "forty-six term, breast-fed infants were divided randomly into two groups and studied in a double-blind fashion" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "studied in a double-blind fashion" Judgement comment: 'double-blind' implies that participants and personnel were blinded to assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: 'double-blind' implies that outcome assessors were blinded; outcome measurements are not subjective and are unlikely to be influenced
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "fifty-eight patients completed the initial 1 1/2 months of the study, 12 in the formula group, 22 in the group fed human milk supplemented with vitamin D_2, and 24 in the group fed human milk and given placebo. All of the 12 formula-fed infants completed 6 months of the study. By 3 months, one infant in each of the human milk-fed groups was eliminated for noncompliance. An additional seven infants dropped out after 3 months because breast-feeding was discontinued. Ultimately, 19 infants in each of the groups fed human milk completed 6 months of the study" Judgement comment: moderate loss to follow-up (17%); no reasons given; no investigations of lost patients; appears to show complete case analysis
Selective reporting (reporting bias)	Unclear risk	Quote: "we measured bone mineral content, growth, and serum concentrations of 25(OH)D_3, 25(OH)D_2, 1,25-$(OH)_2$D, and parathyroid hormone as indicators of vitamin D deficiency or sufficiency" Judgement comment: trial not registered and no protocol available; outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Gupta 2016

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Indian Council of Medical Research **Country:** India **Study period:** 25 August 2012 to 27 January 2015
Participants	**Included criteria:** children age 6 months to 5 years with clinical diagnosis of severe pneumonia (defined as presence of lower chest indrawing in children presenting with cough or difficult breathing); family staying within 10-km radius of the hospital **Excluded criteria:** children with history or clinical features suggestive of rickets (presence of wide wrists, delayed closure of anterior fontanelle, presence of rachitic rosary, bow legs or knock knee), severe acute malnutrition, asthma, hypertension, complicated pneumonia (lung abscess, pleural effusion, empyema) or illness severe enough to require ventilation, chronic respiratory disease, heart disease, renal or hepatic insufficiency, neurological illness resulting in abnormalities of muscle tone/power, and known immunodeficiency. Children having received vitamin D or calcium supplements within 4 weeks before enrolment, those diagnosed with hypercalcaemia or allergy to vitamin D, and those immunised with pneumococcal/flu vaccine were also excluded **Baseline vitamin D status (n (%) < 75 nmol/L)** 1. Control group (placebo): 65 (40) 2. Intervention group (100,000 IU D_3): 61 (38)
Interventions	**Intervention characteristics** 100,000 IU D_3 1. *Vitamin D content and type*: 100,000 IU D_3 2. *Formulation*: dissolved in milk and administered orally or by nasogastric tube to the participant 3. *Frequency of dosage*: once, at enrolment 4. *Duration of administration (study time)*: 180 days 5. *N per group (in analysis)*: 153 to 156 (depending on outcome) 6. *Brand/company*: M/s Zuventus Healthcare Ltd., Mumbai, India Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: dissolved in milk and administered orally or by nasogastric tube to the participant 3. *Frequency of dosage*: once, at enrolment 4. *Duration of administration (study time)*: 180 days 5. *N per group (in analysis)*: 156 to 158 (depending on outcome) 6. *Brand/company*: M/s Zuventus Healthcare Ltd., Mumbai, India
Outcomes	**Primary** 1. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D < 30 nmol/L **Measurement**

Gupta 2016 *(Continued)*

	1. Hypercalcaemia (serum calcium): assay not reported a. Definition: > 10.8 mmol/L b. **Notes:** no events in either arm; data did not contribute to meta-analysis 2. Serum 25(OH)D (nmol/L), radioimmunoassay, Immunotech SAS, Marseille, France **Time points:** baseline, 2 weeks, 3 months
Notes	Sample size calculated and met at randomisation and analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "eligible children were randomized using computer-generated block randomization to receive 100,000 IU of vitamin D (cholecalciferol) or placebo orally. Eight, ten, and twelve blocks consisting of 10, 10, and 12 subjects, respectively were created" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "both drug and placebo were identical in appearance, color, odor, amount, and taste. Five sachets of the drug were weighed and repackaged into three airtight zip pouch containing 100,000 IU of cholecalciferol each with the help of electronic weighing scale (0.001 g calibration). Placebo was also processed in similar manner. Only 15 doses were prepared at a time. Both drug and placebo were stored in a cool, dry, and dark place till dispensed. The next lot was prepared afresh when 4 doses were left. The allocation was further concealed by using sealed opaque envelopes. Randomization, repackaging, sequencing, and allocation concealment were done independently by a biostatistician and an office secretary who were not members of the investigating team. ... None of the investigators, study staff, and participants was aware of the drug or placebo being dispensed. The codes were revealed only at the time of final data analysis" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "none of the investigators, study staff, and participants [were] aware of the drug or placebo being dispensed. The codes were revealed only at the time of final data analysis" Judgement comment: participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "none of the investigators, study staff, and participants [were] aware of the drug or placebo being dispensed. The codes were revealed only at the time of final data analysis." Judgement comment: outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "the effect of vitamin D supplementation on outcome variables was analyzed on an intention-to-treat basis" Judgement comment: reasons for low loss to follow-up are described (migration, address not traceable, left against medical advice, death); seem equal among groups. Intention-to-treat analysis was performed but on final available numbers (not on original randomised numbers)
Selective reporting (reporting bias)	Low risk	Quote: "the primary outcome variables were (a) the time to resolution of severe pneumonia (the duration from the enrolment till the chest indrawing was no longer present, and continued to be absent for next 24 hours); and (b) the proportion of children having a recurrence of pneumonia in next six months"

Gupta 2016 *(Continued)*

		Judgement comment: study was registered prospectively with Clinical Trial Registry of India (CTRI, ctri.nic.in) (ID: CTRI/2013/01/003317). All prespecified outcomes were reported. No protocol was identified
Other bias	Low risk	Judgement comment: no other risks observed

Hanson 2011

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Grant from Nebraska Medical Center and University of Nebraska Medical Center, and Department of Pediatrics, University of Nebraska Medical Center, Omaha, NE, USA **Country:** USA **Study period:** August 2009 to June 2010
Participants	**Included criteria:** 32 weeks' gestational age, birth weight 1500 g, mother indicated intention to formula-feed her infant **Excluded criteria:** infants exclusively receiving maternal breast milk; those with congenital abnormalities; gastrointestinal, liver, or kidney disease; inborn errors of metabolism; parathyroid disease; disorders of calcium metabolism; infants receiving seizure medication or steroids **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (placebo): 40.7 ± 15.2 2. Intervention group (400 IU D_3): 47.7 ± 19.2
Interventions	**Intervention characteristics** Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 21 days 5. *N per group (in analysis)*: 26 6. *Brand/company*: not reported 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 21 days 5. *N per group (in analysis)*: 26 6. *Brand/company*: Mead-Johnson formulation D-Vi-Sol, Mead-Johnson Nutritionals, Evansville, IN, USA
Outcomes	**Primary** 1. Adverse effect: hypercalcaemia **Secondary**

Hanson 2011 *(Continued)*

1. Serum 25-hydroxyvitamin D (serum 25(OH)D, nmol/L)

Measurement

1. Hypercalcaemia (serum calcium): Beckman Coulter assay
   a. Definition: not reported
   b. **Notes:** no events in either arm; data did not contribute to meta-analysis
2. Serum 25(OH)D (nmol/L): radioimmunoassay (RIA) (ImmunoDiagnostics kit, Nichols Institute, San Clemente, CA, USA)

Time points: birth; 7, 14, and 21 days of life

Notes	Calculated sample size met at randomisation but not at analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Unclear risk	Quote: "matching placebo" Judgement comment: suggests placebo was matched to appearance of intervention but does not describe concealment processes. Allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "investigators and neonatal intensive care unit staff were blinded to subject group assignment" Judgement comment: personnel were blinded; no mention of participant blinding. Caregivers were likely blinded because they did not administer the supplement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "investigators and neonatal intensive care unit staff were blinded to subject group assignment" Judgement comment: investigators blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "fifty-six infants were enrolled in the study; the primary reason for exclusion from the study was the mother's intention to provide maternal breast milk for her infant. Fifty-two infants were included in the analysis; four were excluded from the analysis for the following reasons: phenobarbital was initiated in two infants, one infant was discharged, and one infant was transferred to another institution" Judgement comment: reasons for low loss to follow-up are given, but not by arm (reasons are unlikely to be related to outcome). Intention-to-treat analysis was performed
Selective reporting (reporting bias)	Unclear risk	Judgement comment: study was registered prospectively at ClinicalTrials.gov (ID: NCT01042561), which we identified through additional searching; prespecified outcomes are consistent with those reported. No prepublished protocol was identified
Other bias	Low risk	Judgement comment: no other risks observed

Harnot 2017

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Indian Council of Medical Research (ICMR) (Grant no 3/2/2012/PG-thesis-HRD) **Country:** India **Study period:** July 2012 to June 2013
Participants	**Included criteria:** age 3 months to 3 years, attending paediatric outpatient department with evidence of vitamin D deficiency based on clinical (hypocalcaemic seizure or features of rickets like bowing legs or rachitic rosary) or radiological (frying of radius ulna or costochondral beading) features, those found to have vitamin D < 15 ng/mL **Excluded criteria:** chronic liver or kidney disease; congenital malformation; taking anticonvulsants, diuretics, or steroids longer than 1 month within past 6 months; known hypersensitivity to vitamin D **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (300,000 IU D_3): 22.1 ± 10.2 2. Intervention group (400 IU D_3): 20.9 ± 10.2
Interventions	600,000 IU D_3 1. *Vitamin D content and type*: 600,000 IU D_3 2. *Formulation*: sachet 3. *Frequency of dosage*: once, at enrolment 4. *Duration of administration (study time)*: 30 days 5. *N per group (in analysis)*: 27 6. *Brand/company*: Calcirol Sachet, dispensed by Cadila Pharmaceuticals (Gujarat, India) 300,000 IU D_3 1. *Vitamin D content and type*: 300,000 IU D_3 2. *Formulation*: sachet (including glucose) 3. *Frequency of dosage*: once, at enrolment 4. *Duration of administration (study time)*: 30 days 5. *N per group (in analysis)*: 28 6. *Brand/company*: Calcirol Sachet, dispensed by Cadila Pharmaceuticals (Gujarat, India)
Outcomes	**Primary** 1. Adverse effect: hypercalciuria 2. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) > 75 nmol/L **Measurement** 1. Hypercalciuria (urinary calcium-to-creatinine ratio): spot urine test, clinical chemistry analyser a. Definition: > 0.86, 0.6, 0.4 mg/mg for children < 7 months old, 7 to 18 months old, 19 months to 6 years old, respectively

Harnot 2017 *(Continued)*

2. Hypercalcaemia (serum calcium): Dimension RxL Max clinical chemistry analyser (Siemens Medical Solutions, Malvern, PA, USA)
   a. Definition: > 10.9 mg/dL
3. Serum 25(OH)D (nmol/L): electro-chemiluminescence assay (Roche Diagnostics, Mannheim, Germany)

Time points: days 7 to 10

Notes	Sample size calculated and met

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random allocation sequence was generated by computer using block randomization of variable block size; by an independent physician, not involved in patient management" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "allocation concealment was ensured by using serially numbered, tamper proof, opaque and sealed envelopes" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "patient and clinician administering the drug were blinded from the study details" Judgement comment: all personnel and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind randomized" Judgement comment: implies that outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "from the initial cohort of 60 patients, 55 completed the study (Fig. 1). Five patients, two from the 600,000 IU group and three from 300,000 IU group were lost to follow-up (Fig. 1). The reason for lack of follow up could not be ascertained as the caregivers did not come for even a single follow up visit" Judgement comment: reasons for loss to follow-up not ascertained but minimal attrition. Intent-to-treat analysis done only as a sensitivity analysis with no change in study results
Selective reporting (reporting bias)	Low risk	Judgement comment: study was prospectively registered with Clinical Trial Registry of India (CTRI, ctri.nic.in) (ID: CTRI/2012/05/002621), as reported in text. All prespecified outcomes were reported
Other bias	Low risk	Judgement comment: no other risks observed

Hibbs 2018

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group

Hibbs 2018 *(Continued)*

	Funding: 100% non-profit. National Heart, Lung, and Blood Institute (NHLBI) and Office of Dietary Supplements (ODS) (grant R01HL109293) **Country:** USA **Study period:** January 2013 to March 2017
Participants	**Included criteria:** infants at 28 to 36 weeks' gestational age (GA) at birth, child identified by family as black or African American; received 28 days or less of supplemental oxygen; admitted to a participating nursery as a neonate; 40 weeks' adjusted GA or younger at enrolment; lived within predefined geographical area at each site **Excluded criteria:** diagnosed as having bronchopulmonary dysplasia; preexisting diagnosis of moderate to severe osteopenia of prematurity or alkaline phosphatase level > 700 U/L (to convert to µkat/L, multiply by 0.0167), or both; history of fracture; history of gastrointestinal surgery, including for necrotising enterocolitis, known gastrointestinal malabsorption, major congenital anomaly, congenital pulmonary or airway disorder, documented wheezing, or stridor before enrolment; previous vitamin D supplementation > 400 IU/d; family planned to move out of the region. Infants were also ineligible if their serum phosphorus concentration was outside the range of 4.0 to 9.5 mg/dL (to convert to mmol/L, multiply by 0.323) or serum calcium was outside the range of 8.5 to 10.7 mg/dL (to convert to mmol/L, multiply by 0.25). A serum 25-hydroxyvitamin D concentration < 10 ng/mL or > 80 ng/mL also made infants ineligible (to convert to nmol/L, multiply by 2.496) **Baseline vitamin D status (mean ± (IQR); nmol/L)** 1. Control group (placebo): 52.4 (42.4, 62.4) 2. Intervention group (400 IU D_3): 47.7 (39.2, 69.9)
Interventions	**Intervention characteristics** 400 IU D_3 (sustained) 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: until 6 months' adjusted age 5. *N per group (in analysis)*: 135 6. *Brand/company*: D-Vi-Sol (specified in protocol) Placebo (diet limited) 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: until 6 months' adjusted age 5. *N per group (in analysis)*: 134 6. *Brand/company*: D-Vi-Sol (specified in protocol)
Outcomes	**Primary** 1. Adverse effect: hypercalcaemia 2. Adverse effect: hyperphosphataemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Hypercalcaemia (serum calcium): assay not described a. Definition: > 2.65 mmol/L

Hibbs 2018 *(Continued)*

	2. Hyperphosphataemia (serum phosphorus): assay not described a. Definition: > 3.07 mmol/L 3. Serum 25(OH)D (nmol/L): immunoassay a. **Notes:** data presented as mean (interquartile range), which we converted to standard deviation **Time points:** 3, 6, and 12 months' adjusted age
Notes	Sample size calculated and met

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "infants were randomized with randomly permuted blocks, sizes 2 to 6, using computer-generated random numbers" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "they received masked study drug (liquid cholecalciferol or a placebo, dispensed in an amber bottle)" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "families, clinical caregivers, and study staff were blinded to assignment and block size" Judgement comment: all personnel and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "families, clinical caregivers, and study staff were blinded to assignment and block size" Judgement comment: outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "of the 300 infants enrolled in the study, 18 withdrew from the study and 1 died while co-sleeping (Figure 1). Follow-up rates of surviving non withdrawn infants at the 3-, 6-, 9-, and 12-month visits were 97.9%, 96.5%, 95.0%, and 94.0%, respectively. Due to missing 12-month visits in infants who had not yet met criteria for recurrent wheezing, we were unable to determine recurrent wheezing status for 8 children, and these cases were considered as missing data in the primary analysis" Judgement comment: loss to follow-up was well described and missing data were examined. Modified intent-to-treat approach was used
Selective reporting (reporting bias)	Low risk	Judgement comment: study was registered at ClinicalTrials.gov (ID: NCT01601847), as reported in text; study protocol is available. Outcomes proposed match reported outcomes
Other bias	Low risk	Judgement comment: no other risks observed

Holmlund-Suila 2012

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group

Holmlund-Suila 2012 *(Continued)*

	Funding: 100% non-profit: Finnish Foundation for Pediatric Research, Academy of Finland (no 277843), Sigrid Jusélius Foundation, Finska Läkaresällskapet, Biomedicum Helsinki Foundation, Folkhälsan Research Foundation, and a grant from the special governmental subsidy for health sciences research, Helsinki, Finland **Country:** Finland **Study period:** September 2010 to February 2011
Participants	**Included criteria:** born at term, with birth weight appropriate for gestational age **Excluded criteria:** none specified **Pretreatment:** maternal vitamin D supplementation: 88% overall **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (400 IU D_3): 52.0 ± 14.0 2. Intervention group (1200 IU D_3): 54.0 ± 15.0 3. Intervention group (1600 IU D_3): 54.0 ± 15.0
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 10 weeks 5. *N per group (in analysis)*: 35 6. *Brand/company*: Vitamin D_3 Forte, 500 IU per drop (Renapharma, Uppsala, Sweden) 1200 IU D_3 1. *Vitamin D content and type*: 1200 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 10 weeks 5. *N per group (in analysis)*: 35 6. *Brand/company*: Vitamin D_3 Forte, 500 IU per drop (Renapharma, Uppsala, Sweden) 1600 IU D_3 1. *Vitamin D content and type*: 1600 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 10 weeks 5. *N per group (in analysis)*: 37 6. *Brand/company*: Vitamin D_3 Forte, 500 IU per drop (Renapharma, Uppsala, Sweden)
Outcomes	**Primary** 1. Linear growth 2. Adverse effect: hypercalciuria 3. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)

Holmlund-Suila 2012 *(Continued)*

	Measurement 1. Length (cm): equipment not reported 2. Hypercalciuria (urinary calcium-to-creatinine ratio): photometric assay a. Definition: > 2.2 mmol/mmol 3. Hypercalcaemia (serum calcium): photometric assay a. Definition: not reported 4. Serum 25(OH)D (nmol/L): automated ImmunoDiagnosticsSystems analyser (IDS Ltd., Boldon, United Kingdom) **Time points:** 2 weeks of age, 3 months of age
Notes	Sample size calculated and met at randomisation and endpoint when compliance not considered, but not met when compliance considered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "each infant was randomized to receive 10, 30, or 40 g vitamin D3 supplementation daily for 10 wk" Quote: "infants were randomized into three groups stratified by gender and received vitamin D3 10 g (400 IU), 30 g (1200 IU), or 40 g (1600 IU) daily from age 2 weeks to 3 months in a double-blinded fashion" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Unclear risk	Quote: "the Helsinki University Central Hospital Pharmacy prepared the appropriate concentrations (10, 30, and 40 g/ml) and carried out randomization after stratification by gender" Judgement comment: appropriate allocation concealment by a third party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the study was double-blinded; personnel responsible for the subjects' assessments remained blinded to the child's intervention group throughout the study" Judgement comment: personnel were blinded, but blinding of participants was not specified, although double-blinding would indicate that participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the study was double-blinded; personnel responsible for the subjects' assessments remained blinded to the child's intervention group throughout the study" Judgement comment: outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "this study included 113 children; in 93 subjects (82%), compliance with the study vitamin D3 preparation" Quote: "we conducted an intention-to-treat analysis, regardless of compliance" Judgement comment: low loss to follow-up; intention-to-treat analysis performed
Selective reporting (reporting bias)	Low risk	Quote: "our aim was to evaluate the effect of a higher than currently recommended dose of vitamin D supplementation to determine a daily dose ensuring S-25-OHD concentration at or above 80 nmol/liter in infants, without ensuing signs of vitamin D excess"

Holmlund-Suila 2012 *(Continued)*

		Quote: "study protocol was approved by the Finnish Medicines Agency (EudraCT 2009-015940-40) and Children's Hospital, Helsinki University Central Hospital" Judgement comment: study was registered at European Union Clinical Trial Registry (ID: EUDRA2009-015940-40), as well as at ClinicalTrials.gov (ID: NCT01723852), as reported in text. Prespecified outcomes reported
Other bias	Low risk	Judgement comment: no other risks observed

Holst-Gemeiner 1978

Study characteristics	
Methods	**Study design:** quasi-randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Germany **Study period:** January to March 1976
Participants	**Included criteria:** newborns born at Gottfriend von Preyer Children's Hospital in January, February, and March of 1976 **Excluded criteria:** none specified **Baseline vitamin D status**: not reported
Interventions	**Intervention characteristics** 1200 IU D_3 1. *Vitamin D content and type*: 1200 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 8 days 5. *N per group (in analysis)*: 10 6. *Brand/company*: Hoffmann-La Roche, Basel, Switzerland 200,000 IU D_3 1. *Vitamin D content and type*: 200,000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: once 4. *Duration of administration (study time)*: 1 day 5. *N per group (in analysis)*: 11 6. *Brand/company*: Hoffmann-La Roche, Basel, Switzerland
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): radioimmunological method

Holst-Gemeiner 1978 *(Continued)*

	Time points: 2nd to 10th week of life, 4th to 6th week of life
Notes	This study was translated from German; no sample size calculation; may be underpowered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "10 of the children received a daily pro from the 2nd to the 10th day of life phylaxis of 1200 1. E. = 0.03 mg of a gly neutral alcoholic solution of vitamin D3 per os, the remaining 11 got one 200,000 I. E. = 5 mg of vitamin D3 per tablet" Quote: "the studies were performed in 21 consecutive newborns" Judgement comment: sequence appears to be based on date of presentation; possibly convenient or alternating randomisation; considered at high risk of selection bias
Allocation concealment (selection bias)	High risk	Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. However, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: no loss to follow-up described
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registry or protocol available; outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Huynh 2017

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** non-profit + provision of drug. Women's and Children's Division Sunshine Hospital, St Albans, Australia, for provision of trial medications and pharmacy costs. Australian Institute for MusculoSkeletal Science, Sunshine Hospital, St Albans, Australia, funded the publication and conference costs related to this study. Bayer Health donated Infant-Pentavite in kind **Country:** Australia **Study period:** August 2013 to May 2014

Huynh 2017 *(Continued)*

Participants	**Included criteria:** born at 37 to 42 weeks' gestation, singleton pregnancy, birth weight appropriate for gestational age according to standardised Centers for Disease Control growth charts **Excluded criteria:** illicit drug use during pregnancy; infants requiring resuscitation for more than 10 minutes at birth; preexisting maternal conditions such as type 1 and type 2 diabetes mellitus, parathyroid disease, uncontrolled thyroid disease, and systemic glucocorticoid/anti-inflammatory or cytotoxicity; major congenital anomalies and subcutaneous fat necrosis in the newborn **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (400 IU D_3): 32.0 ± 13.6 2. Intervention group (50,000 IU D_3): 33.0 ± 19.3
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 months 5. *Other micronutrient content*: "multivitamin containing vitamin D" (quote) 6. *N per group (in analysis)*: 22 7. *Brand/company*: Pentavite Infant (Bayer Consumer Care, Sydney, New South Wales, Australia) 50,000 IU D_3 1. *Vitamin D content and type*: 50,000 IU D_3 2. *Formulation*: powder dissolved in olive oil drops 3. *Frequency of dosage*: once 4. *Duration of administration (study time)*: 4 months 5. *Other micronutrient content*: none 6. *N per group (in analysis)*: 26 7. *Brand/company*: Professional Compounding Centers of America (PCCA), Houston, TX, USA; Advanced Pharmaceuticals, West Perth, Western Australia
Outcomes	**Primary** 1. Linear growth 2. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D > 50 nmol/L 3. Rickets **Measurement** 1. Length (cm): equipment not reported 2. Hypercalcaemia (serum calcium: Beckman Coulter) a. Definition: > 2.88 mmol/L 3. Serum 25(OH)D (nmol/L): liquid chromatography/tandem mass spectrometry (LC-MS; Shimadzu Nexera ultra high performance liquid chromatography (HPLC) solvent delivery unit (Model LC30AD) (Canby, OR, USA) connected to AbSciex5500 tandem mass spectrometry quadrupole linear ion trap spectrometers (QTRAP System) (Foster City, CA, USA) 4. Rickets: craniotabes, wide fontanelles, rachitic rosary, widened epiphyses or limb deformities **Time points:** birth; 1 and 2 weeks of age

Huynh 2017 *(Continued)*

Notes	Study was underpowered at 3- to 4-month follow-up. Adherence was 31%; therefore this sample size calculation was not performed for a large enough sample size

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation (in random blocks of 2, 4 and 6) was undertaken in a blinded manner. Babies of eligible mothers were randomised at birth using a computer-generated schedule" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "the allocated treatment arm was kept inside opaque, sealed envelopes, which were numbered sequentially and opened, in numerical order by the study recruiters" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "we conducted a single centre, open-label randomised clinical trial" Judgement comment: not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "statistical analyses were undertaken by the trial statistician who was blinded to treatment allocation" Judgement comment: not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "all predetermined analyses were performed according to intention to treat principle" Judgement comment: moderate loss to follow-up at 3 to 4 months, with loss to follow-up reasons given, including patient transport difficulties, did not attend, switched treatment, declined blood tests, loss to follow-up (not contactable/untraceable), foetal arrhythmia, decision to formula-feed (not related to outcome) etc. All analysis was done by intention-to-treat
Selective reporting (reporting bias)	Low risk	Quote: "the full trial protocol can be accessed from the Western Health Centre for Research and Education, Sunshine Hospital, St Albans, Australia" Judgement comment: study was registered at Australian and New Zealand Clinical Trial Registry (ID: ACTRN12613001234707), as reported in text; full protocol may be accessed
Other bias	Low risk	Judgement comment: no other risks observed

Jensen 2016

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. MEJ is supported by Canadian Institute of Health Research/Canadian LungAssociation/GlaxoSmithKline Post-doctoral Fellowship (XCL-120981). Funding for the trial was provid-

Jensen 2016 *(Continued)*

	ed by a Thrasher Research Fund Early Career Award. The Sainte-Justine Research Centre is supported by Fond de recherche Santé Québec **Country:** Canada **Study period:** November 2013 to February 2014
Participants	**Included criteria:** children age 1 to 5 years with (1) physician-diagnosed asthma, based on clinical signs of airflow obstruction and reversibility; (2) upper respiratory tract infection (URTI) as the main exacerbation trigger, as reported by parents; (3) ≥ 4 parent-reported URTIs in the past 12 months; and (4) ≥ 1 exacerbation requiring oral corticosteroids in the past 6 months or ≥ 2 in the past 12 months **Excluded criteria:** extreme prematurity (28 weeks' gestation); high risk of vitamin D deficiency; other chronic respiratory disease; disordered calcium or vitamin D metabolism; oral medications interfering with vitamin D metabolism; vitamin D supplementation > 1000 IU/d in the past 3 months **Baseline vitamin D status (mean (interquartile range); nmol/L)** 1. Placebo + 400 IU D_3: 68.0 (50.0 to 75.0) 2. 100,000 IU D_3: 62.0 (50.0 to 75.0)
Interventions	**Intervention characteristics** 100,000 + 400 IU D_3 1. *Vitamin D content and type*: 100,000 IU + 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: once + daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 11 6. *Brand/company*: Pediavit D400 (Euro-Pharm International Canada, Montreal, QC, Canada) Placebo + 400 IU D_3 1. *Vitamin D content and type*: placebo + 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: once + daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 11 6. *Brand/company*: Pediavit D400 (Euro-Pharm International Canada, Montreal, QC, Canada)
Outcomes	**Primary** 1. Adverse effect: hypercalciuria **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) a. **Notes:** data from Additional File 3 (Jensen 2016) 2. Serum 25(OH)D ≥ 75 nmol/L **Measurement** 1. Hypercalciuria (urinary calcium-to-creatinine ratio), assay not reported a. Definition: > 1.25 mmol/mmol (1 to 2 years of age) and > 1.00 mmol/mmol (2 to 5 years of age) 2. Serum 25(OH)D (nmol/L): tandem mass spectrometry **Time points:** enrolment, 10 days, 3 months, 6 months

Jensen 2016 *(Continued)*

Notes	Sample size was calculated but was not met due to trial termination before sample size target was reached. Study was underpowered for the primary outcome

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using computer-generated randomisation with variable block sizes of 2–4, participants were randomised 1:1 to the intervention or control group. Group assignment, recorded on a sequentially numbered list, was allocated by the Sainte-Justine Hospital Research Pharmacy, which held the randomisation code" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "or identical placebo" Quote: "group assignment, recorded on a sequentially numbered list, was allocated by the Sainte-Justine Hospital Research Pharmacy, which held the randomisation code. To maintain blinding, the intervention and placebo dose were identical in colour, appearance, volume, taste, and packaging" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "all research personnel, physicians, nurses, participants and their parents were blinded to group allocation" Judgement comment: all personnel and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: all personnel and participants were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "twenty-two children were randomised to the intervention (N = 11) or control group (N = 11) (Additional file 2). The trial was terminated before reaching the target sample size, as funding was received to commence the larger definitive trial. Retention in the intervention versus control group was 91% vs. 100% at 3 months, and 73% vs. 91% at 6 months" Judgement comment: from supplementary data, each arm has similar numbers of patients lost to follow-up; no reasons given for loss to follow-up, no explanation of characteristics of patients lost to follow-up. Trial was terminated early due to receipt of more funding for larger study
Selective reporting (reporting bias)	Low risk	Judgement comment: study was prospectively registered at ClinicalTrials.gov (ID: NCT01999907), as reported in text. No protocol was identified
Other bias	Low risk	Judgement comment: no other risks observed

Kislal 2008

Study characteristics

Methods	**Study design:** quasi-randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed

Kislal 2008 *(Continued)*

	Country: Turkey **Study period:** not reported
Participants	**Included criteria:** gestational age 33 weeks, appropriate weight for gestational age **Excluded criteria:** congenital malformations, failure to supplement vitamin D according to protocol **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 200 IU 1. *Vitamin D content and type*: 200 IU/kg body weight 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 15 days 5. *N per group (in analysis)*: 11 6. *Brand/company*: not reported 400 IU 1. *Vitamin D content and type*: 400 IU/kg body weight 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 15 days 5. *N per group (in analysis)*: 15 6. *Brand/company*: not reported 800 IU 1. *Vitamin D content and type*: 800 IU/kg body weight 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 15 days 5. *N per group (in analysis)*: 11 6. *Brand/company*: not reported
Outcomes	None within scope of review
Notes	No sample size calculation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "preterm infants were randomly selected either to receive a vitamin D supplement of 200 IU/kg (group 1, 11 infants) or 400 IU/kg (group 2, 15 infants) or 800 IU/kg" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias)	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know

Kislal 2008 *(Continued)*

All outcomes		the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described; however, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "forty-eight preterm infants were enrolled in the study. ...Thirty-seven infants completed the study" Judgement comment: no reasons given for loss to follow-up and no intention-to-treat analysis performed
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registry or protocol published; all outcomes measured and specified in methods and results
Other bias	Low risk	Judgement comment: no other risks observed

Lagomarsino 1996

Study characteristics	
Methods	**Study design:** quasi-randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Direccion de Investigaciones Universidad Catolica (DIUC 09/84) **Country:** Chile **Study period:** not reported
Participants	**Included criteria:** birth in ambulatory paediatric unit at Diagnostic Centre of the Pontificia Universidad Catolica, in Santiago de Chile (CEDIUC); born at term, with weight appropriate for gestational age; without neonatal conditions; receiving breast milk or formula of known composition and quantity; not taking vitamins other than vitamin D given by the study team **Excluded criteria:** none specified **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 600,000 IU D_3 1. *Vitamin D content and type*: 600,000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: at 1 and 6 months of age 4. *Duration of administration (study time)*: 5 months 5. *N per group (in analysis)*: 35 6. *Brand/company:* Laboratorio Chile 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 5.5 months

Lagomarsino 1996 *(Continued)*

5. *N per group (in analysis)*: 43
6. *Brand/company:* Laboratorio Chile

Outcomes	**Primary** 1. Linear growth **Measurement** 1. Length (cm): equipment not reported a. **Notes:** data from Figure 1 (Lagomarsino 1996). Data not included in meta-analysis due to reported values only in mean without variance **Time points:** various throughout 6-month follow-up
Notes	This study was translated from Spanish to English. No sample size calculation was performed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "the participants were assigned by order of admission to alternating programs: one group 1 of 35 children, received 600 000 IU of Vitamin D, at 1 and 6 months of age; group 2 of 43 children, received 400 IU of Vitamin D per day (20 drops) from the 15th day until 6 months of life" Judgement comment: alternating randomisation based on order of admission
Allocation concealment (selection bias)	High risk	Quote: "in the children from group 1, the solution of Vitamin D was for oral usage packaged in 1 mL ampoules by the Laboratorio Chile, contained 15 mg of vit D, or cholecalciferol, equivalent to 600 000 IU. Since there were no commercially available drops that contained exclusively Vitamin D, the aforementioned laboratory made specially for this study a preparation that in 20 drops contained 400 IU of vitamin D3 for the children in group 2" Judgement comment: sequence generation was at high risk of bias. Allocation concealment was not described, but given different regimens for each group, concealment seems unlikely
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. However, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: children lost to follow-up (reasons, etc.) not discussed; appears to show a complete case analysis
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registry or protocol available; outcomes in methods reported in results
Other bias	Low risk	Judgement comment: no other risks observed

Lava 2011

Study characteristics	
Methods	**Study design:** cross-over trial **Study grouping:** parallel group **Funding:** no funding **Country:** Switzerland **Study period:** 1 March to 30 April 2010
Participants	**Included criteria:** Swiss singleton, newborn infants with gestational age of 36 weeks or more and neonatal body weight of 2 kg or more; not previously exposed to vitamin D **Excluded criteria:** not specified **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** Vi-De$_3$ 1. *Vitamin D content and type*: 2.5 µg D_3 2. *Formulation*: drops ("alcoholic vitamin D_3", dissolved in 65% ethanol (113 µg/mL corresponding to 2.5 µg per drop)) 3. *Frequency of dosage*: once 4. *Duration of administration (study time)*: 5- to 10-minute session 5. *N per group (in analysis)*: 42 6. *Brand/company*: Wild AG, Basel, Switzerland Vitamin D_3 Wild 1. *Vitamin D content and type*: 12.5 µg D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 5- to 10-minute session 5. *N per group (in analysis)*: 42 6. *Brand/company*: Wild AG, Basel, Switzerland
Outcomes	None within scope of review
Notes	Target sample size described and met but not calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "an independent statistician had generated a randomization list to balance the order of presentation of the preparations so that each preparation was tasted first an equal number of times" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Low risk	Quote: "42 sequentially numbered, opaque sealed envelopes containing the assignment. The envelopes were opened in sequence after accompanying the infant with the mother to the test area"

Lava 2011 *(Continued)*

		Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single-blind" Judgement comment: only participants were blinded; if investigators know the intervention allocations, may be biased toward a particular outcome, increasing the risk of bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: outcome assessors were not blinded; however, no outcomes were within the scope of this review
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: no loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no protocol or trial registration found; outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed&&

Manaseki Holland 2010

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. New Zealand Aid Cooperation **Country:** Afghanistan **Study period:** February to May 2007
Participants	**Included criteria:** all children between 1 week and 3 years of age in the socio-economically deprived population of Kabul, diagnosed clinically with pneumonia, defined as (1) age-specific tachypnoea (> 60/min if < 2 months; > 50/min if 2 to 11 months; > 40 if 12 to 24 months) and (2) absence of wheeze (with or without fever) **Excluded criteria:** clinical signs of rickets, known to have received high-dose vitamin D treatment in the past 3 months, severe vomiting, pronounced wheeze, very severe pneumonias, other severe illness (meningitis, heart or renal disorder, measles, severe malnutrition, suspected tuberculosis), likely to migrate out of study area within 3 months **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 100,000 IU D_3 1. *Vitamin D content and type*: 100,000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: once, at enrolment 4. *Duration of administration (study time)*: 90 days 5. *N per group (in analysis)*: 211 6. *Brand/company*: Sinochem Ningbo Laboratory, Ningbo, China

Manaseki Holland 2010 *(Continued)*

	Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: once, at enrolment 4. *Duration of administration (study time)*: 90 days 5. *N per group (in analysis)*: 218 6. *Brand/company*: Sinochem Ningbo Laboratory, Ningbo, China
Outcomes	None within scope of review
Notes	Sample size calculated and met

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the children were individually randomised into intervention or placebo groups using a random number sequence generated in an Excel spreadsheet with no restrictions" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "vitamin D was contained in 1 ml of olive oil and individually packaged into sealed 2-mL plastic syringes at Aga Khan University and labelled with unique ID number (only office was aware of the randomization codes). Placebo (olive oil alone) and vitamin D syringes looked the same and tasted the same" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind... On random questioning of parents, there were no indications at any stage that families or doctors knew which child may have received placebo or vitamin" Judgement comment: all personnel and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind... On random questioning of parents, there were no indications at any stage that families or doctors knew which child may have received placebo or vitamin" Judgement comment: outcome assessors were blinded; however, no outcomes were within the scope of this review
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "all children randomized were included in the analysis on an Intention-to-treat analysis" Judgement comment: minimal loss to follow-up, due for the most part to recovery from pneumonia within the 24-hour period after enrolment; intent-to-treat analysis performed
Selective reporting (reporting bias)	Low risk	Judgement comment: study was registered prospectively at ClinicalTrials.gov (ID: NCT00548379), which we identified through further searching; prespecified outcomes are consistent with those reported. Study protocol was not identified
Other bias	Low risk	Judgement comment: no other risks observed

Manaseki-Holland 2012

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Wellcome Trust and British Council **Country:** Afghanistan **Study period:** 4 November 2008 to August 2009
Participants	**Included criteria:** infants age 1 to 11 months and living in the study region (catchment area of Mai-wand Teaching Hospital, inner city Kabul) **Excluded criteria:** families expecting to move to another town within 18 months, diagnosis of rickets or treatment with vitamin D in previous 3 months, clinical diagnosis of Kwashiorkor or Marasmus **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 100,000 IU D_3 1. *Vitamin D content and type*: 100,000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: every 3 months 4. *Duration of administration (study time)*: 18 months 5. *N per group (in analysis)*: 1524 6. *Brand/company*: Department of Pharmacy, Aga Khan University Hospital, Karachi; olive oil (Sinochem Ningbo Laboratory, Ningbo, China) Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: every 3 months 4. *Duration of administration (study time)*: 18 months 5. *N per group (in analysis)*: 1522 6. *Brand/company*: Department of Pharmacy, Aga Khan University Hospital, Karachi; olive oil (Sinochem Ningbo Laboratory, Ningbo, China)
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D < 50 nmol/L **Measurement** 1. Serum 25(OH)D (nmol/L): ImmunoDiagnosticSystems-iSYS Multi-Discipline Automated Chemiluminescent assay (Immunodiagnostic Systems Ltd., Tyne and Wear, United Kingdom) **Time points:** various across 18-month follow-up
Notes	Sample size calculated and met

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

Manaseki-Holland 2012 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "an independent statistician (Shabbar Jaff ar, London School of Hygiene and Tropical Medicine, London, UK) randomised unique identification numbers individually in fixed blocks of 20 to the vitamin D_3 or placebo group by use of a random number generator with the SAS routine" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "by use of the randomisation list, a pharmacist in the Department of Pharmacy, Aga Khan University Hospital, Karachi prepared 100 000 IU (2.5 mg) of vitamin D_3 (cholecalciferol) in olive oil (Sinochem Ningbo Laboratory, China) or placebo (olive oil) in sealed 2 mL plastic syringes labelled with the unique identification numbers. The vitamin D 3 and the placebo were the same colour (pale yellow), taste, and quantity (0.5 mL) and therefore the study staff and the families did not know to which group the children were assigned. Fieldworkers allocated children to randomisation groups during recruitment and gave vitamin D or placebo" Judgement comment: appropriate allocation concealment by a third party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the study staff and the families did not know to which group the children were assigned. Fieldworkers allocated children to randomisation groups during recruitment and gave vitamin D or placebo" Judgement comment: participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "many children lost at one time because of travel rejoined the study later with rates being similar between the two groups (figure 1). There was no statistically significant difference in any of the baseline characteristics between the groups (table 1), including reported sun exposure" Quote: "by the end of our trial 2616 of the 3046 recruited children were present in our study and 17 had died" Judgement comment: reasons for low loss to follow-up were not given (other than death); children who dropped out rejoined the study in some cases. Intention-to-treat analysis was performed and was compared with per-protocol analysis
Selective reporting (reporting bias)	Low risk	Judgement comment: trial was registered prospectively on ClinicalTrials.gov (ID: NCT00548379), as reported in text. Prespecified outcomes are consistent with those reported
Other bias	Low risk	Judgement comment: no other risks observed

Marchisio 2013

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group

Marchisio 2013 *(Continued)*

	Funding: 100% non-profit. Grant (Ricerca Corrente 2012 850/02) from Italian Ministry of Health to Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ca' Granda Ospedale Maggiore Policlinico **Country:** Italy **Study period:** 1 November 2011 to 31 May 2012
Participants	**Included criteria:** children age 1 to 5 years with history of recurrent acute otitis media (AOM) (defined as ≥ 3 episodes in preceding 6 months or ≥ 4 episodes in preceding 12 months, with most recent episode in the previous 2 to 8 weeks), who were regularly followed by the outpatient section of Pediatric Clinic 1, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Italy. The minimum number of episodes of AOM for inclusion of patients in the otitis-prone group had to be diagnosed by pneumatic otoscopy in the outpatient section of Pediatric Clinic 1 by trained investigators included among the authors of the study and documented by medical records, with ≥ 2 episodes supported also by tympanometric findings. At the time of enrolment, children had to be free of AOM but could be affected by otitis media with effusion **Excluded criteria:** factors that can favour development of AOM, including severe atopy, acquired or congenital immunodeficiency, cleft palate, chronically ruptured eardrum, craniofacial abnormalities or obstructive adenoids, sleep apnoea syndrome, or placement of tympanostomy tubes **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (placebo): 64.4 ± 64.7 2. Intervention group (1000 IU D_3): 63.4 ± 65.9
Interventions	**Intervention characteristics** 1000 IU D_3 1. *Vitamin D content and type*: 1000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 months 5. *N per group (in analysis)*: 58 6. *Brand/company*: Pédiatre, Vitamin D3, Pediatrica, Livorno, Italy Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 months 5. *N per group (in analysis)*: 58 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Change in 25(OH)D 3. Serum 25(OH)D ≥ 75 nmol/L **Measurement** 1. Serum 25(OH)D (nmol/L): DiaSorin quantitative chemiluminescence immunoassay (LIAISON 25 OH Vitamin D Total Assay; DiaSorin, San Francisco, CA, USA) **Time point:** 4 months

Marchisio 2013 *(Continued)*

Notes	No sample size calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a random number generator was then used to randomize the enrolled children to receive oral vitamin D 1000 IU/d (10 drops of Pédiatre, Vitamin D 3, Pediatrica, Livorno, Italy) or placebo for 4 months" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "similarly, the physicians involved in clinical monitoring were blinded to the treatment assignment. The parents were given 4 numbered bottles, each of which contained a number of drops needed for 1 month's treatment" Quote: "the study was blinded by labeling the identical bottles of VD and placebo drops and only revealing the randomization codes to the staff at the data monitoring center, who had no contact with the patients; similarly, the physicians involved in clinical monitoring were blinded to the treatment assignment" Judgement comment: appropriate allocation concealment by a third party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "this prospective, randomised, double-blind and placebo-controlled study" Judgement comment: double-blind implies that participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "physicians involved in clinical monitoring were blinded to the treatment assignment" Judgement comment: double-blind implies that outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "the study involved 116 children (64 males, 55.2%; mean age 33.7 ± 11.7 months) with a history of (recurrent acute otitis media): 58 received placebo and 58 VD" Judgement comment: loss to follow-up not described; appears no loss to follow-up occurred
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registry or protocol identified; all outcomes in methods described in results
Other bias	Low risk	Judgement comment: no other risks observed

Mathur 2016

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed

Mathur 2016 *(Continued)*

	Country: India **Study period:** April to December 2013
Participants	**Included criteria:** very low birth weight (1500 g) neonates who were born preterm (37 weeks) **Excluded criteria:** major congenital malformation, not tolerating at least 100 mL/kg/d enteral feeds by day 10 of life **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (400 IU D_3): 29.2 ± 23.7 2. Intervention group (1000 IU D_3): 33.9 ± 26.2
Interventions	**Intervention characteristics** 400 IU 1. *Vitamin D content and type*: 400 IU vitamin D 2. *Formulation*: enteral 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 weeks 5. *Other micronutrient content*: 100 mg calcium + 44 mg phosphate + Vi-syneral drops (20 µg biotin + 3 mg D-panthenol + 10 mg niacinamide + 2 mg vitamin A + 2 mg vitamin B1 + 1 mg vitamin B2 + 1 mg vitamin B6 + 40 mg vitamin C + 200 IU vitamin D_2 + 1.5 mg vitamin E) 6. *N per group (in analysis)*: 25 7. *Brand/company*: Syrup Ossopan D (TTK Healthcare, Chennai, India) 1000 IU 1. *Vitamin D content and type*: 1000 IU vitamin D 2. *Formulation*: enteral 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 weeks 5. *Other micronutrient content*: 100 mg calcium + 44 mg phosphate + Vi-syneral drops (20 µg biotin + 3 mg D-panthenol + 10 mg niacinamide + 2 mg vitamin A + 2 mg vitamin B1 + 1 mg vitamin B2 + 1 mg vitamin B6 + 40 mg vitamin C + 200 IU vitamin D_2 + 1.5 mg vitamin E) 6. *N per group (in analysis)*: 25 7. *Brand/company*: Syrup Ossopan D (TTK Healthcare, Chennai, India) + Arbivit drops (Raptakos, Mumbai, India)
Outcomes	**Secondary** 1. Linear growth: gain in length 2. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Length (cm): infantometer 2. Serum 25(OH)D (nmol/L): electrochemiluminescence, Cobase analyser kit in Elecsys 2010 auto analyser (Roche Diagnostics, Basel, Switzerland) **Time point:** 6 weeks
Notes	Sample size calculated and met

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Mathur 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "eligible neonates were randomized using a computer-generated random number sequence" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "concealed using sealed opaque envelopes on the day 100 ml/kg enteral feeds were tolerated" Judgement comment: appropriate allocation concealment; sequential numbering not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, double-blinded controlled trial in a teaching hospital" Judgement comment: participants were likely blinded due to sealed envelopes; however personnel blinding was not specified although implied
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the radiologist and biochemist were blinded to the group allocation and intervention given" Judgement comment: radiologist and biochemist were blinded; outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: Figure 1 implies that there was no loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Quote: "Clinical Trial Registry of India (No. 2013/04/004953)" Judgement comment: study was registered retrospectively with Clinical Trial Registry of India (CTRI, ctri.nic.in) (ID: CTRI/2018/02/012058), which we found through additional searching. A different ID number was referenced in the text; however the quoted ID was not found when the CTRI database was searched
Other bias	Low risk	Judgement comment: no other risks observed

Mittal 2014

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Indian Council of Medical Research, New Delhi, India; University College of Medical College, Delhi, India **Country:** India **Study period:** November 2010 to April 2012
Participants	**Included criteria:** age 6 months to 5 years presenting to paediatric outpatient or emergency department with combination of clinical evidence of rickets (wide wrists, bow legs, frontal bossing, rachitic rosary, etc.) and radiological findings (fraying, splaying, and cupping at epiphyseal ends of long bones in wrist/knee) consistent with diagnosis of nutritional rickets **Excluded criteria:** critically ill children; those with coexisting fat malabsorption, liver or renal insufficiency, and hypercalcaemia; those with history of having received vitamin D, calcium supplements, or other medications affecting vitamin D metabolism (e.g. anticonvulsants, steroids, cancer chemotherapy) in previous 6 months

Mittal 2014 *(Continued)*

	Baseline vitamin D status (mean (95% confidence interval); nmol/L) 1. Control group (300,000 IU D_3): 18.9 (13.7 to 26.1) 2. Intervention group (600,000 IU D_3): 16.4 (11.6 to 23.1)
Interventions	**Intervention characteristics** 300,000 IU D_3 1. *Vitamin D content and type*: 300,000 IU D_3 2. *Formulation*: dissolved in milk 3. *Frequency of dosage*: once 4. *Duration of administration (study time)*: 12 weeks 5. *N per group (in analysis)*: 32 6. *Brand/company*: Mankind Pharma Limited, Delhi, India 600,000 IU D_3 1. *Vitamin D content and type*: 600,000 IU D_3 2. *Formulation*: dissolved in milk 3. *Frequency of dosage*: once 4. *Duration of administration (study time)*: 12 weeks 5. *N per group (in analysis)*: 28 6. *Brand/company*: Mankind Pharma Limited, Delhi, India
Outcomes	**Primary** 1. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D < 50 nmol/L a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis 3. Change in 25(OH)D 4. Rickets **Measurement** 1. Hypercalcaemia (serum calcium): assay not reported a. Definition: > 10.8 mmol/L 2. Serum 25(OH)D (nmol/L): radioimmunoassay, commercial kits with gamma counter (DiaSorin Inc., San Francisco, CA, USA) a. **Notes:** data presented as mean (95% CI), which we converted to standard deviation 3. Rickets: radiological score **Time points:** enrolment, 12 weeks
Notes	Sample size calculated, met at randomisation but not at final follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomization was done by block randomization (18 blocks of 4 each and 2 blocks of 2 participants each) to 300,000 IU or 600,000 IU of oral vitamin D3 in a single day" Judgement comment: random sequence generation method not described

Mittal 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "allocation concealment was done by sealed envelope technique" Judgement comment: appropriate allocation concealment (sealed envelopes) but unclear if sequentially numbered or how they were opened
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "design: randomized, open-labeled, controlled trial" Judgement comment: not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "of the 76 children enrolled..." Judgement comment: high loss to follow-up in Group 2 particularly, reasons reported (Figure 1). At randomisation, n = 28/600,000 IU arm and n = 32/300,000 IU arm. Reasons for loss to follow-up before 4 weeks were mostly equal across groups, including (1) did not come in for follow-up and could not be contacted; (2) systemic illness; (3) discontinuation of treatment. Reasons for loss to follow-up before 12 weeks were noted only in the 600,000 IU arm and were (1) and (3); blood samples were not analysable - relation to outcome is possible. Analysis was intention-to-treat but appears to analyse those who adhered to study protocol only
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified; outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Mittal 2018

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** no funding **Country:** India **Study period:** 19 December 2014 to unknown end date
Participants	**Included criteria:** children age 6 months to 5 years with radiological rickets (Thacher score > 1.5) **Excluded criteria:** any participant already diagnosed with any disease affecting absorption, or taking oral steroids, antitubercular, or antiepileptic drugs; patients who had taken calcium or vitamin D supplementation in last 6 months **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (90,000 IU): 14.4 ± 25.2 2. Intervention group (300,000 IU): 23 ± 49.2
Interventions	**Intervention characteristics** 90,000 IU

Mittal 2018 *(Continued)*

1. *Vitamin D content and type*: 900,00 IU vitamin D
2. *Formulation*: tablets, dissolved in milk
3. *Frequency of dosage*: once
4. *Duration of administration (study time)*: 12 weeks
5. *Other micronutrient content*: calcium: 50 mg/kg/d
6. *N per group (in analysis)*: 55
7. *Brand/company*: not reported

300,000 IU

1. *Vitamin D content and type*: 300,000 IU vitamin D
2. *Formulation*: Tablets, dissolved in milk
3. *Frequency of dosage*: once
4. *Duration of administration (study time)*: 12 weeks
5. *Other micronutrient content*: calcium: 50 mg/kg/d
6. *N per group (in analysis)*: 55
7. *Brand/company*: not reported

Outcomes	**Primary** 1. Adverse effect: hypercalcuria 2. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D ≥ 50 nmol/L 3. Rickets **Measurement** 1. Hypercalciuria (urinary calcium/creatinine (mmol/mmol) ratio): assay not reported a. Definition: > 1.25 mmol/mmol (1- to 2-year-olds) or > 1 mmol/mmol (2- to 5-year-olds) 2. Hypercalcaemia (serum calcium): DiaSorin Autoanalyzer (Stillwater, MN, USA) a. Definiton: > 10.8 mmol/L 3. Serum 25(OH)D (nmol/L): chemiluminescence, DiaSorin auto analyser (LIASON, DiaSorin, Inc., Stillwater, MN, USA) 4. Rickets: radiographic scores **Time points:** enrolment; 1, 4, 12 weeks
Notes	Sample size calculated and appropriate at randomisation but not met by first follow-up visit

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was done on the basis of 1:1 subjects in both the groups (random table generated from www.randomization.com)" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "patients were allocated to one of two treatment arms according to web-generated sequence using block randomization (block sizes of 10, 8, and 4). The sequence was transcribed to sequentially numbered opaque sealed envelopes by a person not directly involved in the study" Judgement comment: appropriate allocation concealment

Mittal 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Participants likely unblinded, as 1 group required half tablet and the other required full tablet. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: outcome assessors were blinded; radiological changes were scored by the same radiologist who was blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: equal loss to follow-up across groups (22%); reasons for loss to follow-up not given; intention-to-treat analysis not specified
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified; outcomes in methods and presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Moodley 2015

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. National Institutes of Health grants R21AI084573 and R01NS077874, Early Career Award from Thrasher Research Foundation **Country:** Mexico **Study period:** February 2011 to July 2012
Participants	**Included criteria:** healthy infants born to women age 18 years at Tijuana General Hospital, Mexico, were enrolled within 24 hours after birth and before routine tuberculosis vaccine administration **Excluded criteria:** preterm (37 weeks' gestation), low birth weight (2500 g), had received vitamin D supplementation **Baseline vitamin D status (mean (95% confidence interval); nmol/L)** 1. Control group (placebo): 50.2 (42.9 to 57.2) 2. Intervention group (50,000 IU D_3): 44.2 (37.7 to 50.9)
Interventions	**Intervention characteristics** 50,000 IU D_3 1. *Vitamin D content and type*: 50,000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: once 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 27 6. *Brand/company*: Carlson Laboratories Inc, Arlington Heights, IL, USA Placebo

Moodley 2015 *(Continued)*

1. *Vitamin D content and type*: none
2. *Formulation*: drops
3. *Frequency of dosage*: once
4. *Duration of administration (study time)*: 6 months
5. *N per group (in analysis)*: 22
6. *Brand/company*: not reported

Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): liquid chromatography tandem mass spectrometry a. **Notes:** data presented as mean (95% CI), which we converted to standard deviation **Time points:** birth, 2 and 6 months of age
Notes	No sample size calculation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "infants were then randomized to receive oral vitamin D_3 or placebo. None of the infants vomited or regurgitated the liquid in the 15 min after administration. A randomization list was generated in blocks of 10 using http://www.randomizer.org" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "a clear, tasteless liquid containing 2000 IU of vitamin D_3 (cholecalciferol) per drop was used (Carlson Laboratories Inc., Arlington Heights, IL). The study dose of 50 000 IU was dispensed in 0.7 ml of liquid vitamin D_3 solution. The placebo was a tasteless, colorless liquid that contained 0.7 ml of medium chain triglycerides. Vitamin D_3 and placebo were administered in prefilled and precoded syringes that were indistinguishable" Judgement comment: appropriate allocation concealment; unclear if treatments were packaged by a third party, of if they were sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "a single-center, double-blind, placebo controlled trial was conducted in 51 mother–infant pairs" Judgement comment: double-blind implies that both participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a single-center, double-blind, placebo controlled trial was conducted in 51 mother–infant pairs" Judgement comment: double-blind implies that study staff (i.e. outcome assessors) were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: Tables 3 and 4 indicate that there was loss to follow-up; reasons were not given; intention-to-treat analysis was not specified
Selective reporting (reporting bias)	Low risk	Judgement comment: trial registered prospectively on ClinicalTrials.gov (ID: NCT01288950), which we identified through separate searching. Outcomes

Moodley 2015 *(Continued)*

		specified in methods were presented in results and are consistent with trial registration
Other bias	Low risk	Judgement comment: no other risks observed

Morawa 1963

Study characteristics	
Methods	**Study design:** quasi-randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Germany **Study period:** October 1961 to July 1962
Participants	**Included criteria:** preterm, birth weight between 1500 and 2000 g **Excluded criteria:** none specified **Pretreatment:** all mothers had taken Vigantol menge (vitamin D supplement) in the first trimester **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 720,000 IU D_3 1. *Vitamin D content and type*: total = 720,000 IU irradiated ergosterin D_3 2. *Formulation*: intramuscular + tablet 3. *Frequency of dosage*: 3 mg Vigantol D_2 on day 3 of life (intramuscular); 5 mg D_3 at 4 weeks; 5 mg D_3 at 6 weeks, and 5 mg D_3 at 10 weeks 4. *Duration of administration (study time)*: third day of life to 3 months of age 5. *Other micronutrient content*: none 6. *N per group (in analysis)*: 15 7. *Company/brand*: Vigantol 8. **Note: arm not included in data synthesis** 720,000 IU D_3, CaP+ 1. *Vitamin D content and type*: total = 720,000 IU irradiated ergosterin D_3 2. *Formulation*: intramuscular + tablet 3. *Frequency of dosage*: 3 mg Vigantol D_2 on day 3 of life (intramuscular); 5 mg D_3 at 4 weeks; 5 mg D_3 at 6 weeks, and 5 mg D_3 at 10 weeks 4. *Duration of administration (study time)*: third day of life to 3 months of age 5. *Other micronutrient content*: 0.5 calcium phosphoric bibasicum daily until sixth week 6. *N per group (in analysis)*: 16 7. *Company/brand*: Vigantol 8. **Note: arm not included in data synthesis** 1000 IU D_3 1. *Vitamin D content and type*: total = 70,000 to 80,000 IU irradiated ergosterin D_3 2. *Formulation*: tablet

Morawa 1963 *(Continued)*

3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: eighth day of life to 3 months of age
5. *Other micronutrient content*: none
6. *N per group (in analysis)*: 16
7. *Company/brand*: Vigantol

750 to 1000 IU D_3

1. *Vitamin D content and type*: total = 70,000 to 80,000 IU irradiated ergosterin D_3
2. *Formulation*: tablet
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: eighth day of life to 3 months of age
5. *Other micronutrient content*: none
6. *N per group (in analysis)*: 17
7. *Company/brand*: Vigantol

Outcomes

Secondary

1. Rickets

Measurement

1. Rickets: craniotabes
   a. **Notes:** (+ = penny-sized, 1-sided softening; ++ = 5-piece craniotabes on both sides; +++ = craniotabes larger than a 5-mark piece on both sides)
2. Rickets: rachitic X-ray changes (number + type)

Time point: 3 months of age

Notes

We have not included the first 2 larger-dose groups listed (720,000 IU) because the dose was given intramuscularly or with calcium and therefore was not eligible for analysis. This study was translated from German. No sample size was calculated; appears to be a convenient sample

CaP+: includes calcium and phosphorus

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "the various methods of the Vit.D prophylaxis, which are compared in 4 different groups with each other, were performed strictly alternating in the above-mentioned observation time" Judgement comment: alternating randomisation
Allocation concealment (selection bias)	High risk	Quote: "b) Groups of rickets for the treatment of rickets 1st Group: 15 children On day 3 of life, they received 3 mg Vigantol aquat D3 IM. In addition, the children were given an oral shock of 5 mg D3 at the age of 4 weeks, an additional dose of 5 mg D3 at the age of 6 weeks and 5 mg D3 orally at the age of 10 weeks. 2nd group: 16 children The same procedure as in group 1. In addition to the daily intake of food, 0.5 g Calciumphosphoricum bibasicum was added to the diet daily until the 6th week, when mixed milk (half milk, half pelargon) was administered. From this point on there was no further mineral addition. 3rd group: 16 children The children were given 1 Vigantolette (1 tablet contains 1,000 I.U. Vit.D3) daily for 3 months from the 8th day of life. 4th group: 17 children The children were given limevigantol tablets starting from the 8th day of life, ie 1/2 tablet / kg weight (1 tabl. = 500 I.U. D3 + 0.5 g calcium phosphoricum bibasicum), ie 750 - 1000 I.U. daily, as long as 50% of the women's milk could be replaced by Pelargon, this was the case in the 6th week of life. Then transfer to 1 Vigantolette (1000 I.U. D3), daily until the 3rd month of life. The children of

Morawa 1963 *(Continued)*

		groups 1 - 2 received a total of 720,000 I.E. D3 in the form of small bumps within the first 3 months of life. The children of groups 3 and 4 received 70-80,000 I, E. D in protracted daily dose" Judgement comment: allocation concealment unlikely, as each group was dosed at different times. No description of how interventions were indistinguishable
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding of participants and personnel is unlikely because doses were given at different times. Because rickets symptoms were the main symptoms (soft fontanelles), they could have been assessed by parents who would give kids a higher dose if suspected that the dose was low. Outcomes were more subjective based on scoring craniotabes and X-rays, so were likely to be biased if personnel knew groupings
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: blinding of outcome assessors is not described - introduces detection bias. Outcomes were more subjective based on scoring craniotabes and X-rays, so likely to be biased if personnel knew groupings
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: no loss to follow-up indicated, as per Tables 6 and 7
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified. Primary outcomes were serum alkaline phosphatase, cases of craniotabes, number of rachitic X-ray changes; serum alkaline phosphatase could not be evaluated and reason is not clear; data on craniotabes results and rachitic X-ray changes were reported
Other bias	Low risk	Judgement comment: no other risks observed

Natarajan 2014

Study characteristics	
Methods	**Study design:** randomised-controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Study drug was procured through Indian Council of Medical Research grant 5/7/305/08-RHN **Country:** India **Study period:** August 2011 to March 2012
Participants	**Included criteria:** preterm infants born between 28 and 34 weeks' gestational age and receiving ≥ 100 mL/kg/d of enteral feedings by 2 weeks' postnatal age **Excluded criteria:** infants with major malformations, those who received parenteral nutrition for ≥ 2 weeks, those born to mothers receiving phenytoin therapy or with HIV infection **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (400 IU D3): 24.7 ± 12.0 2. Intervention group (800 IU D3): 30.7 ± 12.5
Interventions	**Intervention characteristics**

Natarajan 2014 *(Continued)*

	800 IU D_3 1. *Vitamin D content and type*: 800 IU D3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (in analysis)*: 42 6. *Brand/company*: Basic Human Health Care Private Ltd., Delhi, India 400 IU D_3 1. *Vitamin D content and type*: 400 IU D3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (in analysis)*: 45 6. *Brand/company*: Basic Human Health Care Private Ltd., Delhi, India
Outcomes	**Primary** 1. Linear growth 2. Adverse effect: hypercalciuria 3. Adverse effect: hypercalcaemia 4. Adverse effect: kidney stones **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D < 50 nmol/L a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis **Measurement** 1. Length (cm): not reported 2. Hypercalciuria (urinary calcium-to-creatinine ratio): Beckman Coulter assay a. Definition: > 0.8 mg/mg 3. Hypercalcaemia (serum calcium): colorimetric method using a Beckman Coulter Synchron-CX9 PRO clinical system (Beckman Coulter, Inc., Pasadena, CA, USA) a. Definition: not reported 4. Kidney stones: method not reported a. **Notes:** no events in either arm; data did not contribute to meta-analysis 5. Serum 25(OH)D (nmol/L): chemiluminescence, autoanalyzer (DiaSorin Liaison, Stillwater, MN, USA) **Time points:** enrolment, 40 weeks' postmenstrual age, 3 months' corrected age
Notes	Sample size calculated and met at randomisation and analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "infants in both strata were randomly assigned to receive oral vitamin D3 at a dose of 800 or 400 IU/day. We used computer-generated random numbers to allocate infants to 1 of the study groups with a fixed block size of 4" Judgement comment: appropriate sequence generation method

Natarajan 2014 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "random allocation was concealed by assigning sequential numbers to identical-appearing bottles containing 2 different amber-colored, identical appearing drug suspensions" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "amber-colored bottles containing identical-appearing drug suspensions ensured blinding of investigator and parents" Judgement comment: participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: double-blind implies blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "we enrolled 96 infants in the study (Fig 1). Clinical and baseline characteristics of the study population were comparable between the 2 groups (Table 1). Study intervention was initiated in 94 infants because consent was withdrawn by 2parentssoonafter randomization.Of these 94 infants, 3 infants died before follow-up at 40 weeks (1 due to stage 3 necrotizing enterocolitis and 2 due to probable milk aspiration); another 4 infants were lost to follow-up. Thus, a total of 87..." Quote: "analysis was performed by intention to treat" Judgement comment: low loss to follow-up overall; reasons documented. Reasons for loss to follow-up included death and loss to follow-up not described. Balanced among groups. Intention-to-treat analysis but seems to include only those finishing follow-up; possible attrition bias
Selective reporting (reporting bias)	Unclear risk	Judgement comment: study was registered retrospectively with Clinical Trial Registry of India (CTRI, ctri.nic.in) (ID: CTRI/2012/02/002459), as reported in text. All prespecified outcomes were reported
Other bias	Low risk	Judgement comment: no other risks observed

Pehlivan 2003

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Turkey **Study period:** December 2012 to February 2013
Participants	**Included criteria:** healthy pregnant women, infants of normal birth weight (> 2.5 kg) **Excluded criteria:** pregnant women with chronic disease or who were taking medication or had obstetrical problems (gestational diabetes, hypertension, preeclampsia, eclampsia, or premature delivery), twin pregnancy **Baseline vitamin D status:** unclear
Interventions	**Intervention characteristics**

Pehlivan 2003 *(Continued)*

	800 IU 1. *Vitamin D content and type*: 800 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: not specified 4. *Duration of administration (study time)*: not specified 5. *N per group (in analysis)*: not clear 6. *Brand/company*: not reported 400 IU 1. *Vitamin D content and type*: 400 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: not specified 4. *Duration of administration (study time)*: not specified 5. *N per group (in analysis)*: not clear 6. *Brand/company*: not reported
Outcomes	None within scope of this review
Notes	Data from this study were not clearly written, and numbers per intervention group were not given; therefore, data could not be included in any analyses in this review. It appears that 78 pregnant women and 65 infants were followed up. It is unclear if these 65 infants were a separate population, or if they were born to these moms, as study authors state that 65 infants were given vitamin D but then mention 65 infants again and label them as "controls". Further, study authors then state that 40 infants who were breastfed and received recommended doses of vitamin D on a regular basis were randomly assigned to either 400 IU per day or 800 IU per day of vitamin D, but do not specify sample sizes per group. One statement regarding results listed vitamin D concentration for the whole population of 83.7 ± 53.7 nmol/L, and indicated that 24.6% of infants were vitamin D deficient (measured as < 40 nmol/L), but it is unclear whether this occurred at baseline or after supplementation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement comment: randomisation of infants is not clear (which population was randomised) and random sequence generation method is not described
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment is not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. However, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: loss to follow-up is not described. Duration of administration is not specified
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial protocol or registration was identified

Pehlivan 2003 *(Continued)*

Other bias	Low risk	Judgement comment: no other risks were observed

Ponnapakkam 2010

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Grant from The Gerber Foundation, a private, independent foundation promoting research in paediatric nutrition and health **Country:** USA **Study period:** August 2007 to December 2009
Participants	**Included criteria:** term babies with no known bone disorders, those whose parents indicated that they intended to breastfeed (> 50% of total intake) for at least the first 3 months of life **Excluded criteria:** none specified **Baseline vitamin D status (mean ± standard error; nmol/L)** 1. Control group (placebo): 64.8 ± 6.6 2. Intervention group (200 IU D_3): 62.6 ± 3.3 3. Intervention group (200 IU D_3 at 2 months): 52.2 ± 4.9
Interventions	**Intervention characteristics** 200 IU D_3 (at birth) 1. *Vitamin D content and type*: 200 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily, beginning at birth 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 8 6. *Brand/company*: Patio Drugs (Metairie, LA, USA) 200 IU D_3 (at 2 months) 1. *Vitamin D content and type*: 200 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily, beginning at 2 months of age 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 9 6. *Brand/company*: Patio Drugs (Metairie, LA, USA) Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 8 6. *Brand/company*: Patio Drugs (Metairie, LA, USA)

Ponnapakkam 2010 *(Continued)*

Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Rickets **Measurement** 1. Serum 25(OH)D (nmol/L): Immuno Diagnostic Systems Ltd. (IDS Inc., Fountain Hills, AZ, USA) a. **Notes:** data from Figure 1 (Ponnapakkam 2010). Data presented as mean (standard error), which we converted to standard deviation 2. Rickets: biochemical and radiographic changes a. **Notes:** rickets was diagnosed based on elevation of alkaline phosphatase and evidence of rachitic changes on hand X-ray. Subclinical rickets were evaluated by comparing average alkaline phosphatase levels between groups. b. **Notes:** no events in either arm; data did not contribute to meta-analysis **Time points:** birth; 2, 4, and 6 months of age
Notes	Sample size not calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the study participants were randomized into 1 of the 3 study groups" Quote: "prior to randomization, the study population was stratified (as low risk and high risk) based on the presence or absence of additional risk factors for rickets (dark skin color or full-body clothing/draping) to reduce the influence of this potentially confounding factor on the overall results" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	High risk	Quote: "commercial preparations of Vitamin D drops (D3) and placebo were purchased from Patio drugs (Metairie, LA). The preparation consisted of 200 IU of vitamin D per 0.5 mL, for daily dosing. Patients were given a new container of medication every 2 months and were encouraged to throw away any leftover medicine. Approximate numbers of missed doses were noted on the questionnaires" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding not indicated; because parents were giving intervention and age at start of intervention was part of the randomisation group, performance bias may be increased. If investigators know the intervention allocations may be biased toward a particular outcome, this increases the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: blinding not indicated; outcomes assessed by parents as well as study personnel who were not blinded to allocation, which could introduce detection bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "we recruited 80 patients into the study; 25 of these patients (30%) completed the study (Table 1). Of the patients completing the study, 18 were low risk, and 7 were high risk. There were 2 adverse events: 1 urinary tract infection in group 1 (Vitamin D starting at birth, unclear if study related) and 1 sudden infant death syndrome in group 3 (placebo, not study related)" Judgement comment: study authors noted if loss to follow-up (30% attrition) reasons were study related but did not compare dropouts to those who ad-

Ponnapakkam 2010 *(Continued)*

		hered to the study protocol. Study authors did not state number randomised to each arm and number of dropouts per arm. Reasons not given for loss to follow-up except for adverse events. Analysis was not intention-to-treat
Selective reporting (reporting bias)	Unclear risk	Quote: "height and weight were documented, and data were collected from the parents through questionnaires at the 0-, 2-, 4-, and 6-month pediatric visits regarding nutrition" Judgement comment: no trial registration or protocol identified; outcomes in methods presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Principi 2013

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Grant from Italian Ministry of Health (Bando Giovani Ricercatori 2007) **Country:** Italy **Study period:** 1 October 2011 and 30 April 2012
Participants	**Included criteria:** children age 2 to 5 years with history of recurrent acute otitis media (defined as ≥ 3 episodes in preceding 6 months, or ≥ 4 episodes in preceding 12 months, with most recent episode in previous 2 to 8 weeks) who had not been previously vaccinated against influenza **Excluded criteria:** free of clinically evident febrile infectious disease, severe atopy, acquired or congenital immunodeficiency, recent administration of blood products, presence of anatomical abnormalities capable of favouring development of acute otitis media, long-term treatment with drugs capable of interfering with absorption or metabolism of vitamin D, such as barbiturates, corticosteroids, and cholestyramine **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (placebo): 64.4 ± 64.7 2. Intervention group (1000 IU D_3): 63.4 ± 65.9
Interventions	**Intervention characteristics** 1000 IU D_3 1. *Vitamin D content and type*: 1000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 months 5. *N per group (in analysis)*: 59 6. *Brand/company*: Dibase, Vitamin D_3, Abiogen Pharma SpA, Pisa, Italy Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: daily

Principi 2013 *(Continued)*

4. *Duration of administration (study time)*: 4 months
5. *N per group (in analysis)*: 57
6. *Brand/company*: not reported

Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): chemiluminescence immunoassay (LIAISON 25 OH Vitamin D Total Assay, DiaSorin, Saluggia, Italy) **Time points:** enrolment, 6 months
Notes	Calculated sample size not given but ~ 55/group stated. This was met by treatment end

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the enrolled children were randomly divided into two groups and assigned to receive daily vitamin D 1,000 IU (four drops of Dibase, Vitamin D3, Abiogen Pharma S.p.A.) or placebo orally for four months" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the study was single blinded because investigators knew whether the children were receiving vitamin D or placebo, but parents were not aware" Judgement comment: caregivers were blinded, while investigators were not blinded; investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: outcome assessors were not blinded; however, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "the study involved 116 children (61 males, 52.6%; mean age 3.0 ± 1.0 y), none of whom had been previously vaccinated against influenza: 59 (50.9%; mean age 3.3 ± 1.1 y) were administered vitamin D and 57 (49.1%; mean age 2.9 ± 0.9 y) received placebo" Judgement comment: no discussion of loss to follow-up; no examination of missing data; intention-to-treat analysis not done
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified
Other bias	Low risk	Judgement comment: no other risks observed

Rao 2016

Study characteristics

Rao 2016 *(Continued)*

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** India **Study period:** not reported
Participants	**Included criteria:** age 2 to 5 years, vitamin D deficiency (20 ng/mL); parents had given informed written consent **Excluded criteria:** children with chronic illness, children taking steroid, other factor influencing vitamin D in children, acute illness for 2 weeks **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (4000 IU D_3): 34.0 ± 14.2 2. Intervention group (30,000 IU D_3): 35.6 ± 11.6
Interventions	**Intervention characteristics** 4000 IU D_3 1. *Vitamin D content and type*: 4000 IU D_3/d for 3 months + 400 IU D_3 for 9 months 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months + 9 months 5. *Other micronutrient content*: 50 mg calcium carbonate/kg/d 6. *N per group (in analysis)*: 15 7. *Brand/company*: not reported 30,000 IU D_3 1. *Vitamin D content and type*: 30,000 IU D_3/week for 3 months + 400 IU D_3 for 9 months 2. *Formulation*: not reported 3. *Frequency of dosage*: weekly 4. *Duration of administration (study time)*: 3 months + 9 months 5. *Other micronutrient content*: 50 mg calcium carbonate/kg/d 6. *N per group (in analysis)*: 15 7. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Change in 25(OH)D **Measurement** 1. Serum 25(OH)D (nmol/L): chemiluminescence immunoassay, auto-analyser (Architect i1000SR, Abbott Laboratories, Abbott Park, IL, USA) **Time points:** baseline, 3 and 12 months
Notes	Study authors describe calculation but do not explicitly state the actual sample size calculated. Assumed that sample size calculation was n = 19. Possibly retrospectively justified

Risk of bias

Rao 2016 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "subjects eligible for the study were divided in 2 strata based on gender (male or female). Stratified randomization with a block size of 3 was used to assign patients to groups 1, 2, and 3. The randomization lists were computer-generated prior to the start of the study and kept confidential" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Unclear risk	Quote: "group 1 received 4,000 IU/day of vitamin D3 for 12 weeks along with calcium carbonate (50-mg elemental calcium/kg/day), group 2 received 30,000 IU/wk of vitamin D3 for 12 weeks along with calcium carbonate (50-mg elemental calcium/kg/day), and group 3 received 3,00,000 IU of vitamin D3 once intramuscular along with calcium carbonate (50-mg elemental calcium/kg/day)" Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "it was a single blind study and patients involved in the study were unaware of assignment to treatment groups" Judgement comment: caregivers were blinded, while investigators were not. Investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: unblinding of study personnel could lead to detection bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "a total of 19 subjects each was included in groups 1, 2, and 3, respectively. In group 1, 3 subjects migrated and were lost to follow up and one subject opted out of the study. In group 2, 4 subjects were lost to follow up. In group 3, 4 subjects opted out of the study" Judgement comment: loss to follow-up; reasons specified. After loss-to-follow-up, n = 15/group, and only those completing the study protocol were analysed. 15% to 21% attrition may be causing bias. No Intention-to-treat analysis. Similar loss to follow-up in each group; no discussion of the characteristics of lost participants. 80% completion rate is borderline. No mention of how study authors dealt with missing data
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified
Other bias	Low risk	Judgement comment: no other risks observed

Rianthavorn 2013

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Thailand

Rianthavorn 2013 *(Continued)*

	Study period: not reported
Participants	**Included criteria:** patients age 18 years with chronic kidney disease, Stage 5 or 5D, and 25-hydroxyvitamin D (serum 25(OH)D, nmol/L) levels of 30 ng/mL; haemoglobin levels of 10.0 to 12.5 g/dL, serum phosphorus levels of 6.5 mg/dL, corrected serum calcium levels of 10.5 mg/dL, and calcium–phosphorus product of 65 mg/dL for ≥ 1 month before recruitment **Excluded criteria:** thalassemia, chronic liver disease, gastrointestinal malabsorption, significant blood loss, serum parathyroid hormone levels > 800 pg/mL, proteinuria > 2 mg/mg of urine creatinine, blood transfusion, long-term anticonvulsant therapy, prior ergocalciferol supplementation, kidney transplantation **Pretreatment:** degree of vitamin D insufficiency in participants was classified into 3 categories based on serum 25(OH)D levels (5, 5 to 15, 16 to 30 ng/mL). In patients with severe 25(OH)D deficiency (serum 25(OH)D level 5 ng/mL), 40,000 IU of ergocalciferol was given weekly for 4 weeks followed by 40,000 IU biweekly for 8 weeks (total 320,000 IU of ergocalciferol). For mild 25D deficiency (25D level 5 to 15 ng/mL), 40,000 IU of ergocalciferol was given biweekly for 12 weeks (total 240,000 IU of ergocalciferol). For 25D insufficiency (25D level 16 to 30 ng/mL), 40,000 IU of ergocalciferol was given every 4 weeks for 12 weeks (total 120,000 IU of ergocalciferol) **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (no intervention): 76.9 ± 46.8 2. Intervention group (40,000 IU D_3): 48.6 ± 16.5
Interventions	**Intervention characteristics** 40,000 IU D_2 1. *Vitamin D content and type (per dose)*: 40,000 IU D_2 2. *Formulation*: capsules 3. *Frequency of dosage*: n = 2: 40,000 every 2 weeks for 8 weeks (320,000 IU); n = 2: 40,000 every 4 weeks for 12 weeks (120,000 IU) 4. *Duration of administration (study time)*: n = 2: 40,000 every 2 weeks for 8 weeks (320,000 IU); n = 2: 40,000 every 4 weeks for 12 weeks (120,000 IU) 5. *N per group (in analysis)*: 4 (stratified data) 6. *Brand/company*: British Dispensary, Bangkok, Thailand No intervention 1. *Duration of administration (study time)*: 12 weeks 2. *N per group (in analysis)*: 3 (stratified data)
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): chemiluminescent immunoassay, LIAISON 25 OH Vitamin D Total Assay (DiaSorin, Stillwater, MN, USA) **Time points:** baseline, 12 weeks
Notes	Post-hoc power calculation showed this study had 50% power to detect a 30% change in effect estimate. Age-stratified data were shared by study author

Risk of bias

Bias	Authors' judgement	Support for judgement

Rianthavorn 2013 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "twenty patients were divided into two groups by simple randomization" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	High risk	Quote: "ten patients received oral ergocalciferol supplementation (treatment), whereas the other group did not (control)" Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: not possible to blind participants due to control group receiving no intervention; investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: blinding of outcome assessors is not described; however, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "all patients completed the 12-week study without any major adverse effects from ergocalciferol" Judgement comment: no loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no registration of trial nor cited study protocol
Other bias	Low risk	Judgement comment: no other risks observed

Robinson 1981

Study characteristics	
Methods	**Study design:** quasi-randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** London **Study period:** July 1977 to February 1978
Participants	**Included criteria:** preterm babies, patients of Professor Scopes **Excluded criteria:** none specified **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (400 IU D_3): 22.7 ± 5.6 2. Intervention group (1000 IU D_3): 22.0 ± 2.6
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily

Robinson 1981 *(Continued)*

4. *Duration of administration (study time)*: 9 weeks
5. *N per group (in analysis)*: 10
6. *Brand/company*: not reported

1000 IU D_3

1. *Vitamin D content and type*: 1000 IU D_3
2. *Formulation*: not reported
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 9 weeks
5. *N per group (in analysis)*: 11
6. *Brand/company*: not reported

Outcomes	**Primary** 1. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Rickets **Measurements** 1. Hypercalcaemia (serum calcium): ethylene glycol tetra-acetic acid titration a. Definition: not reported b. **Notes:** no events in either arm; data did not contribute to meta-analysis 2. Serum 25(OH)D (nmol/L): competitive protein-binding assay 3. Rickets: radiological evidence a. **Notes:** no events in either arm; data did not contribute to meta-analysis **Time points:** 14th day of life, 36 and 39 weeks' postmenstrual age
Notes	No sample size calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "18 babies (13 white and 5 West Indian) were randomly allocated to two groups (1 or 2) between July 1977 and February 1978" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Unclear risk	Quote: "those in group 1 received 400 and those in group 2 1000 IU of vitamin D3 daily by mouth from day 15" Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described; however, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention

Robinson 1981 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: no loss to follow-up described
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified
Other bias	Low risk	Judgement comment: no other risks observed

Rodd 2011

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over **Funding:** 100% for profit. BioEnvelop, a division of Paladin Labs Inc., Laval, Quebec, Canada **Country:** Canada **Study period:** March to July 2009
Participants	**Included criteria:** healthy, term, singleton newborns of any racial background and any feeding method **Excluded criteria:** infants unable to accept the supplement, congenital malformations, and (or) parents not sufficiently fluent in English or French to provide informed consent **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 400 IU D_3 (syrup) 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: syrup 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 weeks per cross-over period 5. *N per group (in analysis)*: 21 6. *Brand/company*: D Vitamin Drops for Infants (Pharmaprix or Life brand; NPN 02243870; Pharmetics Inc., Laval, Quebec, Canada) 400 IU D_3 (filmstrip) 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: filmstrip 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 weeks per cross-over period 5. *N per group (in analysis)*: 21 6. *Brand/company*: BabyVita (BioEnvelop, a division of Paladin Labs Inc., Montreal, Quebec, Canada)
Outcomes	None within scope of review
Notes	Sample size not calculated
Risk of bias	

Rodd 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was performed using the Web site www.randomization. com; selecting the first generator function randomized participants to treatment groups by using the method of randomly permuted blocks" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	High risk	Judgement comment: allocation concealment not possible
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: no blinding, not possible with intervention/comparator formulations. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: no blinding; not possible with intervention/comparator formulations. However, this study did not analyse any outcomes within the scope of this review
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: minimal loss to follow-up (n = 1 from liquid to filmstrip arm; n = 2 from filmstrip to liquid arm)
Selective reporting (reporting bias)	Low risk	Judgement comment: trial registered prospectively on ClinicalTrials.gov (ID: NCT00846677), as reported in text. Prespecified outcomes are consistent with those reported
Other bias	Low risk	Judgement comment: no other risks observed

Rosendahl 2018

Study characteristics	
Methods	**flex Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit **Country:** Finland **Study period:** 14 January 2013 to 30 May 2016
Participants	**Included criteria:** Northern European, term, birth weight within 2 standard deviations of the mean for gestational age **Excluded criteria:** infants requiring intravenous glucose, antibiotics, nasal continuous positive airway pressure treatment longer than 1 day, phototherapy longer than 3 days, or nasogastric tube feeding longer than 1 day; infants with seizures **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (400 IU D_3): 81.7 ± 27.8 2. Intervention group (1200 IU D_3): 82.3 ± 24.0
Interventions	**Intervention characteristics**

Rosendahl 2018 *(Continued)*

400 IU D_3

1. *Vitamin D content and type*: 400 IU D_3
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 24 months
5. *N per group (in analysis)*: 489
6. *Brand/company*: Orion Pharmaceuticals, Kamataka, India

1200 IU D_3

1. *Vitamin D content and type*: 1200 IU D_3
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 24 months
5. *N per group (in analysis)*: 486
6. *Brand/company*: Orion Pharmaceuticals, Kamataka, India

Outcomes	**Primary** 1. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D < 50 nmol/L a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis **Measurement** 1. Hypercalcaemia (serum calcium): flex gas analyser a. Definition: not reported 2. Serum 25(OH)D (nmol/L): fully automated immunoassay (IDS-iSYS; Immunodiagnostic System Inc., Gaithersburg, MD, USA) **Time points:** enrolment, 24 months
Notes	Sample size calculated at n ~ 300/group, which was met by analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "infants were randomized (1:1) to receive 400 IU or 1200 IU of vitamin D_3 daily from age 2 weeks to 24 months. To ensure fair distribution across the year, a pharmacist at Helsinki University Hospital with no relation to the study performed randomization in blocks of 50" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Low risk	Quote: "both study preparations, manufactured by Orion Pharmaceuticals, contained vitamin D_3 dissolved in medium-chain triglyceride oil and were identical in appearance. Participants and investigators were masked to group assignment, and no changes to the methods were made after trial commencement" Judgement comment: appropriate allocation concealment; however, no mention of sequentially labelled envelopes or containers

Rosendahl 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "participants and investigators were masked to group assignment, and no changes to the methods were made after trial commencement" Judgement comment: all personnel and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Judgement comment: possible that outcome assessors were not blinded and grading was done by staff; subjective and possibly increasing risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "we performed pQCT bone scans of the left tibia in 783 of the 823 children (95.1%) attending the age 24-month follow-up. Owing to motion artifacts, 79 (10.1%) of the scans failed and were excluded. A total of 704 scans (89.9%) were included in the analyses. Of these, scan quality was assessed as good in 165 (48.1%) of the 400-IU group and 193 (53.5%) of the 1200-IU group participants, moderate in 124 (36.2%) of the 400-IU group and 133 (36.8%) of the 1200-IU group, and poor in 54 (15.7%) of the 400-IU group and 35 (9.7%) of the 1200-IU group" Quote: "in the analyses, we applied the intention-to-treat principle. Per-protocol analyses included participants with treatment adherence of at least 80%" Judgement comment: loss to follow-up was balanced across groups and reasons were documented. Out of 975 children, 783 (80%) had bone scans. Uncertain if children whose scans had motion artifacts are different from children whose scans did not. Grading of scans was subjective. Possible intention-to-treat analysis in 83.5% of the cohort
Selective reporting (reporting bias)	Low risk	Quote: "the project protocol is provided in Supplement 1 and has been described in a previously published article" Judgement comment: registered on ClinicalTrials.gov (ID: NCT01723852); previously published protocol's prespecified outcomes are reported in study results
Other bias	Low risk	Judgement comment: no other risks observed

Rueter 2019

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. DJP is supported by a Career Development Fellowship funded from the Medical Research Future Fund Next Generation Clinical Researchers Program. This study was supported by grants from Telethon–New Children's Hospital Research Fund, Australia; Asthma Foundation of Western Australia, Australia; and Princess Margaret Hospital Foundation, Australia **Country:** Australia **Study period:** 9 October 2012 to 4 July 2017
Participants	**Included criteria:** healthy, term, singleton, before 28 days of age; first-degree relative (mother, father, or sibling) with history of allergic disease (asthma, eczema, and allergic rhinitis) **Excluded criteria:** infants whose mothers had smoked during pregnancy or had an underlying immunodeficiency/autoimmune disease; those with maternal 25-hydroxyvitamin D (25(OH)D) level serum

Rueter 2019 *(Continued)*

	concentrations < 50 nmol/L or > 100 nmol/L between 36 and 40 weeks' gestation, which was intended to reduce risk of vitamin D deficiency or toxicity in infant participants **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 5 to 6 months 5. *N per group (in analysis)*: 73 6. *Brand/company*: Ddrops, Woodbridge, Ontario, Canada Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 5 to 6 months 5. *N per group (in analysis)*: 68 6. *Brand/company*: Ddrops, Woodbridge, Ontario, Canada
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): competitive chemiluminescent immunoassay, automated on Abbott Architect i2000 (Abbott Laboratories, Abbott Park, IL, USA) **Time points:** birth, 3 and 6 months of age
Notes	Sample size not calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (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. The pharmacy created a randomization plan from an online source (www.randomization.com)" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "both the intervention (vitamin D) and control (placebo) oils were packaged to appear identical and to maintain the blind" Judgement comment: appropriate allocation concealment, by a third party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "all research staff remained blind to the allocations until analyses were completed" Quote: "both the intervention (vitamin D) and control (placebo) oils were packaged to appear identical and to maintain the blind. Pharmacy staff had no con-

Rueter 2019 *(Continued)*

		tact with participants, and all research staff remained blind to the allocations until analyses were completed" Judgement comment: personnel were blinded; double-blind implies that participants were blinded as well
Blinding of outcome assessment (detection 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. Pharmacy staff had no contact with participants, and all research staff remained blind to the allocations until analyses were completed" Judgement comment: outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "analyses were performed according to the intention-to-treat principle" Quote: "a total of 195 infants were randomized into the trial, 97 to the intervention vitamin D group and 98 to the placebo group. Fig 1 shows the participant flow diagram. Baseline characteristics of the 2 groups are described in Table I. Allocations in the vitamin D group compared with those in the placebo group were not different across seasons. Data collection was completed on July 4, 2017. Ninety-two percent (180/195) of infant participants attended their appointment at 3 months of age, and 89% (173/195) of infants attended their appointment at 6 months of age. Nine (n = 6 from the vitamin D group) parents withdrew consent to participate during the intervention period" Judgement comment: low loss to follow-up was balanced across groups; reasons were described. Intention-to-treat analysis was performed; appears that a subsample of infants gave blood, but how the sample was selected is not described
Selective reporting (reporting bias)	Low risk	Judgement comment: trial registered retrospectively on Australian New Zealand Clinical Trials Registry (ID: ACTRN12606000281594), as reported in text. Outcomes on trial registration are consistent with those reported
Other bias	Low risk	Judgement comment: no other risks observed

Saad 2015

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Egypt **Study period:** not reported
Participants	**Included criteria:** infants with bronchiolitis; bronchiolitis diagnosed by 2 senior paediatricians and defined as acute-onset lower respiratory tract symptoms for < 2 weeks with (a) evidence of a viral infection (rhinorrhoea, coryza, cough, or fever); (b) abnormal auscultatory findings (wheeze or crackles, or both); and (c) increased respiratory effort (tachypnoea and intercostal retractions), who presented to the emergency room within 7 days of onset of symptoms **Excluded criteria:** severe respiratory distress, admitted to intensive care unit, evidence of bacterial pneumonia (diagnosis of pneumonia was based on cough, chest wall in-drawing and/or difficult

Saad 2015 *(Continued)*

	breathing and tachypnoea, fever, and lobar, or bronchopneumonic, infiltration demonstrated by X-ray), atopic disorders (asthma, known chronic cardiopulmonary disease, immunodeficiency, chronic medical condition including anaemia, severe malnutrition, meningitis, neurological disease, metabolic disease, gastrointestinal disease associated with malabsorption), any micronutrient supplementation or vitamin D therapy within the 4 weeks before enrolment **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (placebo): 67.6 ± 37.7 2. Intervention group (100 IU D_3/kg): 65.6 ± 31.7
Interventions	**Intervention characteristics** 100 IU D_3/kg 1. *Vitamin D content and type*: 100 IU D_3/kg 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: ≥ 5 days (maximum 9 days) 5. *N per group (in analysis)*: 44 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: ≥ 5 days (maximum 9 days) 5. *N per group (in analysis)*: 45 6. *Brand/company*: not reported
Outcomes	None within scope of review
Notes	Sample size not calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computerized random number generator" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "...drop solutions with identical outer covers and size of bottles. The randomization and allocation process was done by a physician blinded to the study" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind... Throughout the study, the parents of children who administered the medications to their children were blind to assignments" Judgement comment: participants were likely blinded due to adequate allocation concealment; double-blind implies investigator blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double blind" Judgement comment: 'double-blind' implies that outcome assessors were blinded

Saad 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "all side effects were mild and transient and all patients continued with the study" Judgement comment: no loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial protocol or registration identified
Other bias	Low risk	Judgement comment: no other risks observed

Saleem 2018

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Supported by a grant from the Higher Education Commission of Pakistan under its International Research Support Initiative Program; reference no. 1-8/HEC/HRD/2016/6029 **Country:** Pakistan **Study period:** not reported
Participants	**Included criteria:** infants age 6 to 59 months at enrolment, whose parents gave consent for them to participate, provided they had severe acute malnutrition without complications, as defined by WHO (i.e. children with mid-upper arm circumference < 115 mm, weight-for-height z-score < -3, or grade 1 or 2 bilateral oedema who were clinically well and alert with good appetite) **Excluded criteria:** ingestion of a dose of vitamin D > 200,000 IU (5 mg)/mo in the last 3 months (confirmed by medical records, or by maternal recall when these were unavailable), presence of complications of severe malnutrition (severe dehydration, severe anaemia, severe pitting oedema, anorexia, hypothermia, hyperpyrexia, acute lower respiratory tract infection, or hypoglycaemia) **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 200,000 IU D_3 1. *Vitamin D content and type*: 200,000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: at 2 and 4 weeks 4. *Duration of administration (study time)*: 8 weeks 5. *N per group (in analysis)*: 93 6. *Brand/company*: GT Pharma (Pvt.) Ltd., Lahore 7. *Micronutrient content or additional part of intervention*: ready to eat therapeutic food (RUTF) + 7 -day course of oral amoxicillin Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: at 2 and 4 weeks 4. *Duration of administration (study time)*: 8 weeks 5. *N per group (in analysis)*: 92

Saleem 2018 *(Continued)*

6. *Brand/company*: GT Pharma (Pvt.) Ltd., Lahore
7. *Micronutrient content or additional part of intervention*: RUTF + 7-day course of oral amoxicillin

Outcomes	**Secondary** 1. Weight-for-length/height z-score (WL/HZ) 2. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 3. Serum 25(OH)D ≥ 50 nmol/L **Measurement** 1. Weight (kg): UNISCALE 2. Height (cm): length board (SECA GmbH & Co. KG, Hamburg, Germany) 3. Z-score: World Health Organization Child Growth Standards (WHO 2006) 4. Serum 25(OH)D (nmol/L): liquid chromatography tandem mass spectrometry **Time points:** enrolment, 8 weeks
Notes	Sample size calculated and met

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the random allocation sequence was generated on a Microsoft Excel spreadsheet by a statistician who was independent of the study (Mr. Arslan Chughtai, Rashid Latif Medical Collage, Lahore); a copy was held by the principal investigator (JS), but she did not consult this during the trial. Consecutive numbers from 001 to 200 were assigned to active and placebo groups in a 1:1 ratio. No restrictions (e.g. stratification, block size) were applied" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "double-blind; the active and placebo medications were presented identically (syringes of oily solution for oral administration) and had the same appearance and taste" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the parents or guardians of all the study participants were blinded to the allocations, as were the health workers, the research nurse, and the pediatrician who enrolled participants and/or performed study assessments" Judgement comment: all personnel and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind; the parents or guardians of all the study participants were blinded to the allocations, as were the health workers, the research nurse, and the pediatrician who enrolled participants and/or performed study assessments" Judgement comment: outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "one child allocated to the vitamin D 3 group died before taking the first dose of study medication (cause of death: dehydration secondary to gastroenteritis), and a further 8 children (3 allocated to vitamin D 3, 5 allocated to placebo) moved away from the study site prior to administration of the first dose of study medication. The remaining 185 participants (93 allocated to vitamin D 3, 92 allocated to placebo) all took both doses of study medication, completed the follow-up and were included in the analysis"

Saleem 2018 *(Continued)*

		Judgement comment: minimal loss to follow-up (5%), reasons described
Selective reporting (reporting bias)	Unclear risk	Judgement comment: trial registered retrospectively on ClinicalTrials.gov (ID: NCT03170479), as reported in text; primary outcomes listed on registration but not secondary outcomes
Other bias	Low risk	Judgement comment: no other risks observed

Sánchez-Armendáriz 2018

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Mexico **Study period:** April 2013 to March 2014
Participants	**Included criteria:** diagnosed with moderate to severe atopic dermatitis according to Scoring of Atopic Dermatitis index **Excluded criteria:** some primary immunodeficiency, renal tubular acidosis, pregnancy, those who took other supplements, lack of follow-up at 12 weeks **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (placebo): 53.9 ± 17.2 2. Intervention group (100,000 IU D_3): 53.2 ± 16.7
Interventions	**Intervention characteristics** 5000 IU D_3 1. *Vitamin D content and type*: 5000 IU D_3 2. *Formulation*: capsules 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 12 weeks 5. *N per group (in analysis)*: 11 (stratified data) 6. *Brand/company*: not reported 7. *Co-intervention*: topical steroids (hydrocortisone aceponate) Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: capsules (cellulose) 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 12 weeks 5. *N per group (in analysis)*: 10 (stratified data) 6. *Brand/company*: not reported 7. *Co-intervention*: topical steroids (hydrocortisone aceponate)
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)

Sánchez-Armendáriz 2018 *(Continued)*

	Measurement 1. Serum 25(OH)D (nmol/L): direct enzyme-linked immunoassay kit (Immunodiagnostik, AG/American Laboratory Products Company (ALPCO) immunoassays) **Time points:** enrolment, 6 weeks, 12 weeks
Notes	Stratified data sent by study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "simple randomization was performed using the Epidat V3.1 software" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "the patients were divided into two groups; the first group received water-soluble capsules of 5000 IU/day of vitamin D3 (n = 33), and the second group received cellulose capsules (n = 32). The placebo capsules were the same size and color as the vitamin D3 capsules" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both patients and doctors were blind to the study; in this way, a pharmacist who did not participate in the taking of blood samples or in the analysis of results was the only one who knew which patient belonged to each group and gave them the capsules" Judgement comment: all personnel and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind" Judgement comment: all personnel and participants were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "sixty-five patients diagnosed with AD were included; seven (10.8%) were excluded because they dropped out of the study for reasons other than this (lack of follow-up)" Judgement comment: lack of detail on reasons for loss to follow-up. Methods to deal with missing data not described. Intention-to-treat analysis not done
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified
Other bias	Low risk	Judgement comment: no other risks observed

Sarhan 2019

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** no funding **Country:** Egypt

Sarhan 2019 *(Continued)*

	Study period: October 2016 to March 2017
Participants	**Included criteria:** age 1 to 24 months; diagnosed clinically as suffering from acute bronchiolitis; presenting with any of the following: persistent resting oxygen saturation < 92% in room air; marked tachypnoea (> 70/min) or intercostal retractions indicating respiratory distress, or both; difficulty of oral intake; inability of caregivers to care for the child at home. Diagnosis of acute bronchiolitis was defined as a first episode of respiratory distress with wheezing or crackles, or both, preceded by infection of the upper airways (rhinorrhoea, coryza, cough, fever). Disease severity was evaluated using the modified Tal score **Excluded criteria:** history of prematurity (< 37 weeks), chronic cardiopulmonary disease, immunodeficiency, neuromuscular disease, any other chronic medical condition; receiving vitamin D for 4 weeks before the study period; infants with recurrent wheezing or a physician's diagnosis of asthma; patients with acute bronchiolitis having a very severe clinical score **Baseline vitamin D status (n (%) <75 nmol/L)** 1. Control group (placebo): 25 (83) 2. Intervention group (100 IU D_3): 22 (73)
Interventions	**Intervention characteristics** 100 IU D_3/kg 1. *Vitamin D content and type*: 100 IU D_3/kg 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study days, mean ± standard deviation (SD))*: until discharge (2.70 ± 0.53) 5. *N per group (in analysis)*: 30 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: placebo 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study days, mean ± SD)*: until discharge (4.43 ± 0.67) 5. *N per group (in analysis)*: 30 6. *Brand/company*: not reported
Outcomes	None within scope of review
Notes	Sample size calculated and met

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the randomization and allocation process was carried out by a higher nursing staff blinded to the study" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Low risk	Quote: "the assignments were kept in sealed envelopes until data analysis" Judgement comment: appropriate allocation concealment

Sarhan 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the medical staff and parents were blind to assignments during the study period" Judgement comment: all personnel and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "the assignments were kept in sealed envelopes until data analysis" Judgement comment: suggests outcome assessors were blinded, but possibly not those analysing the data
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: no loss to follow-up; all outcomes described in the methods reported
Selective reporting (reporting bias)	Unclear risk	Judgement comment: trial registered retrospectively on ClinicalTrials.gov (ID: NCT03799406), which we identified through separate searching; outcomes on trial registration consistent with those reported
Other bias	Low risk	Judgement comment: no other risks observed

Shajari 2009

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Iran **Study period:** not reported
Participants	**Included criteria:** 15 days old, healthy, exclusively breastfeeding, weighing 2500 to 4100 g **Excluded criteria:** kidney disease, malnutrition, prematurity **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 200 IU D_3 1. *Vitamin D content and type*: 200 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (in analysis)*: 30 6. *Brand/company*: not reported 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months

Shajari 2009 *(Continued)*

5. *N per group (in analysis)*: 30
6. *Brand/company*: not reported

50,000 IU D_3

1. *Vitamin D content and type*: 50,000 IU D_3
2. *Formulation*: not reported
3. *Frequency of dosage*: at 15th and 60th days of life
4. *Duration of administration (study time)*: 3 months
5. *N per group (in analysis)*: 30
6. *Brand/company*: not reported

Outcomes	**Primary** 1. Adverse effect: hypercalciuria **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) < 50 nmol/L a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported 2. Hypercalciuria (urinary calcium-to-creatinine ratio): calcium, cresolphthalein complexone spectrophotometric method; creatinine, jaffé reaction, Cobas-Mira automated analyser (Roche Diagnostics, Mannheim, Germany) a. Definition: > 0.21 mmol/mmol **Time points:** 0 to 15 days of age, 3 months of age
Notes	No sample size calculation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "subjects divided randomly into three groups" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Unclear risk	Quote: "supplemented daily with 200 IU/daily vitamin D3 (Group I), 400 IU/daily vitamin D 3 (Group II) and the third group received 50,000 IU vitamin D3 twice in fifteenth and sixtieth day after birth (Group III)" Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Participants could learn which group they were allocated to by the dosing schedule. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, and investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described; however, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias)	Unclear risk	Judgement comment: analysis using Intention-to-treat analysis not noted; no discussion of loss to follow-up

Shajari 2009 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified
Other bias	Low risk	Judgement comment: no other risks observed

Shakiba 2010

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Iran **Study period:** January to September 2007
Participants	**Included criteria:** healthy breastfed infants weighing 2500 to 4000 g from 3 primary care clinics in urban areas of Yazd City; infants' mothers healthy and not under medication **Excluded criteria:** none specified **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 200 IU D_3 1. *Vitamin D content and type*: 200 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 19 6. *Brand/company*: Pearl vitamin D_3, Alhavy Iran Company, Tehran, Iran 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 26 6. *Brand/company*: Pearl vitamin D_3, Alhavy Iran Company, Tehran, Iran 50,000 IU D_3 1. *Vitamin D content and type*: 50,000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: every 2 months 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 30 6. *Brand/company*: Pearl vitamin D_3, Alhavy Iran Company, Tehran, Iran

Shakiba 2010 *(Continued)*

Outcomes	**Primary**
	
	1. Adverse effect: hypercalcaemia
	
	Secondary
	
	1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)
	2. Serum 25(OH)D < 50 nmol/L
	   a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis
	3. Serum 25(OH)D < 75 nmol/L
	   a. **Notes:** converted to vitamin D sufficiency ≥ 75 nmol/L for meta-analysis
	
	Measurement
	
	1. Hypercalcaemia (serum calcium): assay not reported
	   a. Definition: > 11 mg/dL
	2. Serum 25(OH)D (nmol/L): chemiluminescent immunoassay (DiaSorin, DiaSorin SpA, Via Crescentino, Vercelli, Italy)
	
	Time points: enrolment, 6 months

Notes	Sample size calculated and met at randomisation but not at analysis for group 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the infants were randomised based on a computer-generated randomisation list (restricted randomisation), with a randomisation ratio 3:1, so that for each infant in the bolus group, three infants in the daily group were selected, which distributed them equally within the 200 IU and 400 IU daily dosage groups" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "the paediatrician responsible for the infant allocated the next available number on entry into the trial, and each parent collected the vitamin drop and complete instructions directly from the pharmacy. The code was revealed to the researchers at the end of the analysis of the results" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the paediatrician responsible for the infant allocated the next available number on entry into the trial, and each parent collected the vitamin drop and complete instructions directly from the pharmacy. The code was revealed to the researchers at the end of the analysis of the results" Judgement comment: blinding not described; personnel and participants were unlikely to have been blinded due to different dosing regimens
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the code was revealed to researchers at the end of the analysis of results" Judgement comment: blinding not described; quote implies that outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "the parents of three infants expressed an unwillingness to provide a blood sample from their infants, and these patients were subsequently eliminated from the study"

Shakiba 2010 *(Continued)*

		Quote: "they were eliminated from the study if they failed to give their infants more than 15% of the daily doses (> 4 days in a month [36 infants]), or if they did not remember the number of missed days, or in the case of Group I, if more than 200 IU of vitamin D was consumed per day (6 infants)" Judgement comment: high attrition due to non-compliance or inability to remember the number of missed days; possible attrition bias. Quote and Table 2 suggest that those lost to follow-up were excluded from analysis; complete case analysis was done. Characteristics of those lost to follow-up were not evaluated
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified
Other bias	Low risk	Judgement comment: no other risks observed

Shedeed 2012

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Libya **Study period:** April 2008 to July 2010
Participants	**Included criteria:** admitted with congestive heart failure due to dilated cardiomyopathy or congenital heart disease, with systemic left ventricular systolic dysfunction (dilated left ventricle > 2 standard deviations for age and sex together with an ejection fraction > 40%) **Excluded criteria:** any infant with hypercalcaemia, hypocalcaemia, serum creatinine concentration (> 1.5 mg/dl), and nephrolithiasis; actual intake of supplements containing vitamin D and calcium **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (placebo): 34.9 ± 6.1 2. Intervention group (1000 IU D_3): 33.5 ± 5.5
Interventions	**Intervention characteristics** 1000 D_3 1. *Vitamin D content and type*: 1000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 12 weeks 5. *N per group (in analysis)*: 42 6. *Brand/company*: D-Vi-Sol Infant Drops; Mead Johnson Nutritionals Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: daily

Shedeed 2012 *(Continued)*

4. *Duration of administration (study time)*: 12 weeks
5. *N per group (in analysis)*: 38
6. *Brand/company*: not reported

Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): radioimmunoassay (DiaSorin, Stillwater, MN, USA) **Time points:** enrolment, 12 weeks
Notes	Sample size not calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "subjects randomly allocated by systematic random sampling into two groups: group I included 42 patients who received a daily supplement of 25 µg (1,000 IU) cholecalciferol (D-Vi-Sol Infant Drops; Mead Johnson Nutritionals), and group II included the other 38 subjects who received the placebo oral drops" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Low risk	Quote: "group I included 42 patients who received a daily supplement of 25 lg (1,000 IU) cholecalciferol (D-Vi-Sol Infant Drops; Mead Johnson Nutritionals), and group II included the other 38 subjects who received the placebo oral drops (vitamin D-free distilled water). Both groups and the investigators were unaware with the nature of the oral drops bottles (the vitamin D and placebo bottles were identical in shape)" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both groups and the investigators were unaware with the nature of the oral drops bottles (the vitamin D and placebo bottles were identical in shape)" Judgement comment: blinding of participants and investigators not specifically indicated but implied due to allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement comment: blinding of outcome assessors not specifically indicated; outcomes objective in nature
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: no discussion of loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol cited
Other bias	Low risk	Judgement comment: no other risks observed

Siafarikas 2011

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Northern German Society of Paediatric and Adolescent Medicine **Country:** Germany **Study period:** autumn/winter (October to March) and spring/summer (April to September) (year not reported)
Participants	**Included criteria:** delivery at Hospital Berlin-Lichtenberg, Germany; breastfeeding **Excluded criteria:** vitamin D supplementation during pregnancy, drug abuse, premature delivery, highly pigmented skin **Baseline vitamin D status (mean (95% confidence interval); nmol/L)** 1. Control group (250 IU D_3): 68.0 (53.0 to 83.0) 2. Intervention group (500 IU D_3): 68.0 (58.0 to 83.0)
Interventions	**Intervention characteristics** 250 IU D_3 1. *Vitamin D content and type*: 250 IU D_3 2. *Formulation*: tablet, dissolved 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 weeks 5. *N per group (in analysis)*: 14 6. *Brand/company*: Vigantoletten 500 IE; Merck Pharma, Darmstadt, Germany 500 IU D_3 1. *Vitamin D content and type*: 500 IU D_3 2. *Formulation*: tablet, dissolved 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 weeks 5. *N per group (in analysis)*: 14 6. *Brand/company*: Vigantoletten 500 IE; Merck Pharma, Darmstadt, Germany
Outcomes	**Primary** 1. Linear growth 2. Adverse effect: hypercalciuria 3. Adverse effect: hypercalcaemia 4. Adverse event: hyperphosphataemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Rickets **Measurement** 1. Length (cm): standardised calibrated equipment a. **Notes:** data presented as mean (95% CI), which we converted to standard deviation

Siafarikas 2011 *(Continued)*

2. Hypercalciuria (urinary calcium-to-creatinine): standard equipment/methods
   a. Definition: not reported
   b. **Notes:** no events in either arm; data did not contribute to meta-analysis
3. Adverse effect: hypercalcaemia (serum calcium): standard equipment
   a. Definition: not reported
   b. **Notes:** no events in either arm; data did not contribute to meta-analysis
4. Adverse event: hyperphosphataemia (serum phosphorus): standard equipment
   a. Definition: not reported
   b. **Notes:** no events in either arm; data did not contribute to meta-analysis
5. Serum 25(OH)D (nmol/L): radioimmunoassay (Biosource, Brussels, Belgium)
   a. **Notes:** data presented as mean (95% CI), which we converted to standard deviation
6. Rickets: clinical signs
   a. **Notes:** no events in either arm; data did not contribute to meta-analysis

Time points: birth, 6 weeks

Notes	Sample size calculated but not met

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "using odd and even numbers taken from opaque envelopes, participants were randomised into two subgroups (n=20) on either 250 or 500 units of vitamin D3 as a daily supplement" Judgement comment: even/odd (non-sequentially numbered) envelopes are considered at high risk of selection bias
Allocation concealment (selection bias)	High risk	Quote: "families received detailed instructions on how to dissolve either one (500 IU) or half a tablet (250 IU) in a spoon and administer the tablet to their child" Quote: "using odd and even numbers taken from opaque envelopes, participants were randomised into two subgroups (n=20) on either 250 or 500 units of vitamin D3 as a daily supplement (figure 1)" Judgement comment: opaque envelope but not sequentially numbered; the 2 interventions varied by protocol. Therefore allocation could not have been concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding not described; as allocations varied by protocol, participants may not have been blinded, leading to parental compensation of vitamin D in the control group or impact on nutrition diaries/conduct. Nature of intervention (half tablet and whole tablet) would not facilitate blinding. If investigators knew the intervention allocations, they may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: blinding of outcome assessors is not described. Some outcomes are subjective (clinical signs of rickets)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: a significant number of subjects ended up being excluded due to insufficient blood sample; no discussion of how this many have impacted outcomes. No loss to follow-up; however. Intention-to-treat analysis was not done
Selective reporting (reporting bias)	Unclear risk	Judgement comment: trial registered retrospectively on Australian New Zealand Clinical Trials Registry (ID: ACTRN12609000919213) and World Health

Siafarikas 2011 *(Continued)*

		Organization (ID: U1111–1112-2443), as described in text. Outcomes on registrations are presented in results
Other bias	Low risk	Judgement comment: no other risks observed

Singh 2018a

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** India **Study period:** January 2013 to February 2014
Participants	**Included criteria:** consecutively born, full-term, healthy neonates born to mothers who were residents of Delhi and chose to exclusively breastfeed their infant and consented for participation in this follow-up study **Excluded criteria:** babies with life-threatening congenital malformations, those born to HIV-positive mothers **Group differences:** total alkaline phosphatase was higher in the vitamin D group; serum 25-hydroxyvitamin D (serum 25(OH)D, nmol/L) was higher in the control group; parathyroid hormone was higher in the control group **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (no intervention): 54.7 ± 20.7 2. Intervention group (400 IU D_3): 38.9 ± 36.4
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 49 6. *Brand/company*: not reported No intervention 1. *Duration of administration (study time)*: 6 months 2. *N per group (in analysis)*: 48
Outcomes	**Primary** 1. Linear growth 2. Adverse effect: hypercalciuria 3. Adverse effect: kidney stones **Secondary**

Singh 2018a *(Continued)*

1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)
2. Change in 25(OH)D
3. Serum 25(OH)D < 50 nmol/L
   a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis

Measurement

1. Length (cm): infantometer (Khanna Surgicals, Delhi, India)
2. Hypercalciuria (urinary calcium-to-creatinine ratio): chemiluminescence
   a. Definition: not reported
   b. **Notes:** no events in either arm; data did not contribute to meta-analysis
3. Kidney stones: renal ultrasound
   a. **Notes:** no events in either arm; data did not contribute to meta-analysis
4. Serum 25(OH)D (nmol/L): chemiluminescence (VitroEci Immunoassay Analyser)
   a. **Notes:** data presented as mean (95% CI), which we converted to standard deviation

Time points: enrolment, 6 months of age

Notes	Sample size calculated and met for analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "series of computer-generated random number sequence was prepared by Inclen Trust, New Delhi, using Stata 9.0 software. Block randomisation was done using alternate block sizes of 4 and 6" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "allocation concealment was achieved using sequentially numbered opaque sealed envelopes; safely secured with a person not involved in the study until subject enrolment" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "was an open-label (unblinded), parallel, superiority randomised controlled trial with 1:1 allocation ratio, conducted in post-natal ward setting" Judgement comment: unblinded; as no placebo was used, the nature of the intervention would have made blinding impossible
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "was an open-label (unblinded), parallel, superiority randomised controlled trial with 1:1 allocation ratio, conducted in post-natal ward setting" Judgement comment: unblinded; no mention of outcome assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "a total of 100 babies meeting inclusion criteria were enrolled and randomised to respective groups within 24 hours of birth. Two were lost to follow-up (shifted out of Delhi) and one withdrew consent within initial one week of the study [Table/Fig-2]" Judgement comment: Figure 2 shows minimal loss to follow-up, with balanced, documented reasons (2 were lost to follow-up (shifted out of Delhi) and 1 withdrew consent within first week of the study (Table/Fig 2)). Intention-to-treat analysis analysis was done
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no citation of trial registration or protocol

Singh 2018a *(Continued)*

Other bias	Low risk	Judgement comment: no other risks observed

Singh 2019

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** India **Study period:** January 2013 to September 2014
Participants	**Included criteria:** age 0 to 5 years, diagnosed with recurrent pneumonia according to World Health Organization criteria **Excluded criteria:** diagnosed with rickets, vitamin D deficiency, congenital heart disease, wheezing associated with lower respiratory tract infection, neurological illness, congenital anomaly (kyphosis, scoliosis, cleft lip and palate), measles, whooping cough, tuberculosis, HIV infection, previous vitamin D supplementation, not residing in the given locality for > 1 year **Baseline vitamin D status (n (%) < 75 nmol/L)** 1. Control group (no intervention): 36 (80) 2. Intervention group (400 IU D_3): 35 (76)
Interventions	**Intervention characteristics** 300,000 IU D_3 1. *Vitamin D content and type*: 300,000 IU 2. *Formulation*: granules (dissolved in milk) 3. *Vitamin D type*: D_3 4. *Frequency of dosage*: every 3 months 5. *Duration of administration (study time)*: 20 months 6. *N per group (in analysis)*: 46 7. *Brand/company*: Torflash (Torrent Pharmaceuticals, Ahmedabad, India) Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: granules (castor sugar, dissolved in milk 3. *Frequency of dosage*: every 3 months 4. *Duration of administration (study time)*: 20 months 5. *N per group (in analysis)*: 45 6. *Brand/company*: not reported
Outcomes	None within scope of review
Notes	Sample size not calculated
Risk of bias	

Singh 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	High risk	Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: blinding not described
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: blinding not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: 9 children (9%) were excluded from analysis but only reason appears to be haemolysis of blood samples. Other reasons for loss to follow-up are not described. Intention-to-treat analysis was not done
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified
Other bias	Low risk	Judgement comment: no other risks observed

Somnath 2017

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Jawaharlal Institute of Post-graduate Medical Education & Research (JIPMER) Intramural Grant **Country:** India **Study period:** March 2013 to April 2014
Participants	**Included criteria:** age 2 months to 5 years, lower respiratory infection (LRI) **Excluded criteria:** chronic chest condition presenting as acute LRI such as tuberculosis, bronchial asthma, congenital lung malformation, immunodeficiency state (both congenital and acquired); conditions that interfered with absorption and metabolism of vitamin D (malabsorption syndrome, chronic diarrhoea, liver disease, kidney disease); any known contraindications for vitamin D administration (e.g. nephrocalcinosis, urolithiasis) **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (no intervention): 46.8 ± 35.8 2. Intervention group (100,000 IU D_3): 44.9 ± 28.3
Interventions	**Intervention characteristics** 100,000 IU D_3

Somnath 2017 *(Continued)*

1. *Vitamin D content and type*: 100,000 IU D_3
2. *Formulation*: slurry
3. *Frequency of dosage*: once
4. *Duration of administration (study time)*: 72 hours
5. *N per group (in analysis)*: 78
6. *Brand/company*: not reported

Nothing

1. *Duration of administration (study time)*: 72 hours
2. *N per group (in analysis)*: 76

Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): enzyme-linked immunoabsorbent assay (DIAsource, Chicago, IL, USA) a. **Notes:** data missing for control group; study not part of meta-analysis **Time points:** enrolment, 72 hours
Notes	Sample size calculated n = 70/group. This was met at analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was done by using computer generated random number tables by a resident not involved in the study" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "opaque sealed and serially numbered envelopes were used for allocation concealment" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open labelled" Judgement comment: not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the outcome assessors were blinded to the intervention" Judgement comment: outcome assessors were blinded; outcome measurements are not subjective and are unlikely to be influenced
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "there were a total of 154 children in the age range 2 months 5 years" Judgement comment: no loss to follow-up, but 2 participants had tuberculosis at the end and were excluded. Intention-to-treat analysis was not done
Selective reporting (reporting bias)	Unclear risk	Judgement comment: study was registered retrospectively with Clinical Trial Registry of India (CTRI, ctri.nic.in) (ID: CTRI/2014/09/005032), as reported in text

Somnath 2017 *(Continued)*

Other bias	Low risk	Judgement comment: no other risks observed

Specker 1992

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Thrasher Research Fund, Salt Lake City, UT, USA; and Perinatal Research Institute, Cincinnati, OH, USA **Country:** China **Study period:** fall (September to October 1986) and spring (March and April 1987)
Participants	**Included criteria:** gestational age ≥ 37 weeks **Excluded criteria:** major congenital abnormality, gastrointestinal disease **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 100 IU, North China 1. *Vitamin D content and type*: 100 IU vitamin D 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 47 6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA 200 IU, North China 1. *Vitamin D content and type*: 200 IU vitamin D 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 37 6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA 400 IU, North China 1. *Vitamin D content and type*: 400 IU vitamin D 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 33 6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA 100 IU, South China 1. *Vitamin D content and type*: 100 IU vitamin D 2. *Formulation*: drops 3. *Frequency of dosage*: daily

Specker 1992 *(Continued)*

4. *Duration of administration (study time)*: 6 months
5. *N per group (in analysis)*: 46
6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA

200 IU, South China

1. *Vitamin D content and type*: 200 IU vitamin D
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 6 months
5. *N per group (in analysis)*: 46
6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA

400 IU, South China

1. *Vitamin D content and type*: 400 IU vitamin D
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 6 months
5. *N per group (in analysis)*: 47
6. *Brand/company*: Kremers-Urban Co., Milwaukee, WI, USA

Outcomes

Secondary

1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)
2. Rickets

Measurement

1. Serum 25(OH)D (nmol/L): radioprotein binding assay (Haddad and Chyu)
   a. **Notes:** data not included in meta-analysis due to reported values as mean ± range, which we could not convert to standard deviation
2. Rickets: radiological signs: ossification centres, concavity, fraying of bone, widening of epiphysis
   a. **Notes:** no events in either arm; data did not contribute to meta-analysis

Time points: 3 to 5 days of age, 6 months of age

Notes

Sample size calculated; met for analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "at 3 to 5 days of age each infant was randomly assigned to one of three groups to receive vitamin D supplements of 100, 200, or 400 IU/day" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Unclear risk	Quote: "vitamin D was prepared in propylene glycol (Kremers-Urban Co., Milwaukee, Wis.) and mothers were instructed to give the vitamin preparation to their infants daily. The vitamin D supplements were distributed monthly to mothers... Both mothers and investigators were unaware of assigned dosage" Judgement comment: appropriate allocation concealment; lacking detail
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both mothers and investigators were unaware of assigned dosage" Judgement comment: all personnel and participants were blinded

Specker 1992 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all radiographs were interpreted; ossification centers, as well as signs of rickets (concavity and fraying of bone and widening of epiphysis), were recorded by a pediatric radiologist at Cincinnati Children's Hospital Medical Center who was unaware of the dosage group" Judgement comment: more subjective measures were obtained by a blinded outcome assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "ninety percent of the infants enrolled (280/312) completed the study; cord and 6-month blood samples were available for 256 (82%) of the infants" Judgement comment: loss to follow-up (18%); reasons not given. Appears to be a complete case analysis
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified
Other bias	Low risk	Judgement comment: no other risks observed

Stögmann 1985

Study characteristics	
Methods	**Study design:** quasi-randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Austria **Study period:** not reported
Participants	**Included criteria:** clinical, biochemical, and radiological signs of vitamin D deficiency **Excluded criteria:** none specified **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 200,00 IU D_3 1. *Vitamin D content and type*: 200,000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: day 1 and day 3 4. *Duration of administration (study time)*: 3 days 5. *N per group (in analysis)*: 5 6. *Brand/company*: not reported 9600 IU D_3 1. *Vitamin D content and type*: 9600 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 18 days 5. *N per group (in analysis)*: 5

Stögmann 1985 *(Continued)*

	6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): competitive binding protein assay **Time points:** enrolment; days 3, 7, 14, and 21
Notes	Translated from German to English. Sample size not calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "for this reason, 5 children with vitamin D deficiency echinitis were randomized to receive vitamin D bump therapy or continuous therapy, and the changes in calcium, phosphorus, alkaline phosphatase, 25-OH-cholecalciferol, parathyroid hormone, and calcitonin serum assessed" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Unclear risk	Quote: "children received a vitamin D beating therapy (5 mg each = 200,000 IU of vitamin D3 on day 1 and day 3, referred to below as group I), 5 children a continuous therapy (9600 IU of vitamin D3 (2 x 12 drops) glycollarcolic cholecalciferol solution by 18 days, hereinafter called group II)" Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: no description of blinding; could have led to parental compensation; unlikely parents were blinded, as dosing schedules were different
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: no description of blinding; unlikely outcome assessors were blinded, which may lead to bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: no loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified
Other bias	Low risk	Judgement comment: no other risks observed

Tang 2019

Study characteristics

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group

Tang 2019 *(Continued)*

	Funding: 100% non-profit. Children's Hospital of Chongqing Medical University and Chongqing City Health and Family Planning Committee (grant no 2016MSXM033) **Country:** China **Study period:** 20 October 2016 to 15 February 2018
Participants	**Included criteria:** met 2001 International League of Associations for Rheumatology classification criteria, children with newly diagnosed juvenile idiopathic arthritis (JIA), signed informed consent **Excluded criteria:** history of kidney stones, hypercalciuria, intestinal malabsorption, primary cardiovascular disease, lung disease, blood disease, liver disease; history of using drugs that inhibit bone resorption; history of allergy to vitamin D; refusal to participate in the study; treatment with methylprednisolone, biological agents, or cyclophosphamide **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (no intervention): 51.6 ± 34.8 2. Intervention group (2000 IU D_3): 33.2 ± 12.9
Interventions	**Intervention characteristics** 2000 IU D_3 1. *Vitamin D content and type*: 2000 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 24 weeks 5. *N per group (in analysis)*: 5 (stratified data) 6. *Brand/company*: Xiamen Lipin Pharmaceutical Co., Ltd., Fujian, China 7. *Co-intervention*: standard therapy: glucocorticoids (0.5 to 1 mg/kg/d), non-steroidal anti-inflammatory drugs (30 to 40 mg/kg/d), methotrexate (10 to 15 mg/m^2/week), or sulfasalazine (30 to 50 mg/kg/d) No intervention 1. *Duration of administration (study time)*: 24 weeks 2. *N per group (in analysis)*: 7 (stratified data) 3. *Co-intervention*: standard therapy: glucocorticoids (0.5 to 1 mg/kg/d), non-steroidal anti-inflammatory drugs (30 to 40 mg/kg/d), methotrexate (10 to 15 mg/m^2/week), or sulfasalazine (30 to 50 mg/kg/d)
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): high-performance liquid chromatography apparatus (APS80-16D; AUPOS) **Time points:** enrolment, 12 weeks, 24 weeks
Notes	Stratified data sent by study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were selected using a table of random numbers" Judgement comment: random sequence generation method unclear

Tang 2019 *(Continued)*

Allocation concealment (selection bias)	High risk	Judgement comment: control group received nothing; allocation was not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label" Judgement comment: not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open-label" Judgement comment: not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "the remaining patients were assigned randomly to the CG (n=22) or the EG (n=20). A total of six patients withdrew for personal reasons or were lost to follow-up. Finally, 36 subjects completed the trial and were included in the analysis (n=18 per group)" Judgement comment: some loss to follow-up; intent-to-treat analysis not performed
Selective reporting (reporting bias)	Unclear risk	Judgement comment: trial registered prospectively on Chinese Clinical Trial Registry (ID: ChiCTR-INR-16009235), as described in text. Outcomes listed in trial registration are cytokines but not 25(OH)D, JADAS-27, or BMD z-score
Other bias	Low risk	Judgement comment: no other risks observed

Tergestina 2016

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Institutional Fluid Research Grant **Country:** India **Study period:** January to November 2013
Participants	**Included criteria:** gestational age of 27 to 34 weeks **Excluded criteria:** major congenital anomaly, maternal condition or medication likely to influence vitamin D or calcium metabolism, neonates not attaining 100 mL/kg feeds by 14 days of life **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (400 IU D_3): 61.8 ± 83.4 2. Intervention group (1000 IU D_3): 57.7 ± 38.0
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: enteral 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: ~ 51 days

Tergestina 2016 *(Continued)*

5. *Other micronutrient content*: calcium gluconate 100 mg 3×/d; phosphate (neutral phosphate 50 mg 2×/d); and multi-vitamin drops (400 IU vitamin D) after enteral feeds reached 100 mL/kg per day
6. *N per group (in analysis)*: 48
7. *Brand/company*: not reported

1000 IU D_3

1. *Vitamin D content and type*: 1000 IU D_3
2. *Formulation*: enteral
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: ~ 51 days
5. *Other micronutrient content*: calcium gluconate 100 mg 3×/d; phosphate (neutral phosphate 50 mg 2×/d); and multi-vitamin drops (400 IU vitamin D) after enteral feeds reached 100 mL/kg per day
6. *N per group (in analysis)*: 51
7. *Brand/company*: not reported

Outcomes

Primary

1. Adverse effect: hypercalciuria
2. Adverse effect: hypercalcaemia

Secondary

1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)
2. Serum 25(OH)D < 50 nmol/L
   a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis

Measurement

1. Hypercalciuria (urinary calcium-to-creatinine ratio): urine spot
   a. Definition: > 1.35 mg/mg
   b. **Notes:** "elevated urine spot calcium creatinine ratios were similar in the 2 groups (6.2% vs 13.7%, P = 0.320)" (quote); however, which data belong to which arm is not indicated; therefore they are not included in the meta-analysis
2. Hypercalcaemia (serum calcium): spectrophotometric methods, auto-analyser
   a. Definition: > 10.8 mg/dL
   b. **Notes:** no events in either arm; data did not contribute to meta-analysis
3. Serum 25(OH)D (nmol/L): electrochemiluminescence immunoassay (Roche E 170, Mannheim, Germany)

Time points: enrolment, 40 weeks' corrected gestational age

Notes

Sample size calculated n = 50/arm. This was met at randomisation but not for group 1 at analysis. Study was underpowered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "block randomization with sizes of 2, 4 and 6 with 25, 25 and 50% allocation were used" Judgement comment: random sequence generation method not described
Allocation concealment (selection bias)	Low risk	Quote: "serially numbered opaque sealed envelopes were used to conceal the allocation. The drugs were identical in appearance, color and taste and were contained in amber-colored bottles labeled with serial numbers corresponding to the envelopes. The randomization code was known only to the pharmacy and the statistician"

Tergestina 2016 *(Continued)*

		Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind... blinding the investigators and the family... the randomization code was known only to the pharmacy and the statistician, blinding the investigators and the family" Judgement comment: all personnel and participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind... blinding the investigators and the family... the randomization code was known only to the pharmacy and the statistician, blinding the investigators and the family" Judgement comment: outcome assessors were blinded, although this quote implies that statisticians were not blinded for analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "120 babies were enrolled in the trial, with 60 babies randomized into each arm. Twenty one babies were lost to follow-up—12 babies in the 400 IU arm and 9 babies in the 1000 IU arm. Post discharge, three sets of twins were not exclusively administered 400 or 1000 IU of vitamin D by their caregivers. This constituted a breach of study protocol, was recorded as such and analysis was on an intention to treat basis" Judgement comment: loss to follow-up (18%); reasons were not given; relatively balanced by arm; intention-to-treat analysis done.
Selective reporting (reporting bias)	Low risk	Judgement comment: study was registered retrospectively with Clinical Trial Registry of India (CTRI, ctri.nic.in) (ID: CTRI/2012/11/003154), as reported in text. All prespecified outcomes were reported
Other bias	Low risk	Judgement comment: no other risks observed

Thacher 2014

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Grant Number 1 UL1 RR024150, from the National Center for Research Resources **Country:** Nigeria **Study period:** February 2004 and November 2006
Participants	**Included criteria:** children with active rickets, identified using radiographs of the wrists and knees from among children who presented with leg deformities. Children were eligible for enrolment if they had a radiographic score ≥ 2.5 on a validated 10-point scoring method that assessed the severity of rickets in growth plates of the distal radius and ulna and around the knee **Excluded criteria:** none specified **Pretreatment:** Nigerian children with active rickets treated with calcium carbonate as limestone (approximately 938 mg elemental calcium twice daily) were randomised to receive either oral vitamin D 250,000 IU (calcium and vitamin D, n = 44) or placebo (calcium, n = 28) monthly for 24 weeks. All children were treated with calcium carbonate as powdered limestone. Powdered limestone was locally available at a much lower cost than calcium tablets. The content of elemental calcium in 1.0 g of limestone was 268 mg (courtesy of Michael Gruzak, USA Department of Agriculture/Agriculture Research

Thacher 2014 *(Continued)*

	Service (USDA/ARS), Children's Nutrition Research Center, Houston, TX, USA). Samples of limestone had no toxic concentrations of heavy metals. One level teaspoon of powdered limestone (approximately 3.5 g = 938 mg of elemental calcium) was mixed with the child's food or porridge twice daily **Baseline vitamin D status (mean (95% confidence interval); nmol/L)** 1. Control group (placebo): 31.9 (26.5 to 37.3) 2. Intervention group (50,000 IU D_2): 28.8 (23.9 to 33.7)
Interventions	**Intervention characteristics** 50,000 IU D_2, Ca+ 1. *Vitamin D content and type*: 50,000 IU D_2 2. *Formulation*: gel pill 3. *Frequency of dosage*: every 4 weeks 4. *Duration of administration (study time)*: 24 weeks 5. *Other micronutrient content*: 938 mg calcium, 2× per day 6. *N per group (in analysis)*: 29 (stratified data) 7. *Brand/company*: Pliva, Inc., East Hanover, NJ, USA Placebo, Ca+ 1. *Vitamin D content and type*: none 2. *Formulation*: gel pill 3. *Frequency of dosage*: every 4 weeks 4. *Duration of administration (study time)*: 24 weeks 5. *Other micronutrient content*: 938 mg calcium, 2× per day; B-complex vitamin (no other detail given) 6. *N per group (in analysis)*: 24 (stratified data) 7. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Rickets **Measurement** 1. Serum 25(OH)D (nmol/L): isotope-dilution liquid chromatography with tandem mass spectrometry a. **Notes:** data presented as mean (95% CI), which we converted to standard deviation 2. Rickets: radiographic scores **Time points:** enrolment, 24 weeks
Notes	Received age-stratified information from study author (n = 53 under 5 years of age, out of 68). Due to the coin toss method, the calcium-only group was underpowered. Calculations were done but were not met, target being n = 40/group; this was not met at randomisation nor at analysis. Power to detect was only 46%. However, study authors state that lack of power does not affect conclusions related to findings that were statistically significant Ca+: included calcium

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "enrolled children were randomised by coin toss (performed by TDT) to receive under direct observation either oral vitamin D 2 as 50 000 IU (ergocalciferol; Pliva, Inc., East Hanover, New Jersey) once every 4 weeks (Ca+D group)

Thacher 2014 *(Continued)*

		or placebo, which was a single vitamin B complex tablet, once every 4 weeks (Ca group) for 24 weeks" Judgement comment: coin toss, a low-tech appropriate randomisation method
Allocation concealment (selection bias)	Unclear risk	Quote: "to receive under direct observation either oral vitamin D2 as 50,000 IU (ergocalciferol; Pliva, Inc., East Hanover, New Jersey) once every 4 weeks (calcium and vitamin D group) or placebo, which was a single vitamin B complex tablet, once every 4 weeks (Calcium group) for 24 weeks" Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: no blinding described; it is possible that caregivers were blinded as intervention was given under direct observation of study personnel; however, differences in interventions would make blinding impossible. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: no blinding is described; outcomes such as symptoms of rickets and diet are subjective and therefore are prone to possible bias if not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "total of 254 children presented with leg deformities, and 72 subjects with radiographically active rickets were enrolled between February 2004 and November 2006 (figure 1)" Judgement comment: loss to follow-up: 1 and 3 per arm - a low proportion. Reasons for loss to follow-up not given. Intention-to-treat analysis not done
Selective reporting (reporting bias)	Unclear risk	Quote: "trial registration number ClinicalTrials.gov NCT00949832" Judgement comment: study was carried out between 2004 and 2006, but study was registered in 2009 so was not prespecified. Prespecified and reported outcomes match
Other bias	Low risk	Judgement comment: no other risks observed

Tomimoto 2018

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% for profit. Morishita Jintann Co., Osaka, Japan **Country:** Japan **Study period:** 19 January 2016 to unknown end date
Participants	**Included criteria:** 3 to 4 months of age with vitamin D deficiency (< 50 nmol/L) **Excluded criteria:** underlying disease, mixed feeding (artificial milk > 50 mL/d), fever, anorexia, vitamin D supplementation for mother or child, vitamin D deficiency with clinical manifestations of rickets

Tomimoto 2018 *(Continued)*

	Baseline vitamin D status (n (%) < 50 nmol/L) 1. Control group (160 IU D_3): 45 (100) 2. Intervention group (400 IU D_3): 46 (100)
Interventions	**Intervention characteristics** 160 IU 1. *Vitamin D content and type*: 160 IU vitamin D 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 weeks 5. N *per group (in analysis)*: 45 6. *Brand/company*: not reported 400 IU 1. *Vitamin D content and type*: 400 IU vitamin D 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 weeks 5. N *per group (in analysis)*: 46 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D < 50 nmol/L a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis **Measurement** 1. Serum 25(OH)D (nmol/L): not reported **Time points:** enrolment, 4 weeks
Notes	Sample size not described (abstract of full-text paper only)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: random sequence generation method not described (abstract only)
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described (abstract only)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open label" (trial registration) Judgement comment: unblinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open label" (trial registration) Judgement comment: unblinded study

Tomimoto 2018 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: not described
Selective reporting (reporting bias)	Low risk	Judgement comment: trial registration number available (JMA-IIA00243) and outcomes specified on registration reported, quantitatively and qualitatively, in identified abstract
Other bias	Low risk	Judgement comment: no other risks observed

Trilok-Kumar 2011

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Department of Biotechnology, Ministry of Science and Technology, Government of India; Nutrition Third World; Sight and Life **Country:** India **Study period:** March 2007 to July 2010
Participants	**Included criteria:** singleton, ≥ 37 weeks' gestation, birth weight 1.8 to 2.5 kg, 48 hours of age, living within a 15-km radius of Safdarjung Hospital, parental informed consent **Excluded criteria:** severe congenital abnormality, morbidity severe enough to result in death before age 7 days, intention to live outside catchment area before the infant reaches 6 months of age, lack of consent **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 1400 IU D_3 1. *Vitamin D content and type*: 1400 IU D_3 2. *Formulation*: granulated 3. *Frequency of dosage*: weekly 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 744 (morbidity); 634 (anthropometry) 6. *Brand/company*: Cadilla Pharmaceuticals, Gujarat, India Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: granulated 3. *Frequency of dosage*: weekly 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: 745 (morbidity); 648 (anthropometry) 6. *Brand/company*: Cadilla Pharmaceuticals, Gujarat, India
Outcomes	**Primary** 1. Length/height-for-age z-score (L/HAZ)

Trilok-Kumar 2011 *(Continued)*

2. Stunting

Secondary

1. Weight-for-age z-score (WAZ)
2. Underweight
3. Weight-for-length/height WL/HZ-score
4. Wasting
5. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)
6. Serum 25(OH)D < 50 nmol/L
   a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis

Measurement

1. Length (cm): infantometer (Sumit Surgicals, Delhi, India)
2. Z-score: World Health Organization Child Growth Standards (WHO 2006)
   a. **Notes:** we included raw, unadjusted data in the meta-analysis.
3. Stunting (L/HAZ < 2 standard deviations from reference standard) (WHO 2006)
4. Weight (kg): Prestige Baby Weighing Scale (HM-008A; Hardik Medi Tech, Delhi, India)
5. Serum 25(OH)D (nmol/L): radioimmunoassay, 25OH Vitamin D Total Assay kits (Diasorin; Stillwater, MN, USA)

Time points: enrolment, 6 months, follow-up at 3 to 5 years

Notes	Calculated sample size met at randomisation but not met for analysis of anthropometry or morbidity

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a simple randomisation list without blocking was computer generated and held by the data safety and monitoring board only" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "at enrolment the infants were randomised to receive each week, starting at 7 days of age and continuing to 6 months (maximum of 25 doses), either 35 µg (1400 IU) granulated vitamin D 3 (cholecalciferol), which is the Food and Agriculture Organization/World Health Organization recommended nutrient intake of 5 µg (200 IU) per day, 14 or an identical appearing and tasting placebo (both prepared by Cadilla Pharmaceuticals, Gujarat, India). The ethics committee did not permit use of a larger vitamin D dose. The data safety and monitoring board individually labelled the sachets containing vitamin D or placebo crystals with the participant identification number" Judgement comment: appropriate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the study team remained blinded to treatment allocation until the primary and growth outcomes had been analysed" Judgement comment: double-blind implies that both participants and personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the study team remained blinded to treatment allocation until the primary and growth outcomes had been analysed" Judgement comment: double-blind implies that outcome assessors, as well as statisticians, were blinded

Trilok-Kumar 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "the study's main limitation was the large loss to follow-up, but controlling for factors associated with missing data did not alter the results. In addition, although the death rate was similar to that used in the calculations of sample size, inpatient admissions were much lower so power was reduced and the confidence interval was wide and included the original estimate of a 25% reduction in the primary outcome. We estimate that, with the observed rate for the primary outcome in the placebo group and the observed loss to follow-up, we would have needed to recruit 1500 infants per group to detect the planned 25% reduction in mortality plus admission to hospital" Judgement comment: large loss to follow-up (Figure 1), with reasons documented unrelated to study interventions; missingness was examined. Intention-to-treat was performed
Selective reporting (reporting bias)	Low risk	Judgement comment: trial registered prospectively on ClinicalTrials.gov (ID: NCT00415402), as reported in text. Prespecified outcomes are consistent with those reported
Other bias	Low risk	Judgement comment: no other risks observed

Willi 1959

Study characteristics	
Methods	**Study design:** quasi-randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Switzerland **Study period:** 1954 to 1959
Participants	**Included criteria:** preterm infants with birth weight 1500 g **Excluded criteria:** none specified **Baseline vitamin D status:** not reported
Interventions	**Intervention characteristics** 4000 to 6000 IU D_2 1. *Vitamin D content and type*: 4000 to 6000 IU D_2 2. *Formulation*: mixed with milk 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 weeks 5. *Other micronutrient content*: none 6. *N per group (in analysis)*: 55 7. *Brand/company*: Gewo 1000 to 2000 IU D_2 1. *Vitamin D content and type*: 1000 to 2000 IU D_2 2. *Formulation*: mixed with milk 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 weeks

Willi 1959 *(Continued)*

5. *Other micronutrient content*: none
6. *N per group (in analysis)*: 15
7. *Brand/company*: Gewo

500 to 1000 IU D_2

1. *Vitamin D content and type*: 500 to 1000 IU D_2
2. *Formulation*: mixed with milk
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 4 weeks
5. *Other micronutrient content*: calcium phosphate bibasic 400 to 800 mg/kg
6. *N per group (in analysis)*: 16
7. *Brand/company*: Gewo
8. **Note: arm not included in data synthesis**

500 to 800 IU D_2

1. *Vitamin D content and type*: 500 to 800 IU D_2
2. *Formulation*: mixed with milk
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 4 weeks
5. *Other micronutrient content*: calcium gluconate or calcium lactate, 400 to 800 mg/kg
6. *N per group (in analysis)*: 14
7. *Brand/company*: Gewo
8. **Note: arm not included in data synthesis**

Outcomes	**Secondary** 1. Rickets **Measurements** 1. Rickets: radiographic signs (not specified): not reported **Time point:** 4 weeks of age
Notes	This study was translated from German. Sample size and power were not calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "the experiments were mainly carried out alternately" Judgement comment: alternating randomisation methods indicate high risk of bias
Allocation concealment (selection bias)	High risk	Quote: "preparation (Oldevit Gewo) containing 20 000 IU per ml and a powdered vitamin D 2 preparation containing, in 1 g, 750 IU of vitamin D and 600 mg of calcium phosphoricum bibasicum (decalcit Gewo)" Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias

Willi 1959 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: if blinding was done, this was not described. However, outcomes measured are not subjective in nature and are less likely to be influenced by knowledge of the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: loss to follow-up not described
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or reference protocol found
Other bias	Low risk	Judgement comment: no other risks observed

Zeghoud 1994

Study characteristics	
Methods	**Study design:** quasi-randomised controlled trial **Study grouping:** parallel group **Funding:** undisclosed **Country:** Algeria **Study period:** 1991 to 1992
Participants	**Included criteria:** born during September or October 1991, normal pregnancy **Excluded criteria:** vitamin D supplementation during pregnancy **Pretreatment:** Group 1 was given 1 oral dose (at birth) of 5 mg cholecalciferol; Group 2 was given 3 trimestral oral doses (at birth, 3 months, and 6 months of age) of 2.5 mg cholecalciferol **Baseline vitamin D status (mean, nmol/L)** 1. Control group (100,000 IU D_3): 25.0 2. Intervention group (200,000 IU D_3): 25.0
Interventions	**Intervention characteristics** 200,000 IU D_3 1. *Vitamin D content and type*: 200,000 IU D_3 2. *Formulation*: liquid (in ethanol) 3. *Frequency of dosage*: once 4. *Duration of administration (study time)*: 9 months 5. *N per group (in analysis)*: 15 6. *Brand/company*: Uvedose, Cninex laboratories, Montrouge, France 100,000 IU D_3 1. *Vitamin D content and type*: 100,000 IU D_3 2. *Formulation*: liquid (in ethanol) 3. *Frequency of dosage*: every three months (0, 3, and 6 months) 4. *Duration of administration (study time)*: 9 months 5. *N per group (in analysis)*: 15

Zeghoud 1994 *(Continued)*

	6. *Brand/company*: Uvedose, Cninex laboratories, Montrouge, France
Outcomes	**Primary** 1. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Hypercalcaemia (serum calcium): standard methods a. Defined as > 11.2 mg/dL 2. Serum 25(OH)D (nmol/L): radiocompetitive protein-binding assay (rat serum) after methanol-chloroform extraction and chromatography on silicic acid columns of 50 µL serum samples **Time points:** enrolment; 0.5, 3, 6, 6.5, and 9 months of age
Notes	No sample size calculation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "30 neonates born during September and October were randomly assigned to one of two groups: group" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "group 1 was given one oral dose of 5 mg cholecalciferol at birth (Uvedose; Cninex laboratories, Montrouge, France); group 2 was given 2.5 mg cholecalciferol at birth and 3 and 6 mo of age (Uvedose)" Judgement comment: blinding not described but not possible: Group 1 was given a single dose, and Group 2 was given 3 separate doses across 6 months. Not blinding participants may lead caregivers in control arm to compensate by administering additional vitamin D doses to children, while investigators who know the intervention allocations may be biased toward a particular outcome; both increase the risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	High risk	Judgement comment: blinding not described but unlikely: Group 2 (2.5 mg) was assessed at more time points than Group 1 (5 mg); therefore it is clear to both participants and personnel who was included in each group and what dose they were receiving, and that Group 2 was being assessed more often
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: from Table 2, only the 2.5 mg cholecalciferol group has data reported at all time points. Intent-to-treat analysis was not done. Loss to follow-up was not described. Attrition is not reported
Selective reporting (reporting bias)	Unclear risk	Judgement comment: no trial registration or protocol identified
Other bias	Low risk	Judgement comment: no other risks observed

Ziegler 2014

Study characteristics	
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. National Institutes of Health, grant HD048870 **Country:** USA **Study period:** September 2006 to October 2010
Participants	**Included criteria:** born between June and November, term infants (gestational age ≥ 37 weeks), either gender, birth weight > 2500 g; considered normal by parents, physicians, and investigators; exclusively breastfed at the time of enrolment **Excluded criteria:** none **Baseline vitamin D status (mean ± standard deviation; nmol/L)** 1. Control group (200 IU D_3): 35.1 ± 18.7 2. Intervention group (400 IU D_3): 42.2 ± 18.6 3. Intervention group (600 IU D_3): 43.4 ± 21.0 4. Intervention group (800 IU D_3): 44.2 ± 19.8
Interventions	**Intervention characteristics** 200 IU D_3 1. *Vitamin D content and type*: 200 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 8 months 5. *N per group (in analysis)*: 38 6. *Brand/company*: UnitDrugCo, Centennial, CO, USA 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 8 months 5. *N per group (in analysis)*: 30 6. *Brand/company*: UnitDrugCo, Centennial, CO, USA 600 IU D_3 1. *Vitamin D content and type*: 600 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 8 months 5. *N per group (in analysis)*: 27 6. *Brand/company*: UnitDrugCo, Centennial, CO, USA 800 IU D_3 1. *Vitamin D content and type*: 800 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily

Ziegler 2014 *(Continued)*

4. *Duration of administration (study time)*: 8 months
5. *N per group (in analysis)*: 24
6. *Brand/company*: UnitDrugCo, Centennial, CO, USA

Outcomes	**Primary** 1. Adverse effect: hypercalcaemia **Secondary** 1. Gain in length (linear growth) a. **Notes:** males and females separate; combined for analysis 2. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 3. Serum 25(OH)D < 50 nmol/L a. **Notes:** converted to vitamin D sufficiency ≥ 50 nmol/L for meta-analysis 4. Serum 25(OH)D < 30 nmol/L **Measurement** 1. Length (cm): standardised methods 2. Hypercalcaemia (serum calcium): colorimetric using o-cresolphthalein complexone (Pointe Scientific, Canton, MI, USA) a. Definition: not reported 3. Serum 25(OH)D (nmol/L): equilibrium radioimmunoassay, Heartland Assays (Ames, IA, USA) **Time points:** enrolment (1 month of age); 2, 4, 5.5, 7.5, 9, and 12 months of age
Notes	Sample size re-calculation: n = 32/group. Dose of 800 IU/d was added after study was under way. This was met up until the 4-month time point

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "under the modified design, the new dose (800 IU/day) received three codes and the original doses each received two new codes. In this way, it could be expected that at the conclusion of the trial approximately equal numbers of infants would have received each of the four doses. New random sequences of nine codes (G–O) were generated" Quote: "randomization and blinding: Under the initial design, two letter codes were used for each of the three doses. Random sequences of the six codes (A–F) were generated using SAS proc plan. Randomization was stratified for gender and birth weight (2,500–3,350 g vs. >3,350 g). At enrollment, infants were assigned to the next letter code on the list. Infants continued to receive the assigned supplement until 9 mo of age. All study personnel and parents were blinded to the identity of the supplements" Judgement comment: appropriate sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "the study vD supplements were prepared by UnitDrugCo in Centennial, CO, who also kept the code until the intervention was completed. Supplements were supplied in opaque bottles containing 50 ml each" Judgement comment: appropriate allocation concealment by a third party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind... Under the modified design, the new dose (800 IU/day) received three codes and the original doses each received two new codes. In this way, it could be expected that at the conclusion of the trial approximately equal numbers of infants would have received each of the four doses. New

Ziegler 2014 *(Continued)*

		random sequences of nine codes (G–O) were generated. The identity of all codes was kept by the manufacturer of the supplements and was broken only after all study data had been gathered" Judgement comment: double-blind implies that participants and study personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind... The identity of all codes was kept by the manufacturer of the supplements and was broken only after all study data had been gathered" Judgement comment: double-blind implies that outcomes assessors were blinded, and code was kept by a third party
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "the data were analyzed on an intention-to-treat basis" Judgement comment: intention-to-treat analysis analysis; moderate loss to follow-up throughout study period due to parental feeding choices; characteristics of infants who withdrew from the study did not differ from those of infants who completed the study to 9 or 12 months
Selective reporting (reporting bias)	Low risk	Quote: "the trial was registered with ClinicalTrials.gov under NCT00494104" Quote: "at the time the study was initiated, the recommended dose of supplemental vD was 200 IU/day (11). In its original design, the study was to test 200, 400, and 600 IU/day. The addition of a dose of 800 IU/day was deemed necessary when a number of infants showed 25(OH)D levels <50 nmol/l in spite of receiving [vitamin D] supplements. The primary endpoint was plasma 25(OH)D concentration. Secondary outcomes were illness incidence and growth. Bone mineral content and measures of bone turnover were determined, but the findings are to be reported separately" Judgement comment: trial registered retrospectively on ClinicalTrials.gov (ID: NCT00494104), which we identified through separate searching; outcomes in registration are presented in results
Other bias	Low risk	Judgement comment: no other risks observed

AOM: acute otitis media.
CI: confidence interval.
HPLC: high-performance liquid chromatography.
L/HAZ: length/height-for-age z-score.
NEC: necrotising enterocolitis.
NICU: neonatal intensive care unit.
PMA: postmenstrual age.
RIA: radioimmunoassay.

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

Study	Reason for exclusion
Abrams 2013	No stratified data available for study population; age group 4 to 8 years (study author contacted via email but no response received)
Atkinson 2017	No stratified data available for study population; age group 1 to 21 years (study author contacted via email but no response received)

Study	Reason for exclusion
Camargo 2014	No stratified data available for study population; age group 2 to 17 years (study author contacted via email and responded: no time to re analyse data)
Dehbroki 2019	No stratified data available for study population; age group 2 to 18 years (study author contacted via email but no response received)
Galli 2015	No stratified data available for study population; age group 6 to 195 months (study author contacted via email but no response received)
Gottschlich 2017	No stratified data available for study population; age group 0.7 to 18.4 years (study author contacted via email but no response received)
Hamidieh 2016	No stratified data available for study population; age group 1 to 15 years (study author contacted via email but no response received)
Homola 2011	No stratified data available for study population; age group not explicitly stated (study author contacted via email and responded: no time to share raw data)
Kakalia 2011	Age group above 5 years (study author contacted via email and responded that stratified data were available for study age group of 3 to 18 years, but only 3 participants were under 5 years of age; they did not provide the data in response to follow-up emails)
Kashif 2014	No stratified data available for study population; age group 1 to 12 years (study author contacted via email and responded, but follow-up attempts were unsuccessful)
Kazemi 2010	No stratified data available for study population; age group over 3 years; upper age range not stated (study author contacted via email but no response received)
Kerley 2017	No stratified data available for age group under 18 years (study author contacted via email and responded: data are not retrievable)
Lal 2018	No stratified data available for study population; age group 1.5 to 18 years (study author contacted via email but no response received)
Lara-Corrales 2019	No stratified data available for study population; age group 0 to 18 years (study author contacted via email but no response received)
Lee 2018	No stratified data for study population; age group 3 to 20 years (study author contacted via email but no response received)
Loeb 2019	No stratified data for study population; data on age group 3 to 17 years were available via study authors (study authors contacted and responded: provided information via email)
Mazahery 2019	No stratified data for study population; age group 2.5 to 8 years (study author contacted via email but no response received)
Merrikhi 2018	No stratified data available for study population; age group 2 to 12 years (study author contacted via email but no response received)
Morcos 1998	No stratified data available for study population; age group 1.5 to 13 years (study author contacted via email but no response received)
Mortensen 2016	No stratified data available for study population; age group 4 to 8 years (study author contacted via email but no response received)

Study	Reason for exclusion
Muske 2018	No stratified data available for study population; age group 1 to 18 years (study author contacted via email but no response received)
Nwosu 2014	No stratified data available for study population; age group 3 to 18 years (study author contacted via email but no response received)
Rahmati 2018	No stratified data available for study population; age group 3 to 14 years (study author contacted via email but no response received)
Saad 2018	Retracted
Sharma 2017	No stratified data available for study population; age group 1 to 18 years (study author contacted via email but no response received)
Shroff 2012	No stratified data available for study population; age group under 18 years (study author contacted via email and responded: requested blank spreadsheet to provide stratified data, which was sent; no further response received)
Siafarikas 2009	Meeting abstract. No stratified data available for study population; age group ≤ 16 years (study author contacted via email but no response received)
Sidbury 2008	No stratified data available for study population; age group 1 to 18 years (study author contacted via email and responded: most study participants were older than 5 years; could not share stratified data)
Simon 2016	No stratified data available for study population; age group 1 to 18 years (study author contacted via email but no response received)
Singh 2018b	No stratified data available for study population; age group 1 to 18 years (study author contacted but no response received) Note: study cites CTRI registration number as "CTRI/2015/10/009984" with the title, "Comparison of the efficacy of two dosing regimens of Vitamin D for bone protection in children with difficult nephrotic syndrome"; however, the correct CTRI number with this title is "CTRI/2016/10/007405," as referenced in this review
Suryanto 2018	No stratified data available for study population; age group 1 to 18 years (study author contacted via email but no response received)
Swangtrakul 2020	No children younger than 5 years included in study (study author contacted via email and responded with confirmation)
Talaat 2016	No stratified data available for study population; age group 2 to 16 years (study author contacted via email but no response received)
Tannous 2018	No stratified data available for study population; age group 1 to 18 years (study author contacted via email but no response received)
Udompataikul 2015	No stratified data available for study population; age group 1 to 18 years (study author contacted via email but no response received)
Wadia 2018	No stratified data available for study population; age group 5.5 months to 16 years (study author contacted via email but no response received)
Zulkarnain 2019	No stratified data available for study population; age group 2 to 12 years (study author contacted via email but no response received)

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

Bantz 2015

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** USA
Participants	**Included criteria:** atopic children with inadequate vitamin D levels **Excluded criteria:** not specified
Interventions	**Intervention characteristics** 1000 IU, for children with serum 25-hydroxyvitamin D (25(OH)D) concentration 20 to 30 ng/mL 1. *Vitamin D content and type*: 1000 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (preliminary analysis)*: not clear* 6. *Brand/company*: not reported 2000 IU, for children with serum 25(OH)D concentration < 20 ng/mL 1. *Vitamin D content and type*: 2000 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (preliminary analysis)*: not clear* 6. *Brand/company*: not reported 400 IU 1. *Vitamin D content and type*: 400 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (preliminary analysis)*: not clear* 6. *Brand/company*: not reported *Meeting abstract indicates n = 47 total were randomised
Outcomes	**Secondary** 1. Serum 25(OH)D < 75 nmol/L 2. Serum 25(OH) D < 50 nmol/L **Measurement** 1. Serum 25-hydroxyvitamin D (nmol/L): assay not reported **Time point:** 3 months
Notes	**Notes:** age group not specified in meeting abstract; not enough information to assess eligibility. Study author contacted but no response received

Behnamfar 2011

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Iran
Participants	**Included criteria:** young children in day care centres **Excluded criteria:** not specified
Interventions	**Intervention characteristics** Treatment 1. *Vitamin D content and type*: not reported 2. *Formulation*: not reported 3. *Frequency of dosage*: not reported 4. *Duration of administration (study time)*: 3 months 5. *N per group (preliminary analysis)*: not clear* 6. *Brand/company*: not reported Base of vitamin D/placebo 1. *Vitamin D content and type*: not reported 2. *Formulation*: not reported 3. *Frequency of dosage*: not reported 4. *Duration of administration (study time)*: 3 months 5. *N per group (preliminary analysis)*: not clear* 6. *Brand/company*: not reported *Meeting abstract indicated a total of n = 50 children were randomised.
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) deficiency, not defined **Measurement** 1. Serum 25(OH) D (nmol/L): assay not reported **Time point:** 3 months
Notes	**Notes:** age group not specified in meeting abstract; not enough information to assess eligibility. Study author contacted via email but no response received

CTRI/2014/04/004574

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** no funding **Country:** India

CTRI/2014/04/004574 *(Continued)*

Participants	**Included criteria:** age 1 to 12 years with iron deficiency anaemia **Excluded criteria:** history of fever within last 4 weeks, acute or chronic medical disorder, haemolytic anaemia, haemoglobin 6 gm%, receiving iron/vitamin/mineral supplements (including herbal drugs), blood transfusion within 8 weeks, malignancy, congestive cardiac failure, congenital heart disease/rheumatic heart disease/cardiomyopathy, features of rickets
Interventions	**Intervention characteristics** 400 IU D_3 + Iron 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 8 weeks 5. *N per group (target)*: 15 6. *Brand/company*: not reported 7. *Micronutrient content:* sodium feredetate 4 mg/kg Iron only 1. *Vitamin D content and type*: none 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 8 weeks 5. *N per group (target)*: 15 6. *Brand/company*: not reported 7. *Micronutrient content:* sodium feredetate 4 mg/kg
Outcomes	None within scope of this review
Notes	**Notes:** completed recruitment (26 December 2012). Study author contacted to inquire about additional outcomes but no response received

CTRI/2015/08/006084

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** none **Country:** India
Participants	**Included criteria:** age 1 to 13 years, apparently healthy **Excluded criteria:** vitamin D/mineral supplements (including herbal drugs) within 8 weeks from the day of screening for the study; chronic medical disorder (e.g. chronic diarrhoea, chronic liver disease, chronic renal disease); children taking anticonvulsant medications, glucocorticoids, antifungals such as ketoconazole, and antiretroviral drugs; blood transfusion within 3 months from the day of screening for the study; obese children; malignancy; features of rickets; history of recurrent fractures; refusal of parents/guardians to consent
Interventions	**Intervention characteristics** 1000 IU D_3

CTRI/2015/08/006084 *(Continued)*

1. *Vitamin D content and type*: 1000 IU D_3
2. *Formulation*: not reported
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 90 days
5. *N per group (sample size calculation)*: not clear*
6. *Brand/company*: not reported

600 IU D_3

1. *Vitamin D content and type*: 600 IU D_3
2. *Formulation*: not reported
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 90 days
5. *N per group (target)*: not clear*
6. *Brand/company*: not reported

*Trial registration indicates total enrolment of n = 45 participants

Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time point:** 90 days
Notes	**Notes:** completed recruitment (3 August 2015). Study author contacted but no response received

CTRI/2019/02/017374

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. All India Institute of Medical Sciences (AIIMS), Jodhpur, India-342005 **Country:** India
Participants	**Included criteria:** inborn healthy, term, singleton, appropriate for gestational age (as defined by Fenton's growth charts) infants **Excluded criteria:** birth weight < 2.5 kg, multiple pregnancy, families from far off places not willing for follow-up, mother or infant on anticonvulsant or antitubercular treatment, major congenital malformations, severe birth asphyxia, need for neonatal intensive care unit stay > 48 hours
Interventions	**Intervention characteristics** 800 IU D_3 1. *Vitamin D content and type*: 800 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 14 weeks' postnatal age 5. *N per group (target)*: 46 6. *Brand/company*: not reported

CTRI/2019/02/017374 *(Continued)*

	400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 14 weeks' postnatal age 5. *N per group (target)*: 46 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time point:** 14 weeks' postnatal age
Notes	**Notes:** completed recruitment (31 December 2019). Study author contacted but no response received

Hagag 2020

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Egypt
Participants	**Included criteria:** neonates with sepsis **Excluded criteria:** none noted
Interventions	**Intervention characteristics** Vitamin D + antibiotics 1. *Vitamin D content and type*: not reported 2. *Formulation*: not reported 3. *Frequency of dosage*: not reported 4. *Duration of administration (study time)*: not reported 5. *N per group (in analysis)*: 30 6. *Brand/company*: not reported 7. *Co-intervention*: antibiotic therapy Antibiotics only 1. *Vitamin D content and type*: none 2. *Formulation*: not reported 3. *Frequency of dosage*: not reported 4. *Duration of administration (study time)*: not reported 5. *N per group (sample size calculation)*: 30 6. *Brand/company*: not reported 7. *Co-intervention*: antibiotic therapy

Hagag 2020 *(Continued)*

Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time points:** not specified
Notes	**Notes:** study design unclear from abstract; full-text study not obtainable. Study author contacted but no response received

IRCT20111206008307N

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Tabriz University of Medical Science, Tabriz, Iran **Country:** Iran
Participants	**Included criteria:** age 14 to 28 days, very low birth weight (< 1500 g), born in Alzahra Teaching Hospital, consent provided by parents, tolerating 120 cc/kg/d breast milk or breast milk with formula (full feed) **Excluded criteria:** infants with major malformation, congenital cardiac disease, familial history of bone disease, receiving corticosteroids, born from mothers with renal failure
Interventions	**Intervention characteristics** Calcitriol 1. *Vitamin D content and type*: 0.2 µg/kg (8 IU) calcitriol ($1,25(OH)_2D_3$) 2. *Formulation*: liquid, by nasogastric tube 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: discharge (6 weeks) 5. *N per group (target)*: 35 6. *Brand/company*: not reported 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: liquid, by nasogastric tube 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: discharge (6 weeks) 5. *N per group (target)*: 35 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported

IRCT20111206008307N *(Continued)*

	Time points: 3 weeks, 6 weeks
Notes	**Notes:** completed recruitment (16 July 2018). Study author contacted but no response received. Duplicate registration found under the registration number IRCT20111206008307N28 in the World Health Organization International Clinical Trials Registry

IRCT20131013014994N5

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Kermanshah University of Medical Sciences, Kermanshah, Iran **Country:** Iran
Participants	**Included criteria:** desire for parental collaboration, age range 3 to 13 years, diagnosis of autism disorder based on DSM-5 criteria **Excluded criteria:** reluctance to continue co-operation; children with significant hearing loss and vision loss; other neurological disorders such as cerebral palsy, phenylketonuria, seizure disorders; history of head trauma; genetic abnormalities; premature children; children with nutritional and malnutrition problems; children with digestive problems; immune disorders; children with endocrine, cardiovascular, pulmonary, kidney, or liver disease; children 2 months before study given supplements or the following medications: vitamin A, vitamin D, fish liver oil, steroids, cimetidine, heparin, diuretics, digoxin, diltiazem, and verapamil; children with serum vitamin D level > 80 ng/mL
Interventions	**Intervention characteristics** 6000 IU 1. *Vitamin D content and type*: 300 IU/kg vitamin D, maximum 6000 IU 2. *Formulation*: drops 3. *Frequency of dosage*: not reported 4. *Duration of administration (study time)*: 3 months 5. *N per group (target)*: 24 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: not reported 4. *Duration of administration (study time)*: 3 months 5. *N per group (target)*: 24 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time point:** 3 months

IRCT20131013014994N5 *(Continued)*

Notes	**Notes:** completed recruitment (18 April 2018). Study author contacted but no response received

IRCT2014053117843N3

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Ardabil University of Medical Sciences, Ardabil, Iran **Country:** Iran
Participants	**Included criteria:** age 4 to 18 years; has asthma; Bouali Hospital admission **Excluded criteria:** pneumonia; rickets; use of higher-dose vitamin D in last 3 months; severe mal-nutrition; diseases such as cystic fibrosis
Interventions	**Intervention characteristics** 100,000 IU D_3 1. *Vitamin D content and type*: 100,000 IU vitamin D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: once, at enrolment 4. *Duration of administration (study time)*: 8 weeks 5. *N per group (target)*: 30 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: liquid (sweet oil) 3. *Frequency of dosage*: once, at enrolment 4. *Duration of administration (study time)*: 8 weeks 5. *N per group (target)*: 30 6. *Brand/company*: not reported
Outcomes	None within scope of this review
Notes	**Notes:** completed recruitment (04 August 2014). Study author contact information was inaccurate or out of date for successful communication

NCT01229189

Methods	**Study design:** interventional randomised clinical trial **Study grouping:** parallel group **Funding:** not reported **Country:** Pakistan
Participants	**Included criteria:** pregnant women from 20 to 22 weeks' gestation and their infants

NCT01229189 *(Continued)*

	Excluded criteria: pregnant women with preexisting type 1 or 2 diabetes, women with multiple foetuses/babies
Interventions	**Intervention characteristics** 400 IU 1. *Vitamin D content and type*: 400 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: not reported 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: not reported 6. *Brand/company*: not reported
Outcomes	**Primary** 1. Adverse effect: hypercalciuria 2. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported 2. Hypercalciuria (urinary calcium-to-creatinine ratio): not reported a. Definition: not reported 3. Hypercalcaemia (serum calcium): not reported a. Definition: not reported **Time point:** 6 months
Notes	**Notes:** completed (August 2011). Study author contacted but no response received

NCT01419821

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Israel
Participants	**Included criteria:** infants 9 to 12 months old in Tipat Chalav and Kupat Holim Clalit in Beitar Illit undergoing a blood draw for CBC at 1 year of age

NCT01419821 *(Continued)*

	Excluded criteria: parents who refuse to participate in this study, infants with any diagnosed chronic disease, preterm infants at less than 34 weeks
Interventions	**Intervention characteristics** 800 IU (serum vitamin D < 15 ng/mL) 1. *Vitamin D content and type*: 800 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 1 to 2 years* 5. *N per group (target)*: 100 6. *Brand/company*: TipTipot Vitamin D Placebo (serum vitamin D < 15 ng/mL) 1. *Vitamin D content and type*: none 2. *Formulation*: not reported 3. *Frequency of dosage*: not reported 4. *Duration of administration (study time)*: 1 to 2 years* 5. *N per group (target)*: 100 6. *Brand/company*: not reported No intervention (serum vitamin D > 15 ng/mL) 1. *Duration of administration (study time)*: 1 to 2 years* 2. *N per group (target)*: 100 *Trial registration lists both 1 year and 2 years
Outcomes	**Primary** 1. Length **Measurement** 1. Length (cm): equipment not reported **Time point:** 3 years of age
Notes	**Notes:** unknown recruitment status (estimated study completion September 2016). Study authors contacted but no response received

NCT01656070

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Italy
Participants	**Included criteria:** vertically acquired HIV infection, age < 30 years, serum 25(OH)D concentration < 30 ng/mL, signed written informed consent **Excluded criteria:** hyperparathyroidism, as detected by an intact serum parathyroid hormone (PTH) ≥ 65 pg/mL; black ethnic group; any supplementation with vitamin D in previous 12 months;

NCT01656070 *(Continued)*

	use of any treatment known to alter vitamin D status in previous 6 months (excluding antiretroviral treatment); any concomitant severe illness
Interventions	**Intervention characteristics** 100,000 IU D_3 1. *Vitamin D content and type*: 100,000 IU D_3 2. *Formulation*: liquid in olive oil 3. *Frequency of dosage*: every 3 months 4. *Duration of administration (study time)*: 12 months 5. *N per group (preliminary analysis)*: 25 6. *Brand/company*: DIBASE - Abiogen Pharma SpA, Pisa, Italy Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: liquid (olive oil) 3. *Frequency of dosage*: every 3 months 4. *Duration of administration (study time)*: 12 months 5. *N per group (preliminary analysis)*: 25 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) < 75 nmol/L **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time point:** 12 months
Notes	**Notes:** completed (July 2012). Study author contacted but no response received

NCT01724190

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** USA
Participants	**Included criteria:** age 4 to 18 years with newly diagnosed type 1 diabetes **Excluded criteria:** under 4 years of age, pregnant female, previous or known history of vitamin D deficiency or insufficiency, current daily use of vitamin D supplementation or multi-vitamin containing > 800 IU, concurrent development or history (or both) of other significant systemic illness or non-endocrine autoimmune disorder
Interventions	**Intervention characteristics** 3000 IU D_3 1. *Vitamin D content and type*: 3000 IU D_3 2. *Formulation*: liquid

NCT01724190 *(Continued)*

3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 9 months
5. *N per group (sample size calculation)*: 18
6. *Brand/company*: not reported

Placebo

1. *Vitamin D content and type*: none
2. *Formulation*: liquid
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: 9 months
5. *N per group (sample size calculation)*: 18
6. *Brand/company*: not reported

Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time point:** 9 months
Notes	**Notes:** completed (June 2014). Study author contacted but no response received

NCT02054182

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** South Africa
Participants	**Included criteria:** 1 month to 5 years of age, admitted to paediatric unit of Dr George Mukhari Hospital with acute lower respiratory tract infection (i.e. bronchiolitis or pneumonia (or both)) **Excluded criteria:** children whose caregivers decline participation in the study, those with comorbid chronic respiratory condition(s), those who have received vitamin D supplementation in the past 30 days
Interventions	**Intervention characteristics** 500 IU D_3 1. *Vitamin D content and type*: 500 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: until hospital discharge (~ 7 days) 5. *N per group (target)*: 160 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: not reported 3. *Frequency of dosage*: daily

NCT02054182 *(Continued)*

	4. *Duration of administration (study time)*: until hospital discharge (~ 7 days) 5. *N per group (target)*: 160 6. *Brand/company*: not reported
Outcomes	None within scope of this review
Notes	**Notes:** unknown recruitment status (estimated study completion January 2015). Study authors contacted but no response received

NCT02185196

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Bangladesh
Participants	**Included criteria:** 3 to 59 months of age, clinical diagnosis of severe pneumonia with or without diarrhoea **Excluded criteria:** known case of hypercalcaemia or allergy to vitamin D, as determined by history or previous medical records; congenital heart disease, as evidenced by clinical exam or past medical records; renal or hepatic insufficiency, as evidenced by clinical exams or past medical records; known case of tuberculosis, as evidenced by medical records; known case of asthma, as evidenced by history and clinical exam findings; critically ill children requiring ICU care, such as those with septic shock or cardiac arrest or apnoea; those who have received vitamin D or calcium supplementation within the last 4 weeks before current admission, as evidenced by history or medical prescription; any children diagnosed with hypernatraemia during the main phase of the study
Interventions	**Intervention characteristics** Vitamin D 1. *Vitamin D content and type*: (1) age < 6 months, 20,000 IU D_3; age 6 to 12 months, 50,000 IU D_3; age 13 to 59 months, 100,000 IU D_3; and (2) 10,000 IU D_3 2. *Formulation*: liquid 3. *Frequency of dosage*: (1) once; (2) daily 4. *Duration of administration (study time)*: (1) once; (2) 4 days thereafter. Full follow-up: 12 months 5. *N per group (sample size calculation)*: not clear* 6. *Brand/company*: Vigantol-oil Placebo 1. *Vitamin D content and type*: none** 2. *Formulation*: liquid (propylene glycol dicaprylate/dicaprate oil) 3. *Frequency of dosage*: (1) once; (2) 4 days thereafter 4. *Duration of administration (study time)*: (1) once; (2) 4 days thereafter. Full follow-up: 12 months 5. *N per group (sample size calculation)*: not clear* 6. *Brand/company*: Miglyol oil *Trial registration indicates a total of 197 participants **Trial registration indicates same dosages of IU in placebo arm but this is likely reported in error
Outcomes	None within scope of this review

NCT02185196 *(Continued)*

Notes	**Notes:** completed (31 December 2017). Study authors contacted but no response received

NCT02186028

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** India
Participants	**Included criteria:** age up to 48 hours, gestation > 37 weeks, birth weight > 2.5 kg, informed consent of 1 of the parents, place of residence < 10 km **Excluded criteria:** presence of gross congenital malformation, need for resuscitation at birth, need for admission to neonatal intensive care unit, refusal of consent
Interventions	**Intervention characteristics** 400 IU 1. *Vitamin D content and type*: 400 IU vitamin D 2. *Formulation*: liquid 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (sample size calculation)*: 100 6. *Brand/company*: not reported 200 IU 1. *Vitamin D content and type*: 200 IU vitamin D 2. *Formulation*: liquid 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (sample size calculation)*: 100 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D > 50 nmol/L 3. Serum 25(OH)D = 37 to 50 nmol/L 4. Serum 25(OH)D < 37 nmol/L **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time point:** 6 months
Notes	**Notes:** completed (September 2016). Study authors contacted but no response received

NCT02936895

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Iran
Participants	**Included criteria:** 2 months to 6 years of age, definitive diagnosis of pneumonia **Excluded criteria:** immunocompromised patients, airway hypersensitivity or asthma, allergies, nasal polyps, use of inhaled medications to 1 month before the study, receiving high doses of vitamin D, avoiding signing of informed consent form
Interventions	**Intervention characteristics** 50,000 IU D_3 1. *Vitamin D content and type*: 50,000 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 days 5. *N per group (sample size calculation)*: 50 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 days 5. *N per group (sample size calculation)*: 50 6. *Brand/company*: not reported
Outcomes	None within scope of this review
Notes	**Notes:** completed (July 2015). Study authors contacted but no response received

NCT03176849

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** USA
Participants	**Included criteria:** preterm infants born at between 24 and 32 weeks of gestation (estimated by ultrasound), in-born or admitted to the unit within 48 hours from birth, randomisation within 7 days from birth, mothers willing to return for follow-up visits **Excluded criteria:** preterm delivery (at least 33 weeks of gestation or term delivery, estimated by ultrasound), major congenital abnormality, participation in another trial, severe illness at birth deemed incompatible with survival, congenital human immunodeficiency virus infection, total parenteral nutrition > 14 days, cholestasis
Interventions	**Intervention characteristics**

NCT03176849 *(Continued)*

Higher-dose

1. *Vitamin D content and type* (< 3 years of age, vitamin D sufficient): 100,000 IU D_3 bolus + 400 to 600 IU D_3 (daily)
   a. *Frequency of dosage*: once, at enrolment + daily
2. *Vitamin D content and type* (< 3 years of age, vitamin D deficient or insufficient): 150,000 IU D_3 to 200,000 IU D_3 bolus + 50,000 IU D_3 (weekly)
   a. *Frequency of dosage*: once at enrolment + weekly
3. *Vitamin D content and type* (3 to 12 years of age, vitamin D sufficient): 200,000 IU D_3 bolus + 400 to 600 IU D_3 (daily)
   a. *Frequency of dosage*: once at enrolment + daily
4. *Vitamin D content and type* (3 to 12 years of age, vitamin D deficient or insufficient): 350,000 IU D_3 to 400,000 IU D_3 bolus + 50,000 IU D_3 (weekly)
   a. *Frequency of dosage*: once, at enrolment + weekly
5. *Vitamin D content and type* (> 12 years of age, vitamin D sufficient): 300,000 IU D_3 bolus + 400 to 600 IU D_3 (daily)
   a. *Frequency of dosage*: once, at enrolment + daily
6. *Vitamin D content and type* (> 12 years of age, vitamin D deficient and insufficient): 500,000 IU D_3 to 600,000 IU D_3 bolus + 50,000 IU D_3 (weekly)
   a. *Frequency of dosage*: once, at enrolment + weekly
7. *Formulation*: drops
8. *Duration of administration (study time)*: 100 days
9. *N per group (target)*: 25
10. *Brand/company*: not reported

Standard

1. *Vitamin D content and type*: 400 to 600 IU D_3 (vitamin D sufficient) or 50,000 IU D_3 (vitamin D deficient or insufficient)
2. *Formulation*: drops
3. *Frequency of dosage*: daily
4. *Duration of administration (study time)*: daily or weekly
5. *N per group (target)*: 25
6. *Brand/company*: not reported

Outcomes

Primary

1. Adverse effect: hypercalcaemia
2. Adverse effect: hyperphosphataemia

Secondary

1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L)

Measurement

1. Serum 25(OH)D (nmol/L): assay not reported
2. Hypercalcaemia (serum calcium): not reported (threshold not defined)
3. Hyperphosphataemia (serum phosphorus): not reported (threshold not defined)

Time point: 100 days

Notes

Notes: enrolling by invitation (estimated completion: 1 September 2019). Study authors contacted but no response received

NCT03544671

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Mexico
Participants	**Included criteria:** 12 to 30 months of age; attend day care centres; children whose parents accepted their child to participate and signed informed consent **Excluded criteria:** children receiving multiple micronutrient supplementation or other vitamin D supplement; children whose parents did not accept to participate; children with capillary haemoglobin concentration < 90 g/L at baseline
Interventions	**Intervention characteristics** 1000 IU D_3 1. *Vitamin D content and type*: 1000 IU D_3 2. *Formulation*: liquid 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 16 weeks 5. *N per group (sample size calculation)*: 55* 6. *Brand/company*: not reported 7. *Micronutrient content*: none 800 IU D_3 1. *Vitamin D content and type*: 800 IU D_3 2. *Formulation*: liquid 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 16 weeks 5. *N per group (sample size calculation)*: 55* 6. *Brand/company*: not reported 7. *Micronutrient content*: iron; vitamins A, C, and E; folic acid; niacin; vitamins B1, B2, B6, B12 400 IU D_2 1. *Vitamin D content and type*: 800 IU D_2 2. *Formulation*: liquid 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 16 weeks 5. *N per group (sample size calculation)*: 55* 6. *Brand/company*: not reported 7. *Micronutrient content*: iron; vitamins A, C, and E; folic acid; niacin; vitamins B1, B2, B6, B12 Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: liquid 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 16 weeks 5. *N per group (sample size calculation)*: 55* 6. *Brand/company*: not reported 7. *Micronutrient content*: multiple vitamins (not specified) *Actual total sample size enrolled: n = 220

NCT03544671 *(Continued)*

Outcomes	**Secondary** 1. Change in serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time point:** 16 weeks
Notes	**Notes:** completed (27 December 2017). Study authors contacted but no response received

NTR477

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** The Netherlands
Participants	**Included criteria:** age 4 to 18 with acute lymphoblastic leukaemia, without physical handicap **Excluded criteria:** age < 3 years
Interventions	**Intervention characteristics** Trial registration is unclear as to what are the intervention and comparator groups, which appear to contain physical activities, vitamin D, and calcium
Outcomes	None within the scope of this review
Notes	**Notes:** no longer recruiting; completed 27 January 2006. Study authors contacted but no response received

Özkan 2000

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Turkey
Participants	**Included criteria:** age 4 to 19 months with nutritional rickets **Excluded criteria:** not specific
Interventions	**Intervention characteristics** 300,000 IU D_3 1. *Vitamin D content and type*: 300,000 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: once, at enrolment

Özkan 2000 *(Continued)*

4. *Duration of administration (study time)*: 25 to 30 days
5. *N per group (preliminary analysis)*: not reported
6. *Brand/company*: not reported

600,000 IU D_3

1. *Vitamin D content and type*: 600,000 IU D_3
2. *Formulation*: not reported
3. *Frequency of dosage*: once, at enrolment
4. *Duration of administration (study time)*: 25 to 30 days
5. *N per group (preliminary analysis)*: not reported
6. *Brand/company*: not reported

300,000 IU D_3 (intramuscular)

1. *Vitamin D content and type*: 300,000 IU D_3 (intramuscular)
2. *Formulation*: not reported
3. *Frequency of dosage*: once, at enrolment
4. *Duration of administration (study time)*: 25 to 30 days
5. *N per group (preliminary analysis)*: not reported
6. *Brand/company*: not reported
7. **Arm not to be included in data synthesis**

Outcomes	**Primary** 1. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported 2. Hypercalcaemia: not defined **Time point:** 25 to 30 days
Notes	**Notes:** an additional third intervention group was randomly assigned to receive 300,000 IU intramuscular vitamin D, once at enrolment. Study design unclear as control group was included with age- and sex-matched children who may not have been randomised. Study authors contacted but no response received

ICU: intensive care unit.
PTH: parathyroid hormone.

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

ACTRN12614000334606/NCT02112734

Study name	**Public trial:** Can vitamin D supplementation in infants prevent food allergy in the first year of life? The VITALITY trial **Scientific title:** A placebo-controlled, randomised trial of vitamin D supplementation for infants in their first year of life, to prevent the development of food allergy by age 12 months. The VITALITY trial
Methods	**Study design:** randomised controlled trial

ACTRN12614000334606/NCT02112734 *(Continued)*

	Study grouping: parallel group **Funding:** 100% non-profit. Isabel & John Gilbertson Charitable Trust and Murdoch Children's Research Institute. KJA, MP, JJK, SCD, A-LP, LCG, MW all receive fellowship funding from National Health and Medical Research Council (NHMRC) of Australia. NC receives funding from University of Melbourne, McKenzie Postdoctoral Fellowship **Country:** Australia
Participants	**Included criteria:** healthy, term, 6– to 8-week-old breastfed infants whose mothers intend to continue to predominantly breastfeed until 6 months **Excluded criteria:** already receiving vitamin D supplementation, born premature (< 37 weeks) or at low birth weight (< 2500 g), multiple births, poor health due to current or past significant disease state or congenital abnormality or taking medication that interferes with vitamin D metabolism
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 10 to 11 months 5. *N per group (sample size calculation)*: 1506 6. *Brand/company*: D Drops Company (Ontario, Canada) Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 10 to 11 months 5. *N per group (sample size calculation)*: 1506 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D deficiency, not defined **Time point:** endpoint (12 months of age)
Starting date	December 2014
Contact information	Michael Field, Murdoch Children's Research Institute; email: vitality@mcri.edu.au Jennifer Koplin, Murdoch Children's Research Institute; email: jennifer.koplin@mcri.edu.au
Notes	**Notes:** recruiting (estimated study completion: December 2022)

ACTRN12616000659404

Study name	**Public title:** PREVARID - PREVention of Acute Respiratory Infections with Vitamin D

ACTRN12616000659404 *(Continued)*

	Scientific title: Does vitamin D supplementation prevent acute respiratory infection health care visits among children under 2 years old? A randomised controlled trial
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Cure Kids, Auckland, New Zealand **Country:** New Zealand
Participants	**Included criteria:** New Zealand residents, < 2 years old at the time of acute lower respiratory infection hospital admission, reside in Auckland District Health Board catchment area **Excluded criteria:** receiving vitamin D supplements, have a complex chronic condition known to be associated with recurrent hospital admission (e.g. cystic fibrosis, tracheostomy)
Interventions	**Intervention characteristics** 5000 IU D_3 1. *Vitamin D content and type*: 5000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: weekly 4. *Duration of administration (study time)*: 12 months 5. *N per group (sample size calculation)*: 150 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops (coconut oil) 3. *Frequency of dosage*: weekly 4. *Duration of administration (study time)*: 12 months 5. *N per group (sample size calculation)*: 150 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) a. **Notes:** in 10% subsample **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time points:** enrolment, 6 months and 12 months after enrolment
Starting date	July 2016
Contact information	Cameron Grant, University of Auckland, Principal Investigator; email: cc.grant@auckland.ac.nz
Notes	**Notes:** not yet recruiting (estimated recruitment completion 30 November 2017)

CTRI/2013/04/003566

Study name	**Public title:** Vitamin D supplementation and responses to vaccines in infants

CTRI/2013/04/003566 *(Continued)*

	Scientific title: Vitamin D supplementation to improve immune responses to vaccines administered in early infancy - the Nutrivac-D trial
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Government funding agency **Country:** India
Participants	**Included criteria:** Inclusion criteria during pregnancy and labour are: pregnant at any gestation when screened antenatally; Pregnancy full term (> 37 and < 41 completed weeks) when screened again at labour (consent will only be taken in the antenatal period and not during labour); will stay in study area for a period of at least 6 months after delivery; delivery by vaginal route or by elective Cesarean section. Inclusion criteria at birth and within 24 hours: single term newborn (gestational age > 37 and < 41 weeks at birth) < 24 hours old; born by normal vaginal route or elective caesarean section; will stay in study area for a period of at least 6 months after delivery; breastfeeding established **Excluded criteria:** Exclusion criteria during pregnancy and intrapartum period: a mother with a history of > 5 pregnancies; multiple gestation; presence of any documented major maternal medical or surgical illness e.g. HIV, Hepatitis B, Tuberculosis, TORCH infections, syphilis, malignancy or immunodeficiency, etc; presence of fetal (major) congenital anomalies diagnosed in utero; any infection during pregnancy that required hospitalisation; blood transfusion during pregnancy; history of maternal eclampsia / preeclampsia / hypertension with significant proteinuria (> 3+) during pregnancy. Exclusion criteria at birth and within 24 hrs: one minute Apgar of < 7/10; birth weight < 1.8 kg; multiple gestation; major congenital anomalies diagnosed prior to birth or during a clinical examination by a paediatrician performed within the first 24 hours; newborn required admission to neonatal intensive care prior to randomisation; informed written consent not provided by parents
Interventions	**Intervention characteristics** 400 IU 1. *Vitamin D content and type*: 400 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months of age 5. *N per group (target)*: 450 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months of age 5. *N per group (target)*: 450 6. *Brand/company*: not reported
Outcomes	**Primary** 1. Linear growth **Measurements** 1. Length (not defined) **Time point:** 6 months of age

CTRI/2013/04/003566 *(Continued)*

Starting date	December 2012
Contact information	Uma Chandra Mouli Natchu, Translational Health Science and Technology Institute, Principal Investigator; email: unatchu@thsti.res.in
Notes	**Notes:** open to recruitment (first recruitment 21 December 2012)

CTRI/2015/08/006132

Study name	**Public title:** A clinical trial to evaluate the need for routine vitamin D supplementation till six months age in full term babies who are being exclusively breastfed **Scientific title:** Vitamin D oral supplementation evaluation in full-term, exclusively breastfed infants - a randomised controlled study
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** India
Participants	**Included criteria:** born at 37 weeks' completed gestation or thereafter, birth weight ≥ 2500 g, exclusively breastfed, parents provided written consent for infant to participate in the study after detailed information was disseminated to them **Excluded criteria:** infants born before 37 completed weeks of gestation; low birth weight (i.e. birth weight < 2500 g); sick neonate, including birth asphyxia; neonate not exclusively breastfed from birth for any reason even though may afterward be on exclusive breastfeeds; neonate with major congenital anomaly; neonate whose parents decline consent to participate in the study (presence of any 1 criterion will result in exclusion)
Interventions	**Intervention characteristics** 400 IU 1. *Vitamin D content and type*: 400 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months of age 5. *N per group (target)*: 150 6. *Brand/company*: not reported No intervention 1. *Duration of administration (study time)*: 6 months of age 2. *N per group (target)*: 150
Outcomes	**Primary** 1. Linear growth **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurements**

CTRI/2015/08/006132 *(Continued)*

	1. Length (cm) 2. Serum 25(OH)D (nmol/L): assay not reported **Time points:** birth (cord blood), 1 month of age, 6 months of age
Starting date	July 2015
Contact information	Shankar Narayan, Indian Naval Hospital Ship (INHS) Asvini, Principal Investigator; email: dr-shankarnarayan@gmail.com
Notes	**Notes:** open to recruitment (first enrolment 1 July 2015)

CTRI/2016/12/007519

Study name	**Public title:** Vitamin D levels in preterm babies **Scientific title:** Vitamin D levels of the term small-for-date newborns at birth and at 3 month of age after vitamin D supplementation with 2 different doses 400 IU v/s 800 IU - a randomised controlled trial
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Sri Devaraj Urs Academy of Higher Education and Research **Country:** India
Participants	**Included criteria:** healthy, small-for-gestational-age infants born with normal delivery, gestational period ≥ 37 weeks, birth weight < 2500 g, exclusively breastfed for 3 months **Excluded criteria:** preterm babies with gestational age < 36 weeks; birth weight < 2500 g; liver, renal, intestinal, and other problems that can affect vitamin D metabolism; on medications such as anticonvulsants, glucocorticoids, antifungal medications; mother with systematic disease that can alter vitamin D metabolism (renal, hepatic); malignancy; features of rickets; repeated fractures
Interventions	**Intervention characteristics** 1400 IU 1. *Vitamin D content and type*: 1400 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (target)*: not clear* 6. *Brand/company*: not reported 2800 IU 1. *Vitamin D content and type*: 2800 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (target)*: not clear* 6. *Brand/company*: not reported Total target sample size: n = 35

CTRI/2016/12/007519 *(Continued)*

Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time points:** birth, 3 months of age
Starting date	February 2016
Contact information	Syed Manazir Ali, Jawaharlal Nehru Medical College, Aligarh Muslim University, Principal Investigator; email: manazir1958@yahoo.com
Notes	**Notes:** open to recruitment (first enrolment 2 February 2016)

CTRI/2017/10/010274

Study name	**Public title:** Role of vitamin D3 intake and decrease in respiratory infections **Scientific title:** Randomised trial of two different doses of vitamin D supplementation and risk of acute respiratory infection in children in rural Kolar, Karnataka
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Jawaharlal Nehru Medical College Aligarh Muslim University Aligarh **Country:** India
Participants	**Included criteria:** healthy, age 3 to 6 years, attends RL Jallappaschool in Kolar **Excluded criteria:** chronic illness (except asthma), clinical rickets, child on vitamin supplementation
Interventions	**Intervention characteristics** 3000 IU 1. *Vitamin D content and type*: 3000 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months, 6 months of no intervention, then 3 additional months of intervention (12 months of follow-up) 5. *N per group (target)*: 85 6. *Brand/company*: not reported 600 IU 1. *Vitamin D content and type*: 600 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months, 6 months of no intervention, then 3 additional months of intervention (12 months of follow-up) 5. *N per group (target)*: 85

CTRI/2017/10/010274 *(Continued)*

	6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time points:** 3 and 12 months
Starting date	January 2018
Contact information	Kanak N Venkateshwara Prasad, Sri Devraj Urs Medical College, Principal Investigator; email: drknvp@gmail.com
Notes	**Notes:** not yet recruiting (record last modified 28 October 2017)

CTRI/2017/11/010385

Study name	**Public title:** Dose of vitamin D in children with chronic kidney disease **Scientific title:** Optimal dose of cholecalciferol supplementation in Indian children with chronic kidney disease - a randomised controlled trial
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Navajbai Ratan Tata Trust, Bombay House, 24 Homi Mody Street, Mumbai - 400 001, Maharashtra, India (reference no: Health-CKCC-20141118). This being an "Investigator initiated trial" will receive only partial support from the Trust towards supporting expenses of clinical tests and vitamin D supplements **Country:** India
Participants	**Included criteria:** 1 to 18 years of age, chronic kidney disease stages 2 to 4 (estimated glomerular filtration rate 15 to 90 mL/min/1.73 m^2), serum 25-hydroxyvitamin D level < 30 ng/mL **Excluded criteria:** therapy with cholecalciferol, including over-the-counter multi-vitamin or intramuscular serum 25-hydroxyvitamin D, in preceding 3 months; known nephrocalcinosis; refusal to give consent; known poor adherence to medications; inability to attend a follow-up visit
Interventions	**Intervention characteristics** 3000 IU D_3 1. *Vitamin D content and type*: 3000 IU D_3 2. *Formulation*: sachet 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months + additional treatment, depending on serum 25(OH)D concentration* 5. *N per group (sample size attained, preliminary data)*: 30 6. *Brand/company*: Pharmacy of St John's Medical College Hospital 7. *Other micronutrient content*: children with serum calcium less than expected by age they will receive calcium supplements (75 to 100 mg/kg/d) 25,000 IU D_3

CTRI/2017/11/010385 *(Continued)*	1. *Vitamin D content and type*: 25,000 IU D_3 2. *Formulation*: sachet 3. *Frequency of dosage*: weekly 4. *Duration of administration (study time)*: 3 months + additional treatment, depending on serum 25(OH)D concentration* 5. *N per group (sample size attained, preliminary data)*: 29 6. *Brand/company*: Pharmacy of St John's Medical College Hospital 7. *Other micronutrient content*: children with serum calcium less than expected by age they will receive calcium supplements (75 to 100 mg/kg/d) 100,000 IU D_3 1. *Vitamin D content and type*: 100,000 IU D_3 2. *Formulation*: sachet 3. *Frequency of dosage*: monthly 4. *Duration of administration (study time)*: 3 months + additional treatment, depending on serum 25(OH)D concentration* 5. *N per group (sample size attained, preliminary data)*: 31 6. *Brand/company*: Pharmacy of St John's Medical College Hospital 7. *Other micronutrient content*: children with serum calcium less than expected by age they will receive calcium supplements (75 to 100 mg/kg/d) *After 3 months, children with serum 25-hydroxyvitamin D ≥ 30 ng/mL will receive maintenance 1000 IU D_3 orally daily for 9 months. Children with serum 25-hydroxyvitamin D < 30 ng/mL will be given a second course of intensive treatment, using same dosage schedule as per allocation at randomisation. Those who fail to achieve serum 25-hydroxyvitamin D ≥ 30 ng/mL will receive a third course of intensive replacement therapy
Outcomes	**Primary** 1. Adverse effect: hypercalcaemia 2. Adverse effect: hypercalciuria **Secondary** 1. Change in serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D deficiency **Measurement** 1. Hypercalcaemia (serum calcium): not defined 2. Hypercalciuria (urinary calcium-to-creatinine ratio): not defined 3. Serum 25(OH)D (nmol/L): liquid chromatography-tandem mass spectrometry 4. Vitamin D deficiency: not defined **Time points:** end of an intensive phase
Starting date	January 2016
Contact information	Arpana Aprameya Iyengar, Government Medical College; email: drarpanaiyengar@gmail.com
Notes	**Notes:** trial completed (ended: 20 November 2019), trial protocol publication and meeting abstract with preliminary data available. Study author contacted and indicated manuscript is forthcoming Note: trial protocol lists Clinical Trials Registry of India registration number as "CTRI/2015/11/010180"; however; this was not found in the CTRI database. The CTRI registration referenced in this review, "CTRI/2017/11/010385", appears to be the correct number

CTRI/2017/12/010827

Study name	**Public title:** Effect of vitamin D supplementation on postoperative surgical outcomes in children with cyanotic congenital heart disease undergoing open heart surgery: a randomised controlled trial **Scientific title:** Effect of vitamin D supplementation on outcome in children undergoing open heart surgery: a randomised controlled trial
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Institutional research fund, All India Institute of Medical Science (AIMS), New Delhi, India **Country:** India
Participants	**Included criteria:** 1 month to 12 years of age, transposition of great arteries, total anomalous pulmonary venous connection, tetralogy of Fallot, tricuspid atresia, univentricular physiology, shunts with reversal of flow, left-to-right shunt like atrial septal defect, ventricular septal defect, undergoing open heart surgery electively under cardiopulmonary bypass **Excluded criteria:** urgent/emergency surgery, syndromic child, closed heart surgery, preoperative infection/antibiotic administration and ventilation
Interventions	**Intervention characteristics** 400,000 IU 1. *Vitamin D content and type*: 10,000 IU/kg vitamin D body weight not exceeding 400,000 IU vitamin D 2. *Formulation*: powder 3. *Frequency of dosage*: once, at enrolment 4. *Duration of administration (study time)*: not clear 5. *N per group (target)*: 50 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: powder (sugar) 3. *Vitamin D type*: not applicable 4. *Frequency of dosage*: Once, at enrolment 5. *Duration of administration (study time)*: not clear 6. *N per group (target)*: 50 7. *Brand/company*: not reported
Outcomes	**Primary** 1. Adverse effect: hypercalcaemia 2. Adverse effect: hypercalciuria **Measurement** 1. Hypercalcaemia (not described) 2. Hypercalciuria (not described) **Time points:** postoperative course in intensive care unit

CTRI/2017/12/010827 *(Continued)*

Starting date	January 2018
Contact information	Manoj Kumar Sahu, AIMS, Principal Investigator; email: drmanojsahu@gmail.com
Notes	**Notes:** not yet recruiting (record last modified 26 November 2019)

CTRI/2018/04/013300

Study name	**Public title:** A clinical trial to compare three different regimes for treatment of nutritional rickets in children **Scientific title:** To evaluate the efficacy of daily vitamin D therapy versus Stoss therapy in nutritional rickets in Indian children: a randomised controlled trial
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Maulana Azad Medical College and Lok Nayak Hospital **Country:** India
Participants	**Included criteria:** age 6 months to 12 years; diagnosis of nutritional rickets defined by clinical, biochemical, and radiological parameters; residence within 50 km of hospital; willing for follow-up visits **Excluded criteria:** patients with confirmed or suspected diagnosis of malabsorption or chronic kidney or hepatic disease, severe systemic illness compromising oral intake (tachycardia, tachypnoea, shock, weak peripheral pulses, increased capillary refill time); have taken calcium supplements or vitamin D preparation in last 6 months
Interventions	**Intervention characteristics** 60,000 IU 1. *Vitamin D content and type*: 60,000 IU vitamin D 2. *Formulation*: liquid 3. *Frequency of dosage*: weekly 4. *Duration of administration (study time)*: 3 or 6 weeks 5. *N per group (target)*: 66 6. *Brand/company*: not reported 2000 IU 1. *Vitamin D content and type*: 2000 IU vitamin D 2. *Formulation*: liquid 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 12 weeks 5. *N per group (target)*: 66 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Change in serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D < 12 ng/mL **Measurement**

CTRI/2018/04/013300 *(Continued)*

	1. Serum 25(OH)D (nmol/L): assay not reported **Time point:** 12 weeks
Starting date	April 2018
Contact information	Aashima Dabas, Maulana Azad Medical College, Principal Investigator; email: dr.aashimagupta@gmail.com
Notes	**Notes:** not yet recruiting (record last modified 13 December 2018)

CTRI/2018/12/016760

Study name	**Public title:** Daily versus bolus oral vitamin D3 for treatment of rickets In children **Scientific title:** Daily versus depot oral vitamin D3 for treating nutritional rickets
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. University College of Medical Sciences and GTB Hospital, Dilshad Garden, New Delhi, India 110095 **Country:** India
Participants	**Included criteria:** 3-month-old to 5-year-old children with nutritional rickets presenting in outpatient department, wards, emergency of paediatrics department based on history, examination, and biochemical (serum calcium - normal/low, serum phosphorus - normal/low and serum alkaline phosphatase - high) and radiological features (Thacher score ≥ 1.5) **Excluded criteria:** previous treatment of rickets, child admitted to paediatric intensive care unit, secondary cause of rickets such as medication, vitamin D disorder of metabolism, fat malabsorption syndrome
Interventions	**Intervention characteristics** 60,000 IU to 150,000 IU 1. *Vitamin D content and type*: 60,000 IU vitamin D (3 to 12 months of age); 150,000 IU vitamin D (1 to 5 years of age) 2. *Formulation*: not reported 3. *Frequency of dosage*: once, at enrolment 4. *Duration of administration (study time)*: 12 weeks 5. *Brand/company*: not reported 6. *N per group (target)*: 33 7. *Micronutrient content*: calcium: 250 mg (3 to 12 months of age); 500 mg (1 to 5 years of age) 2000 IU to 4000 IU 1. *Vitamin D content and type*: 2000 IU vitamin D (3 to 12 months of age); 4000 IU vitamin D (1 to 5 years of age) 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 12 weeks 5. *Brand/company*: not reported 6. *N per group (target)*: 33

CTRI/2018/12/016760 *(Continued)*

	7. *Micronutrient content:* calcium: 250 mg (3 to 12 months of age); 500 mg (1 to 5 years of age)
Outcomes	**Primary** 1. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Hypercalcaemia (serum calcium): not defined 2. Serum 25(OH)D (nmol/L): assay not reported **Time points:** 4 weeks, 12 weeks
Starting date	January 2019
Contact information	Ravneet T Kaur Saluja, University College of Medical Sciences and Guru Teg Bahadur Hospital, Principal Investigator
Notes	**Notes:** closed to recruitment (last enrolment November 2019)

Galdo 2018

Study name	**Public title:** Effect of supplementation with vitamin D on acute bronchitis prevention during the first year of life **Scientific title:** Effect of supplementation with vitamin D on acute bronchitis prevention during the first year of life
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Grant from Spanish Ministry of Health (EC11-476) **Country:** Spain
Participants	**Included criteria:** healthy, on-term newborns of appropriate size for gestational age during first 2 weeks of age (range 5 days), on exclusive breastfeeding or exclusive formula feeding **Excluded criteria:** infant with gestational age < 37 weeks; low birth weight for gestational age (birth weight < 2500 g); mixed feeding at baseline; newborn with major congenital anomaly; infant with chronic gastrointestinal, hepatic, renal, respiratory, cardiac, neurological, or metabolic disorder; any disease that is accompanied by hypercalcaemia and hypercalciuria, calcium lithiasis, hypersensitivity to vitamin D, hypervitaminosis D, renal osteodystrophy with hyperphosphataemia
Interventions	**Intervention characteristics** 2000 IU D_3 1. *Vitamin D content and type*: 2000 IU D_3 2. *Formulation*: liquid 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 1 year 5. *N per group (target)*: 359 6. *Brand/company*: VITAMINA D3 Kern Pharma Solución Oleosa, Kern Pharma, Terrassa, Spain

Galdo 2018 *(Continued)*

	Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: liquid 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 1 year 5. *N per group (target)*: 359 6. *Brand/company*: not reported
Outcomes	**Primary** 1. Linear growth 2. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Linear growth: length (not defined) 2. Hypercalcaemia (not defined) 3. Serum 25(OH)D (nmol/L): assay not reported **Time point:** 12 months
Starting date	February 2013
Contact information	Antonio Moreno Galdó, University Hospital Vall d'Hebron, Principal Investigator; email: amoreno@vhebron.net
Notes	**Notes:** completed recruitment (ended 20 August 2018). Meeting abstract (preliminary results) available; study author contacted and indicated publication is forthcoming

IRCT20171030037093N4

Study name	**Public title:** Effect of vitamin D supplement on the level of serum vitamin D in preterm neonates **Scientific title:** Comparing the effect of different doses of vitamin D supplement on the level of serum 25(OH) vitamin D and bone metabolism related factors in preterm neonates
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Shahrekord University of Medical Sciences, Shahrekord, Iran **Country:** Iran
Participants	**Included criteria:** gestational age between 28 and 34 weeks; absence of major disorders and malformations; absence of systemic disease, such as asphyxia or cholestasis **Excluded criteria:** supportive nutrition longer than 2 weeks, use of anticonvulsant and anti-HIV drugs by infant's mother, use of injectable vitamin D during the study, formula feeding, nephrocalcinosis in the infant
Interventions	**Intervention characteristics** 300 IU

IRCT20171030037093N4 *(Continued)*

1. *Vitamin D content and type*: 300 IU vitamin D
2. *Formulation*: "FMS supplement"
3. *Frequency of dosage*: not reported
4. *Duration of administration (study time)*: 40 weeks after last menstrual period
5. *N per group (target)*: 50
6. *Brand/company*: Behsa Pharmeceutical, Tehran, Iran
7. *Micronutrient content*: 100 IU vitamin A, 400 IU vitamin D drop + vitamin D 1000 IU through Vitabiotics

300 IU

1. *Vitamin D content and type*: 300 IU vitamin D
2. *Formulation*: "FMS supplement" (quote)
3. *Frequency of dosage*: not reported
4. *Duration of administration (study time)*: 40 weeks after last menstrual period
5. *N per group (target)*: 50
6. *Brand/company*: Behsa Pharmeceutical, Tehran, Iran
7. *Micronutrient content*: 100 IU vitamin A, 400 IU vitamin D drop

Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurements** 1. Serum 25(OH)D (nmol/L): assay not reported **Time point:** modified age 40 weeks after last menstrual period
Starting date	July 2018
Contact information	Roya Choopani, Shahrekord University of Medical Sciences, Principal Investigator; email: choopani.r@skums.ac.ir
Notes	**Notes:** recruitment completed (ended 25 July 2019); study author contacted to clarify interventions but no response received

Kishore 2019

Study name	Study of daily vitamin D supplementation in preterm infants: a randomised trial
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** India
Participants	**Included criteria:** preterm neonates **Excluded criteria:** not reported
Interventions	**Intervention characteristics** 400 IU 1. *Vitamin D content and type*: 400 IU vitamin D

Kishore 2019 *(Continued)*

	2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 40 weeks' postmenstrual age 5. *N per group (in preliminary analysis):* 46 6. *Brand/company*: not reported 800 IU 1. *Vitamin D content and type*: 800 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 40 weeks' postmenstrual age 5. *N per group (in preliminary analysis):* 46 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D deficiency **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported 2. Vitamin D deficiency: not defined **Time point:** 40 weeks' postmenstrual age
Starting date	Not reported
Contact information	Sai Sunil Kishore, Maharajah Institute of Medical Sciences; email: mssk81@gmail.com
Notes	**Note:** preliminary results included in meeting abstract; study author contacted but no response received

NCT01050387

Study name	**Public title:** A randomised trial of vitamin D supplementation in healthy inner-city children **Official title:** A randomised, controlled trial of vitamin D supplementation in infants and children: effects of vitamin D dose and genotype of the binding protein
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Thrasher Research Fund **Country:** USA
Participants	**Included criteria:** 6 months to 6 years of age, healthy or free from any disease or condition that may affect nutritional status or bone metabolism, willingness of family to participate in a 6-month study of vitamin D supplementation. *In preliminary data (meeting abstract), children 2 to 10 years of age of predominantly Hispanic background were included **Excluded criteria:** chronic disease, prematurity < 32 weeks' gestational age, liver disease such as hepatitis or renal/urologic disease (e.g. recurrent urinary tract infection), use of pharmacological or prescription-level dosage of vitamin D or its metabolites. Also excluded are users of any systemic

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	glucocorticoid preparation and users of inhaled steroids that are considered greater than medium dose for age 4 years. Specifically, this would exclude users of more than 1 mg/d of budesonide, and more than 352 mcg/d of fluticasone. Current or recent (within 1 month) use of anticonvulsants or other medications known to affect bone and mineral homeostasis or alkaline phosphatase levels also excluded
Interventions	**Intervention characteristics** 1000 IU 1. *Vitamin D content and type*: 1000 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in preliminary analysis)*: not clear* 6. *Brand/company*: not reported 400 IU 1. *Vitamin D content and type*: 400 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (in preliminary analysis)*: not clear* 6. *Brand/company*: not reported *Trial registration indicated total enrolment of 193 participants **Intervention characteristics (preliminary data from meeting abstract)** 7000 IU D_3 1. *Vitamin D content and type*: 7000 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: weekly 4. *Duration of administration (study time)*: 6 months 5. *N per group (in preliminary analysis)*: not reported 6. *Brand/company*: not reported 2800 IU D_3 1. *Vitamin D content and type*: 2800 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: weekly 4. *Duration of administration (study time)*: 6 months 5. *N per group (in preliminary analysis)*: not reported 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Change in serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time point:** 6 months
Starting date	January 2010

NCT01050387 *(Continued)*

Contact information	Thomas Carpenter, Yale University, Principal Investigator; email: thomas.carpenter@yale.edu
Notes	**Notes:** recruitment completed (ended February 2013); study authors contacted, who indicated that data are currently being analysed (meeting abstract is available) and reflect trial registration NCT01050387; publication is forthcoming

NCT01363167

Study name	**Public title:** Identifying vitamin D deficiency in very low birth weight (VLBW) infants part 2 **Official title:** Identifying vit D deficiency in VLBW infants part 2
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. **Country:** USA
Participants	**Included criteria:** any infant born at Medical University of South Carolina at < 34 weeks' gestation, < 1500 g at birth, adequate gestational age, must be African American or Caucasian. Each infant born of twin or triplet pregnancy also eligible **Excluded criteria:** major congenital anomaly or haemolytic disease requiring exchange transfusion, infant born small-for-gestational-age or large-for-gestational-age, maternal uncontrolled thyroid disease, maternal parathyroid disease, other race (non-African American or Caucasian)
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: liquid 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: until term age equivalent (2 to 4 months) 5. *N per group (in preliminary analysis)*: 19 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: liquid (fractionated coconut oil) 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: until term age equivalent (2 to 4 months) 5. *N per group (in preliminary analysis)*: 19 6. *Brand/company*: not reported
Outcomes	**Primary** 1. Linear growth 2. Adverse effect: hypercalciuria **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement**

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	1. Length: equipment not reported 2. Hypercalciuria (urinary calcium excretion): not reported (threshold not defined) 3. Serum 25(OH)D (nmol/L): assay not reported 4. Bone health: alkaline phosphatase (IU/L): assay not reported 5. Bone health: serum phosphorus (mmol/L): assay not reported 6. Bone health: parathyroid hormone (mmol/L): assay not reported 7. Bone health: bone-specific alkaline phosphatase (IU/L): assay not reported 8. Bone health: urinary phosphorus (mmol/L): assay not reported **Time point:** 2 to 4 months
Starting date	October 2011
Contact information	Sarah N Taylor, MD, Medical University of South Carolina, Principal Investigator; email: taylorse@musc.edu
Notes	**Notes:** recruitment completed (ended October 2013)

NCT01698840

Study name	**Public title:** Effect of vitamin D in diets of preterm infants **Official title:** An evaluation of the effects of two levels of vitamin D in infants fed preterm or transitional formula on serum 25-hydroxyvitamin D and bone status in preterm infants: a double-blind, randomised controlled trial
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** USA
Participants	**Included criteria:** born at 28 0/7 to 34 6/7 weeks' postmenstrual age (PMA) and 1000 to 2250 g birth weight. Currently, 34 0/7 to 38 6/7 weeks' PMA at time of consent. Born at Texas Children's (including Pavilion for Women) or Methodist campus hospital or transferred within 48 hours of birth. Care expected to be provided at one of these institutions until discharge to home. Any initial feeding will be permitted but expected to transition to primarily (80% of feeds or up to 2 breast milk feeds per day) infant formula by 38 6/7 weeks' PMA or hospital discharge, whichever comes first. Able to tolerate 22 kcal/oz transitional formula and to receive a volume of ≥ 130 mL/kg/d total feeding volume. No longer receiving any form of mechanical ventilation or diuretics. Low-flow nasal cannula will be permitted if it is anticipated, and this will be discontinued before hospital discharge **Excluded criteria:** bronchopulmonary dysplasia requiring daily use of diuretics beyond 38 6/7 weeks; PMA (or hospital discharge, whichever comes first) and > 22 kcal/oz concentration formula beyond 38 6/7 weeks' PMA; major congenital anomaly; history of proven stage 2 or above necrotising enterocolitis or severe feeding intolerance; caloric density > 22 kcal/oz; higher-order multiples - however, twins are acceptable and will be randomised together but only data from 1 twin picked at random will be used in the final analyses
Interventions	**Intervention characteristics** Vitamin D 1. *Vitamin D content and type*: not reported 2. *Formulation*: drops

NCT01698840 *(Continued)*

3. *Frequency of dosage*: not reported
4. *Duration of administration (study time)*: 52 weeks' postmenstrual age
5. *N per group (in preliminary analysis)*: not clear*
6. *Brand/company*: not reported

Placebo

1. *Vitamin D content and type*: none
2. *Formulation*: drops
3. *Frequency of dosage*: not reported
4. *Duration of administration (study time)*: 52 weeks' postmenstrual age
5. *N per group (in preliminary analysis)*: not clear*
6. *Brand/company*: not reported

*Trial registration reports total sample size of n = 39 participants

Outcomes	**Secondary** 1. Change in serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time points:** last 7 days of hospitalisation, 52 weeks' postmenstrual age
Starting date	January 2013
Contact information	Amy Hair, Baylor College of Medicine, Principal Investigator
Notes	**Notes:** active, not recruiting (estimated trial completion December 2021)

NCT01838447

Study name	**Public title:** Prevention of vitamin D deficiency following pediatric chronic heart disease surgery: a phase II dose evaluation randomised controlled trial comparing usual care with a high dose preoperative supplementation regimen based on the Institute of Medicine Daily Upper Tolerable Intake Level (HICCUPS 2) **Official title:** Prevention of post-cardiac surgery vitamin D deficiency in children with congenital heart disease: a pilot dose evaluation randomised controlled trial
Methods	**Study design:** randomised double-blind controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Canada
Participants	**Included criteria:** newborn (corrected gestational age between 36 weeks and 18 years) with chronic heart disease that will require surgery within the next 12 months, chronic heart failure requiring surgical intervention with cardiopulmonary bypass **Excluded criteria:** born at less than 32 weeks' gestational age, corrected gestational age < 36 weeks, cardiac or gastrointestinal disease preventing enteral feeds or drug administration before surgery, confirmed or suspected Williams syndrome, proposed surgery to take place at another centre (outside of Children's Hospital of Eastern Ontario)

NCT01838447 *(Continued)*

Interventions	**Intervention characteristics** 400 IU (0 to 1 year); 600 IU (1 to 17 years); placebo (formula-fed, 0 to 1 year) 1. *Vitamin D content and type*: 400 to 600 IU vitamin D (in non-placebo groups) 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: < 12 months 5. *N per group (in analysis)*: 20 6. *Brand/company*: not reported 1200 to 1600 IU (0 to 1 year); 2400 IU (1 to 17 years); 1200 IU (formula-fed, 0 to 1 year) 1. *Vitamin D content and type*: 1200 to 1400 IU vitamin D (in non-placebo groups) 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: < 12 months 5. *N per group (in analysis)*: 21 6. *Brand/company*: not reported
Outcomes	**Primary** 1. Adverse effect: hypercalciuria 2. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D **Measurement** 1. Hypercalciuria (urinary calcium-to-creatinine): not reported a. Defintion: age-specific, not reported 2. Hypercalcaemia (serum calcium): not reported a. Definition: > 1.40 mmol/L for children older than age 8 weeks; or > 1.45 mmol/L for children younger than 8 weeks of age 3. Serum 25(OH)D (nmol/L): assay not reported **Time points:** days 1, 3, 5, and 10
Starting date	July 2013
Contact information	James Dayre McNally, Children's Hosptial of Eastern Ontario, Principal Investigator; email: dmcnally@cheo.on.ca
Notes	**Notes:** recruitment completed (ended December 2015); study author contacted via email, who shared unpublished meeting abstract

NCT01996423

Study name	**Public title:** Impact of vitamin D supplementation on severity of pediatric atopic dermatitis (VIDATOPIC) **Official title:** Impact of vitamin D supplementation on clinical severity and immunologic tolerance of pediatric atopic dermatitis
Methods	**Study design:** randomised controlled trial

NCT01996423 *(Continued)*

	Study grouping: parallel group **Funding:** 100% non-profit. National Fund for Scientific and Technological Development (FONDECYT) **Country:** Chile
Participants	**Included criteria:** atopic dermatitis diagnosed according to Hanifin and Rajka criteria, age 2 to 17 years, Scoring of Atopic Dermatitis (SCORAD) score of 10 to 103 **Excluded criteria:** active skin infection; history of underlying illness causing immunosuppression within past 2 years; immunosuppressor taken within past month; parathyroid disease; sarcoidosis; acute or chronic renal disease; hypercalcaemia or hypocalcaemia; thyroid disease; osteomalacia or Paget's disease of bone malabsorption; use of vitamin D supplements (> 400 IU daily) or fish oil supplements in past month; treatment for known VD deficiency in last 6 months; treatment with moderate- or high-potency topical corticosteroids, oral or topical antibiotics, oral antivirals, immune enhancers, or topical calcineurin inhibitors in past 7 days; phototherapy in past month; autoimmune disease or immunodeficiency; planned trip to sunny climate during 6-week study.
Interventions	**Intervention characteristics** 8000 IU D_3 1. *Vitamin D content and type*: 8000 IU D_3 2. *Formulation*: oral suspension 3. *Frequency of dosage*: weekly 4. *Duration of administration (study time)*: 6 weeks 5. *N per group (sample size calculation)*: not clear* 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: oral suspension 3. *Frequency of dosage*: weekly 4. *Duration of administration (study time)*: 6 weeks 5. *N per group (sample size calculation)*: not clear* 6. *Brand/company*: not reported *Trial registration indicated n = 101 participants enrolled
Outcomes	None within the scope of this review
Starting date	April 2014
Contact information	Arturo Borzutzky, MD, Pontifica Universidad Catolica de Chile, Principal Investigator; email: arturobor@med.puc.cl
Notes	**Notes:** trial completed (ended December 2014); study author contacted via email and indicated manuscript is in progress

NCT02046577

Study name	**Publict title:** Study of vitamin D for the prevention of acute respiratory infections in children

NCT02046577 *(Continued)*

	Official title: A randomised, double-blind, controlled trial of vitamin D for the prevention of acute respiratory infections in children age 18 to 36 months in Santiago, Coyhaique, and Punta Arenas, Chile
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Award Fonis SA13I20173, Fondo Nacional de Investigación y Desarrollo en Salud **Country:** Chile
Participants	**Included criteria:** age 18 to 36 months, attending day care in Santiago, Coyhaique, or Punta Arenas, Chile **Excluded criteria:** history of chronic illness requiring immunosuppression; history of metabolic bone disease; use of vitamin D supplementation > 400 IU daily, by milk formula or by vitamin supplements, in last 3 months; use of fish oil supplements in last 3 months; immunodeficiency; planned trip to sunny climate during study period
Interventions	**Intervention characteristics** 5600 IU D_3 1. *Vitamin D content and type*: 5600 IU D_3 2. *Formulation*: liquid 3. *Frequency of dosage*: weekly 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: not clear* 6. *Brand/company*: not reported 11,200 IU D_3 1. *Vitamin D content and type*: 11,200 D_3 2. *Formulation*: liquid 3. *Frequency of dosage*: weekly 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: not clear* 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: liquid 3. *Frequency of dosage*: weekly 4. *Duration of administration (study time)*: 6 months 5. *N per group (in analysis)*: not clear* 6. *Brand/company*: not reported *Trial registration indicates n = 276 participants enrolled; meeting abstract describes n = 303 participants included in analysis
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported

NCT02046577 *(Continued)*

	Time point: 6 months
Starting date	January 2010
Contact information	María L Reyes, Pontificia Universidad Catolica de Chile, Principal Investigator
Notes	**Notes:** trial completed (ended May 2016); meeting abstract with preliminary data available; study author contacted via email, specified that primary outcomes were not measured (e.g. growth)

NCT02404623

Study name	**Public title:** The effect of vitamin D administration to premature infants on vitamin D status and respiratory morbidity **Official title:** The effect of vitamin D administration to premature infants on vitamin D status and respiratory morbidity during the first year of life
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Israel
Participants	**Included criteria:** preterm infant born at 32 + 6 to 36 + 6 weeks of gestational age, born at Saroka University Medical Center, with signed informed consent **Excluded criteria:** chromosomal abnormality; neurological or muscular congenital anomaly; congenital cardiac defect; congenital respiratory anomaly; congenital gastrointestinal, liver, or renal anomaly that affects absorption or metabolism (or both) of vitamin D or other substances (or both); admission after birth to neonatal intensive care unit persisting longer than 5 days
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 12 months 5. *N per group (in preliminary analysis)*: 17 (6 months); 11 (12 months) 6. *Brand/company*: not reported 800 IU D_3 1. *Vitamin D content and type*: 800 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 11 months 5. *N per group (in preliminary analysis)*: 20 (6 months); 14 (12 months) 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement**

NCT02404623 *(Continued)*

	1. Serum 25(OH)D (nmol/L): assay not reported **Time points:** enrolment, 12 months of age
Starting date	April 2015
Contact information	Inbal Golan-Tripto, Soroka University Medical Center, Principal Investigator; email: inbal-gt@clalit.org.il
Notes	**Notes:** recruitment completed (ended 12 February 2018). Meeting abstract and conference poster shared by study author

NCT02452762

Study name	**Public title:** Rapid normalization of vitamin D in critically ill children: a phase II dose evaluation randomised controlled trial (VITdAL-PICU) **Official title:** Rapid normalization of vitamin D in critically ill children: a phase II dose evaluation randomised controlled trial
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** Canadian Institutes of Health Research through the Project Scheme Grant and the Academic Health Sciences Centre Alternative Funding Plan Innovation Fund 2014–2015 at Children's Hospital of Eastern Ontario; Euro-Pharm International Canada Inc. provided study drug in kind; Qualigen Inc. provided FastPak (R) Vitamin D immunoassay kits in kind **Country:** Canada, Austria, Chile
Participants	**Included criteria:** admitted to intensive care unit (ICU), corrected gestational age > 37 weeks to age < 18 years, expected ICU admission in excess of 48 hours and likely to have access for blood work at 7 days of hospital stay (determined by medical team), 25-hydroxyvitamin D level < 50 nmol/L **Excluded criteria:** significant gastrointestinal disorder preventing enteral drug administration; hypercalcaemia, excluding transient abnormality and related to parenteral calcium administration for hypocalcaemia; confirmed or suspected Williams syndrome; patient known to have nephrolithiasis or nephrocalcinosis; imminent plan for withdrawal of care or transfer to another ICU; physician refusal; previous enrolment in VITdAL-PICU pilot study; patient known to have granulomatous disease (tuberculosis or sarcoidosis); severe liver dysfunction or failure; patient known to have hypersensitivity or allergy to vitamin D or any of the non-medicinal ingredients of the formulation; patient on thiazide diuretics and also receiving regular ongoing calcium supplementation above daily recommended intake for reasons other than hypocalcaemia; adolescent female of childbearing age with positive pregnancy serum test; patient on digoxin therapy
Interventions	**Intervention characteristics** 10,000 IU D_3 1. *Vitamin D content and type*: 10,000 IU/kg D_3, maximum 400,000 IU D_3 2. *Formulation*: liquid 3. *Frequency of dosage*: once, at enrolment 4. *Duration of administration (study time)*: hospital discharge (≥ 90 days) 5. *N per group (in preliminary analysis)*: 40 6. *Brand/company*: Euro-Pharm International Canada Inc.*

NCT02452762 *(Continued)*

	Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: syrup (caramel colour, cherry flavour, citric acid (anhydrous), glycerin, polysorbate 80, propylene glycol, purified water, sucralose) 3. *Frequency of dosage*: once, at enrolment 4. *Duration of administration (study time)*: hospital discharge (≥ 90 days) 5. *N per group (in preliminary analysis)*: 20 6. *Brand/company*: Euro-Pharm International Canada Inc.* *Sites in Austria and Chile will use vitamin D and placebo from Fresenius Kabi (Oleovit D3) and Laboratorios Andromaco SA (D'Vidamax 50,000 IU Oral Solution), respectively
Outcomes	**Primary** 1. Adverse effect: hypercalcaemia 2. Adverse effect: hypercalciuria **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D > 75 nmol/L **Measurement** 1. Hypercalcaemia (serum calcium): not reported a. Definition: > 1.40 mmol/L or > 1.45 mmol/L for children under 8 weeks 2. Hypercalciuria (urinary calcium/creatinine): not reported a. Definition: > 2.2 mol/mol, < 1 year; > 1.5 mol/mol, 1 to 2 years; > 1.4 mol/mol, 2 to 3 years; > 1.1 mol/mol, 3 to 5 years; > 0.8 mol/mol, 5 to 7 years; > 0.7 mol/mol, 7 to 17 years) 3. Serum 25(OH)D (nmol/L): assay not reported **Time points:** days 1, 2, 3, 7, 30, 60, and 90; at hospital discharge
Starting date	January 2016
Contact information	James Dayre McNally, Children's Hosptial of Eastern Ontario, Principal Investigator; email: dmcnally@cheo.on.ca
Notes	**Notes:** trial completed (ended January 2018); study author contacted and indicated that data are currently being analysed

NCT02563015

Study name	**Public title:** Can correction of low vitamin D status in infancy program for a leaner body composition? **Official title:** Novel functional outcomes of vitamin D in infancy; can correction of low vitamin D status program for a leaner body composition phenotype?
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Canada

NCT02563015 *(Continued)*

Participants	**Included criteria:** term, healthy, appropriate weight for gestational age; infants born to mothers with otherwise healthy pregnancy and free of medications that impact vitamin D metabolism (except vitamin or mineral supplements) or faetal growth; intent to breastfeed to at least 3 months; age up to 1 week **Excluded criteria:** preterm, small-for-gestational-age, maternal smoking in pregnancy, diabetes, preeclampsia, celiac disease, inflammatory bowel disease, medications that impact vitamin D or mineral metabolism
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 years 5. *N per group (in analysis)*: not clear* 6. *Brand/company*: not reported 1000 IU D_3 1. *Vitamin D content and type*: 1000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 years 5. *N per group (in analysis)*: not clear* 6. *Brand/company*: not reported 400 IU D_3 "reference" 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 years 5. *N per group (in analysis)*: not clear* 6. *Brand/company*: not reported *Trial registration reports a total of N = 132 participants enrolled
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time point:** 3 years
Starting date	March 2016
Contact information	Hope Weiler, McGill University, Principal Investigator; email: catherine.vanstone@mcgill.ca
Notes	**Notes:** trial terminated (stopped 20 September 2020) due to the coronavirus disease 2019 (COVID-19) pandemic, stopping recruitment

NCT02975492

Study name	**Public title:** Assessing the impact of a mode of vitamin D supplementation (sequential dose vs daily dose) on the incidence of hypercalciuria in children age from 2 to 6 years (DonneDVit) **Official title:** Evaluation de l'impact d'un mode de supplémentation en vitamine D (dose séquentielle vs dose quotidienne) sur l'incidence de l'hypercalciurie chez des enfants des départements du gard et de l'hérault agés de 2 à 6 ans. Etude contrôlée randomisée en 2 groupes parallèles
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** France
Participants	**Included criteria:** age 2 to 6 years included, obtaining signed informed consent of parents **Excluded criteria:** none reported
Interventions	**Intervention characteristics** 100,000 IU D_3 1. *Vitamin D content and type*: 100,000 IU D_3 2. *Formulation*: liquid 3. *Frequency of dosage*: twice 4. *Duration of administration (study time)*: 3 months 5. *N per group (target)*: not clear* 6. *Brand/company*: not reported 1000 IU D_3 1. *Vitamin D content and type*: 1000 IU D_3 2. *Formulation*: liquid 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (target)*: not clear* 6. *Brand/company*: not reported *Trial registration indicates estimated enrolment of N = 280 participants
Outcomes	None within the scope of this review
Starting date	December 2017
Contact information	Denis Morin, MD, University Hospital, Montpelier, Principal Investigator; email: d-morin@chu-montpellier.fr
Notes	**Notes:** recruiting (estimated recruitment completion November 2023)

NCT03087149

Study name	**Public title:** Monitored vs standard supplementation of vitamin D in preterm infants (MOSVID) **Official title:** Supplementation of vitamin D in preterm infants - monitored therapy vs standard therapy. A randomised controlled trial

NCT03087149 *(Continued)*

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** no funding **Country:** Poland
Participants	**Included criteria:** preterm infants born between 24 and 32 weeks of gestation (estimated by ultrasound), born or admitted to the unit within 48 hours from birth, randomisation within 7 days from birth, mothers willing to return for follow-up visits **Excluded criteria:** preterm delivery (at least 33 weeks of gestation or term delivery, estimated by ultrasound), major congenital abnormalities, participation in another trial, severe illness at birth deemed incompatible with survival, congenital HIV infection, total parenteral nutrition > 14 days, cholestasis
Interventions	**Intervention characteristics** Monitored 1. *Vitamin D content and type*: 500 IU vitamin D (from seventh day of age); modified at 4 weeks based on vitamin D status for infants born at < 30 weeks' gestational age, at 8 weeks of age for infants born at < 26 weeks' gestational age, at 35 ± 2 weeks' postmenstrual age ± at 40 ± 2 weeks' post-menstrual age 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: < 12 months 5. *N per group (in analysis)*: 20 6. *Brand/company*: not reported Standard 1. *Vitamin D content and type*: 500 IU vitamin D 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: < 12 months 5. *N per group (in analysis)*: 20 6. *Brand/company*: not reported
Outcomes	**Primary** 1. Adverse effect: hypercalciuria 2. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D > 75 nmol/L 3. Serum 25(OH)D > 125 nmol/L **Measurement** 1. Hypercalciuria (urinary calcium-to-creatinine ratio) a. Definition: > 3.8 mmol/mmol for 0 to 4 weeks of age; > 3.5 mmol/mmol for 5 to 8 weeks of age; > 2.8 mmol/mmol for 9 to 12 weeks of age; > 2.5 mmol/mmol for 13 to 18 weeks of age; > 2.2 mmol/mmol for > 19 weeks of age 2. Hypercalcaemia (serum calcium): assay not reported a. Definition: > 2.75 mmol/L 3. Serum 25(OH)D (nmol/L): assay not reported

NCT03087149 *(Continued)*

	Time points: 35, 40, and 52 ± 2 weeks' postmenstrual age
Starting date	May 2017
Contact information	Alicja Kołodziejczyk, Medical University of Warsaw, Warsaw, Poland; email: alicja.kolodziejczyk@uwr.edu.pl
Notes	**Notes:** unknown recruitment status (estimated recruitment completion May 2020)

NCT03365687

Study name	**Public title:** Vitamin D In the prevention of viral-induced asthma in preschoolers **Official title:** Vitamin D In the prevention of viral-induced asthma in preschoolers: a randomised controlled multicenter trial (DIVA)
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** 100% non-profit. Canadian Institutes of Health Research, grant no. 153252 **Country:** Canada
Participants	**Included criteria:** age 1 to 5 years, with a physicians' diagnosis of asthma based on clinical signs of airflow obstruction and reversibility according to Canadian guidelines, a recent history of asthma exacerbation(s) requiring oral corticosteroids (OCSs) (≥ 1 in the past 6 months or ≥ 2 in the past year, as documented in pharmacy or medical records, or both), frequent upper respiratory tract infections (URTIs) (≥ 4 in the past year), and URTIs identified by parents as the main asthma trigger **Excluded criteria:** current intake or intention to use > 400 IU/d of vitamin D supplement, or combined dietary and supplemental vitamin D intake that would exceed the recommended daily upper limit (i.e. 2500 IU for children age 1 to 3 years and 3000 IU for children age 4 to 8 years) if combined with the intervention dose; extreme prematurity (< 28 weeks' gestation); no vitamin D supplementation if exclusively breastfed in the past 6 months; vitamin D restrictive diet; undernourished (body mass index (BMI)-for-age in children ≥ 2 years of age, or either weight- or length-for-age in those < 2 years less than the third percentile); recent (< 1 year) refugees and immigrants from regions at high risk of rickets; other chronic respiratory disease; diagnosed condition(s) or use of medication(s) that alter calcium or vitamin D absorption/metabolism, and anticipated follow-up difficulties
Interventions	**Intervention characteristics** 100,000 IU D_3 1. *Vitamin D content and type*: 100,000 IU D_3 (+ 400 IU D_3) 2. *Formulation*: liquid 3. *Frequency of dosage*: 100,000 IU D_3 at enrolment, and after 3.5 ± 0.5 months; 400 IU D_3 daily 4. *Duration of administration (study time)*: 7 ± 0.5 months 5. *N per group (calculated, estimated)*: 400 6. *Brand/company*: Euro-Pharm International Canada Inc., Montreal, QC, Canada 7. *Co-intervention*: daily inhaled corticosteroids (ICSs) or preemptive ICSs with or without additional therapies such as dietary changes or supplements to reach calcium estimated average requirement (500 mg for 1 to 3 years of age; 800 mg for 4 to 8 years of age) Placebo 1. *Vitamin D content and type*: none

NCT03365687 *(Continued)*

2. *Formulation*: liquid
3. *Frequency of dosage*: at enrolment and after 3.5 ± 0.5 months
4. *Duration of administration (study time)*: 7 ± 0.5 months
5. *N per group (calculated, estimated)*: 400
6. *Brand/company*: Euro-Pharm International Canada Inc., Montreal, QC, Canada
7. *Co-intervention*: daily ICS or preemptive ICS with or without additional therapies such as dietary changes or supplements to reach calcium estimated average requirement (500 mg for 1 to 3 years of age; 800 mg for 4 to 8 years of age)

Outcomes	**Primary** 1. Adverse effect: hypercalciuria 2. Adverse effect: hypercalcaemia **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurements** 1. Hypercalciuria (urinary calcium-to-creatinine): exceeding pre-established laboratory standards 2. Hypercalcaemia (serum calcium): exceeding pre-established laboratory standards 3. Serum 25(OH)D (nmol/L): assay not reported **Time points:** 3.5 ± 0.5 months, 7 ± 0.5 months
Starting date	October 2018
Contact information	Connie Yang, British Columbia Children's Hospital, Principal Investigator; email: connie.yang@cw.bc.ca
Notes	**Notes:** recruiting (estimated recruitment completion December 2023)

NCT03536845

Study name	**Public title:** Vitamin D supplementation to prevent vitamin D deficiency for children with epilepsy **Official title:** Vitamin D supplementation to prevent vitamin D deficiency for children with epilepsy: a randomised controlled clinical trial
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** non-profit and for-profit. Dallah Healthcare, Kingdom of Saudi Arabia. Grant number (CM-RC-DHG-1/006) **Country:** Saudi Arabia
Participants	**Included criteria:** age 2 to 16 years, being treated with antiepileptic drugs **Excluded criteria:** preexisting vitamin D metabolism problems such as vitamin D-dependent rickets, malabsorption syndrome, kidney disease, or liver disease. In addition to hypercalcaemia at baseline, total corrected calcium > 2.5 mg/dL, serum 25-hydroxyvitamin D (25(OH)D) level > 250 nmol/L, or urine calcium-to-creatinine ration > 1.2 mol/mol or > 0.41 g/g **Notes:** children with baseline serum 25-hydroxyvitamin D < 75 nmol/L will be given a treatment course of 5000 IU vitamin D_3 daily for 8 weeks + 30 to 75 mg/kg/d of elemental calcium in 3 divid-

NCT03536845 *(Continued)*

	ed doses for 4 weeks, and given the option of taking 35,000 IU weekly during the treatment phase according to patient preference. Upon normalisation of serum vitamin D level, patients will be randomised. Children with serum vitamin D > 75 nmol/L will be randomised immediately to the maintenance intervention
Interventions	**Intervention characteristics** 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (sample size calculation)*: 67 6. *Brand/company*: not reported 1000 IU D_3 1. *Vitamin D content and type*: 1000 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (sample size calculation)*: 67 6. *Brand/company*: not reported
Outcomes	**Primary** 1. Adverse effect: hypercalciuria **Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D < 75 nmol/L **Measurement** 1. Hypercalciuria (urinary calcium-to-creatinine ratio): assay not reported a. Definition: > 1.2 mol/mol 2. Serum 25(OH)D (nmol/L): electro chemiluminescence binding assay (Roche Diagnostics, Basel, Switzerland) **Time points:** 3 months, 6 months
Starting date	January 2018
Contact information	Reem Al Khalifah, MBBS, FRCPs Msc, King Saud University, Principal Investigator; email: ralkahlifah@ksu.edu.sa
Notes	**Notes:** recruiting (estimated recruitment completion January 2021)

NCT03742310

Study name	**Public title:** The relationship between VDR gene polymorphism and children's physical and intellectual development (RVDRGPCPID) **Official title:** Multi-center clinical study on the relationship between vitamin D receptor gene polymorphism and children's physical and intellectual development

NCT03742310 *(Continued)*

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** China
Participants	**Included criteria:** age 0 to 3 years, healthy, no history of specific diseases **Excluded criteria:** current or past serious lung infection, nervous system disease, kidney disease, malignant tumour; bone metabolic disease or other genetic metabolic disease; taking drugs that affect bone metabolism
Interventions	**Intervention characteristics** Low-risk vitamin D receptor (VDR) genotype 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 years 5. *N per group (target)*: 125 6. *Brand/company*: not reported Middle-risk VDR genotype 600 IU D_3 1. *Vitamin D content and type*: 600 D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 years 5. *N per group (target)*: 125 6. *Brand/company*: not reported High-risk VDR genotype 800 IU D_3 1. *Vitamin D content and type*: 800 D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 years 5. *N per group (target)*: 125 6. *Brand/company*: not reported General 400 IU D_3 1. *Vitamin D content and type*: 400 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 years 5. *N per group (target)*: 125 6. *Brand/company*: not reported
Outcomes	**Primary** 1. Linear growth **Measurement** 1. Length/height (cm): equipment not reported

NCT03742310 *(Continued)*

	Time point: 3 years of age
Starting date	January 2019
Contact information	Hui Li, PhD, First Affiliated Hospital of Xi'an Jiaotong University, Principal Investigator; email: huili@mail.xjtu.edu.cn
Notes	**Notes:** not yet recruiting (estimated start 1 March 2021)

NCT03742505

Study name	**Public title:** Rapid normalization of vitamin D deficiency in PICU (VITdALIZE-KIDS) **Official title:** Rapid normalization of vitamin D deficiency in PICU: a multi-centre phase III double-blind randomised controlled trial
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Canada
Participants	**Included criteria:** anticipated paediatric intensive care unit stay ≥ 48 hours; corrected gestational age 37 weeks to age 18 years; expected to require clinically indicated blood work > 48 hours following study enrolment (range 2 to 7 days); vitamin D deficiency, defined by blood 25-hydroxyvitamin D (25(OH)D) < 50 nmol/L at the time of screening **Excluded criteria:** treating physician refuses enteral drug administration due to gastrointestinal disorder; persistent hypercalcaemia (ionised calcium > 1.40 mmol/L (age ≥ 2 months), > 1.45 (age < 2 months)) excluding transient abnormalities and those related to parenteral calcium administration for hypocalcaemia; confirmed or suspected Williams syndrome; known nephrolithiasis or nephrocalcinosis; imminent plan for withdrawal of treatment or transfer to another intensive care unit not participating in the VITdALIZE-KIDS trial; physician refusal; previous enrolment in this trial; granulomatous disease (tuberculosis or sarcoidosis); severe liver failure; hypersensitivity or allergy to vitamin D or any of the non-medicinal ingredients of the formulation; taking thiazide diuretics while receiving regular ongoing calcium supplementation above daily recommended intake; adolescent female of childbearing age with positive pregnancy serum test; receiving digoxin therapy; treating physician intends to administer vitamin D doses above 1000 IU (e.g. patient presents with isolated clinical symptoms of severe VDD, severe burns)
Interventions	**Intervention characteristics** 400,000 IU D_3 1. *Vitamin D content and type*: 10,000 IU/kg D_3, max 400,000 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: once, at enrolment 4. *Duration of administration (study time)*: 90 days 5. *N per group (target)*: 383 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: not reported 3. *Frequency of dosage*: once, at enrolment

NCT03742505 *(Continued)*

	4. *Duration of administration (study time)*: 90 days 5. *N per group (target)*: 383 6. *Brand/company*: not reported
Outcomes	**Primary** 1. Adverse effect: hypercalcaemia 2. Adverse effect: kidney stones **Measurement** 1. Hypercalcaemia: not defined 2. Kidney stones: not defined **Time point:** up to 90 days post randomisation
Starting date	June 2019
Contact information	James Dayre McNally, Children's Hospital of Eastern Ontario, Principal Investigator; email: dmcnally@cheo.on.ca
Notes	**Notes:** recruiting (estimated recruitment completion 31 August 2023)

NCT03871322

Study name	**Public title:** The vitamin K_2 and D_3 intervention trial in children and adolescents with low-energy fractures **Official title:** Rationale and design of the vitamin K_2 and vitamin D_3 intervention trial in children and adolescents with low-energy bone fractures
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Poland
Participants	**Included criteria:** age 3 to 18 years, presence of low-energy fracture, vitamin D serum level < 30 ng/mL **Excluded criteria:** age > 18 years, lack of low-energy bone fracture, oral anticoagulant treatments that interfere with vitamin K cycle, current supplementation with vitamin K_2 or vitamin D_3, osteogenesis imperfecta or other bone disease, vitamin D concentration > 30 ng/mL
Interventions	**Intervention characteristics** 2000 IU D_3 1. *Vitamin D content and type*: 2000 IU D_3 2. *Formulation*: soft gel capsules 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (target)*: 30 6. *Brand/company*: not reported 7. *Micronutrient content*: none

NCT03871322 *(Continued)*

	2000 IU D_3 + Vitamin K_2 1. *Vitamin D content and type*: 2000 IU D_3 2. *Formulation*: soft gel capsules 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (target)*: 30 6. *Brand/company*: not reported 7. *Micronutrient content*: vitamin K_2 90 µg **Arm not to be included in analysis** Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: soft gel capsules with olive oil 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months 5. *N per group (target)*: 30 6. *Brand/company*: not reported 7. *Micronutrient content*: none
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time point:** 3 months
Starting date	July 2019
Contact information	Michał Karpiński, Medical University of Bialystok, Principal Investigator; email: gufkarp@gmail.com
Notes	**Notes:** recruiting (estimated recruitment completion 20 January 2021)

NCT03999580

Study name	**Public title:** The vitamin D in pediatric Crohn's disease (ViDiPeC-2) (ViDiPeC-2) **Official title:** A pragmatic randomised controlled trial on high dose vitamin D to prevent relapses of Crohn's disease in children
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Canada
Participants	**Included criteria:** age at randomisation between 4 and 17 years inclusive; Pediatric Crohn's Disease (CD) Activity Index (PCDAI) ≤ 10 with no clinical symptoms (abdominal pain or blood in the stool) at inclusion; receiving a stable dose for at least 4 weeks of any of the following drugs: thiopurines, methotrexate, or tumour necrosis factor-α inhibitors (infliximab/adalimumab); dosage of fecal calprotectin < 250 µg/g stool at inclusion

NCT03999580 *(Continued)*

	Excluded criteria: history of surgery resulting in a permanent colostomy or ileostomy (because of inability to calculate PCDAI at baseline), patients who have already been included in the pilot vitamin D trials, patients actively enrolled in other CD drug trials
Interventions	**Intervention characteristics** 3000 to 4000 IU D_3 1. *Vitamin D content and type*: 3000 IU or 4000 IU, then 2000 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 4 weeks (3000 to 4000 IU), 48 weeks (2000 IU) 5. *N per group (target)*: 158 6. *Brand/company*: not reported 600 IU D_3 1. *Vitamin D content and type*: 600 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 52 weeks 5. *N per group (target)*: 158 6. *Brand/company*: not reported
Outcomes	None within scope of this review
Starting date	August 2019
Contact information	Prevost Jantchou, MD, PhD, St Justine's Hospital, Principal Investigator; email: prevost.jantchou@umontreal.ca
Notes	**Notes:** not yet recruiting (estimated trial completion December 2024)

RBR-4r6p5v

Study name	Effect of physical exercise and nutritional programs on the health status of schoolchildren age 4 to 11 years old from Santo Antônio de Goiás
Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over **Funding:** 100% non-profit. Fundação Cargill - Goiânia, GO, Brazil **Country:** Brazil
Participants	**Included criteria:** age between 4 and 11 years; both genders; residing in Santo Antônio de Goiás; enrolled in the city elementary school **Excluded criteria:** cognitive or physical disabilities; pathologies such as respiratory, cardiologic, renal, or hepatic chronic disease, which prevent data collection, and vitamin D supplementation; using any medication that influences the serum concentration of lipoproteins; having used cholecalciferol supplement in the last 10 weeks; serum 25-hydroxyvitamin D levels > 75 ng/dL
Interventions	**Intervention characteristics**

RBR-4r6p5v *(Continued)*

	1000 IU D_3 1. *Vitamin D content and type*: 1000 IU D_3 2. *Formulation*: drops 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months, 10-week washout, 3 months 5. *N per group (in analysis)*: 31 6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: drops (sunflower oil) 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 3 months, 10-week washout, 3 months 5. *N per group (in analysis)*: 31 6. *Brand/company*: not reported
Outcomes	None within scope of this review
Starting date	September 2017
Contact information	Ana Gabriella Pereira Alves, Universidade Federal de Goiás, Principal Investigator; email:anagabriela_alves@hotmail.com
Notes	**Notes:** recruitment completed (ended January 2020); study author contacted and indicated that few children were under 5 years of age and additional data are forthcoming

UMIN000034864

Study name	**Public title:** Prevention of allergic march by vitamin D supplementation during infancy **Scientific title:** Prevention of allergic march by vitamin D supplementation during infancy
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** other **Country:** Japan
Participants	**Included criteria:** age 1 to 5 years **Excluded criteria:** premature; surgical disease (oesophageal atresia, diaphragmatic hernia) requiring tube feeding or inability to take vitamin D; ineligible per judgement of research facility director or doctor
Interventions	**Intervention characteristics** 400 IU 1. *Vitamin D content and type*: 400 IU vitamin D 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (sample size calculation)*: 150

UMIN000034864 *(Continued)*

	6. *Brand/company*: not reported Placebo 1. *Vitamin D content and type*: none 2. *Formulation*: not reported 3. *Frequency of dosage*: daily 4. *Duration of administration (study time)*: 6 months 5. *N per group (sample size calculation)*: 150 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) **Measurement** 1. Serum 25(OH)D (nmol/L): assay not reported **Time points:** 6 months of age, 1 year of age
Starting date	July 2018
Contact information	Taiji Nakano, Chiba University, Department of Pediatrics, Principal Investigator; email: t-nakano@chiba-u.jp
Notes	**Notes:** recruiting (estimated recruitment completion July 2023)

Yani 2018

Study name	Vitamin D supplementation and tuberculin skin test conversion among healthy under-five children with tuberculosis contact
Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group **Funding:** not reported **Country:** Indonesia
Participants	**Included criteria:** healthy children < 5 years of age with tuberculosis contact with negative tuberculin tests **Excluded criteria:** none noted
Interventions	**Intervention characteristics** 25,000 IU D_3 1. *Vitamin D content and type*: 25,000 IU D_3 2. *Formulation*: not reported 3. *Frequency of dosage*: baseline and day 42 4. *Duration of administration (study time)*: 12 weeks 5. *N per group (in analysis)*: not reported 6. *Brand/company*: not reported Placebo

Yani 2018 *(Continued)*	1. *Vitamin D content and type*: none 2. *Formulation*: not reported 3. *Frequency of dosage*: baseline and day 42 4. *Duration of administration (study time)*: 12 weeks 5. *N per group (in analysis)*: not reported 6. *Brand/company*: not reported
Outcomes	**Secondary** 1. Serum 25-hydroxyvitamin D (25(OH)D, nmol/L) 2. Serum 25(OH)D sufficiency **Measurement** 1. Serum 25(OH)D (nmol/L): enzyme-linked immunoabsorbent assay 2. Serum 25(OH)D sufficiency: not defined **Time point:** 12 weeks
Starting date	March 2014
Contact information	Finny Fitry Yani, MD, University Andalas, Principal Investigator; email: finny_fy@yahoo.com
Notes	**Notes:** trial completed (ended December 2015); study author contacted and indicated that manuscript is forthcoming

BMI: body mass index.
ICU: intensive care unit.
PMA: postmenstrual age.

DATA AND ANALYSES

Comparison 1. Vitamin D versus placebo or no intervention

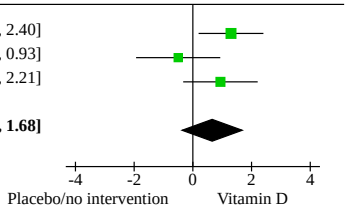
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Linear growth	3	240	Mean Difference (IV, Random, 95% CI)	0.66 [-0.37, 1.68]
1.2 Length/height-for-age	1	1258	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.00, 0.22]
1.3 Stunting	1	1247	Risk Ratio (IV, Fixed, 95% CI)	0.90 [0.80, 1.01]
1.4 Adverse effect: hypercalciuria	2	68	Risk Ratio (IV, Random, 95% CI)	2.03 [0.28, 14.67]
1.5 Adverse effect: hypercalcaemia	2	367	Risk Ratio (IV, Random, 95% CI)	0.82 [0.35, 1.90]
1.6 Weight-for-age	1	1273	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.02, 0.20]
1.7 Underweight	1	1282	Risk Ratio (IV, Fixed, 95% CI)	0.94 [0.80, 1.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8 Weight-for-length/height	2	1442	Mean Difference (IV, Random, 95% CI)	0.65 [-0.67, 1.97]
1.9 Wasting	1	1282	Risk Ratio (IV, Fixed, 95% CI)	1.25 [0.82, 1.91]
1.10 Serum 25-hydroxyvitamin D	21	2202	Mean Difference (IV, Random, 95% CI)	30.91 [21.82, 40.00]
1.11 Change in 25(OH)D levels (nmol/L)	3	495	Mean Difference (IV, Random, 95% CI)	28.36 [10.41, 46.32]
1.12 Vitamin D sufficiency (≥ 50 nmol/L)	6	982	Risk Ratio (IV, Random, 95% CI)	1.88 [1.63, 2.17]
1.13 Vitamin D sufficiency (≥ 75 nmol/L)	2	138	Risk Ratio (IV, Random, 95% CI)	5.75 [0.49, 67.59]
1.14 Vitamin D severe deficiency (< 25 to 30 nmol/L)	3	836	Risk Ratio (IV, Random, 95% CI)	0.26 [0.19, 0.36]
1.15 Rickets (continuous)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 1: Linear growth

Study or Subgroup	Vitamin D Mean [cm]	Vitamin D SD [cm]	Vitamin D Total	Placebo/no intervention Mean [cm]	Placebo/no intervention SD [cm]	Placebo/no intervention Total	Weight	Mean Difference IV, Random, 95% CI [cm]
Chandy 2016	61.6	2.37	52	60.3	3.33	53	37.8%	1.30 [0.20 , 2.40]
Greer 1989	65.8	2.1	19	66.3	2.4	19	29.0%	-0.50 [-1.93 , 0.93]
Singh 2018a	62.54	3.5	49	61.6	2.85	48	33.1%	0.94 [-0.33 , 2.21]
Total (95% CI)			**120**			**120**	**100.0%**	**0.66 [-0.37 , 1.68]**

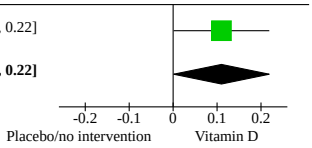
Heterogeneity: Tau² = 0.41; Chi² = 3.96, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 2: Length/height-for-age

Study or Subgroup	Vitamin D Mean [z-score]	Vitamin D SD [z-score]	Vitamin D Total	Placebo/no intervention Mean [z-score]	Placebo/no intervention SD [z-score]	Placebo/no intervention Total	Weight	Mean Difference IV, Fixed, 95% CI [z-score]
Trilok-Kumar 2011	-1.84	0.98	620	-1.95	0.99	638	100.0%	0.11 [0.00 , 0.22]
Total (95% CI)			**620**			**638**	**100.0%**	**0.11 [0.00 , 0.22]**

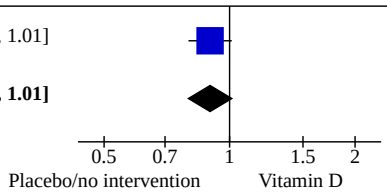
Heterogeneity: Not applicable
Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 3: Stunting

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no intervention Events	Placebo/no intervention Total	Weight	Risk Ratio IV, Fixed, 95% CI
Trilok-Kumar 2011	270	614	310	633	100.0%	0.90 [0.80 , 1.01]
Total (95% CI)		**614**		**633**	**100.0%**	**0.90 [0.80 , 1.01]**
Total events:	270		310			

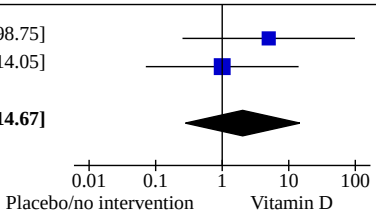
Heterogeneity: Not applicable
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 4: Adverse effect: hypercalciuria

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no intervention Events	Placebo/no intervention Total	Weight	Risk Ratio IV, Random, 95% CI
Ducharme 2019	2	23	0	23	44.0%	5.00 [0.25 , 98.75]
Jensen 2016	1	11	1	11	56.0%	1.00 [0.07 , 14.05]
Total (95% CI)		**34**		**34**	**100.0%**	**2.03 [0.28 , 14.67]**
Total events:	3		1			

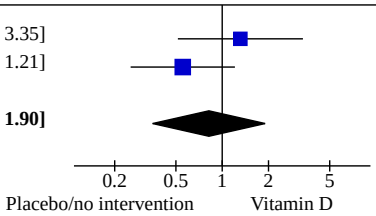
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 5: Adverse effect: hypercalcaemia

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no intervention Events	Placebo/no intervention Total	Weight	Risk Ratio IV, Random, 95% CI
Chandy 2016	8	47	7	54	45.3%	1.31 [0.51 , 3.35]
Hibbs 2018	9	134	16	132	54.7%	0.55 [0.25 , 1.21]
Total (95% CI)		**181**		**186**	**100.0%**	**0.82 [0.35 , 1.90]**
Total events:	17		23			

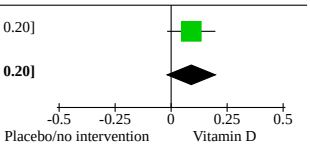
Heterogeneity: Tau² = 0.18; Chi² = 1.93, df = 1 (P = 0.17); I² = 48%
Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 6: Weight-for-age

Study or Subgroup	Vitamin D Mean [z-score]	Vitamin D SD [z-score]	Vitamin D Total	Placebo/no intervention Mean [z-score]	Placebo/no intervention SD [z-score]	Placebo/no intervention Total	Weight	Mean Difference IV, Fixed, 95% CI [z-score]
Trilok-Kumar 2011	-1.51	0.98	627	-1.6	0.98	646	100.0%	0.09 [-0.02 , 0.20]
Total (95% CI)			**627**			**646**	**100.0%**	**0.09 [-0.02 , 0.20]**

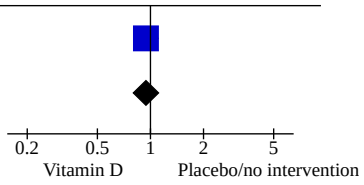
Heterogeneity: Not applicable
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 7: Underweight

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no intervention Events	Placebo/no intervention Total	Weight	Risk Ratio IV, Fixed, 95% CI
Trilok-Kumar 2011	190	634	206	648	100.0%	0.94 [0.80 , 1.11]
Total (95% CI)		**634**		**648**	**100.0%**	**0.94 [0.80 , 1.11]**
Total events:	190		206			

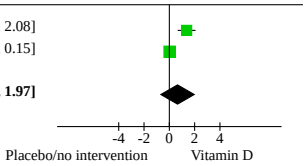
Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 8: Weight-for-length/height

Study or Subgroup	Vitamin D Mean [z-score]	Vitamin D SD [z-score]	Vitamin D Total	Placebo/no intervention Mean [z-score]	Placebo/no intervention SD [z-score]	Placebo/no intervention Total	Weight	Mean Difference IV, Random, 95% CI [z-score]
Saleem 2018	0.15	2.83	93	-1.22	2	92	46.6%	1.37 [0.66 , 2.08]
Trilok-Kumar 2011	-0.34	1.17	620	-0.36	1.16	637	53.4%	0.02 [-0.11 , 0.15]
Total (95% CI)			**713**			**729**	**100.0%**	**0.65 [-0.67 , 1.97]**

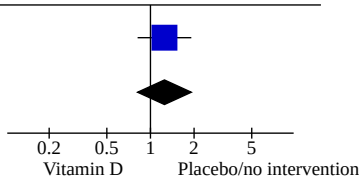
Heterogeneity: Tau² = 0.84; Chi² = 13.61, df = 1 (P = 0.0002); I² = 93%
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 9: Wasting

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no intervention Events	Placebo/no intervention Total	Weight	Risk Ratio IV, Fixed, 95% CI
Trilok-Kumar 2011	44	634	36	648	100.0%	1.25 [0.82 , 1.91]
Total (95% CI)		**634**		**648**	**100.0%**	**1.25 [0.82 , 1.91]**
Total events:	44		36			

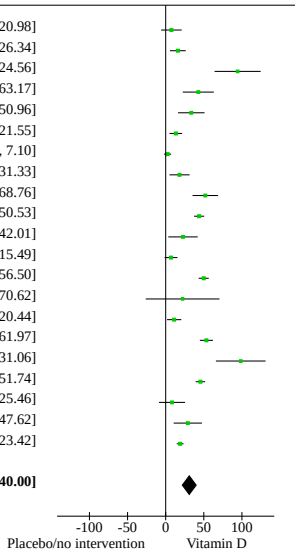
Heterogeneity: Not applicable
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 10: Serum 25-hydroxyvitamin D

Study or Subgroup	Vitamin D Mean [nmol/L]	Vitamin D SD [nmol/L]	Vitamin D Total	Placebo/no intervention Mean [nmol/L]	Placebo/no intervention SD [nmol/L]	Placebo/no intervention Total	Weight	Mean Difference IV, Random, 95% CI [nmol/L]
Alonso 2011	99.6	24	28	92.1	33.9	43	5.0%	7.50 [-5.98 , 20.98]
Chandy 2016	61.3	25.19	47	45.3	27.8	54	5.2%	16.00 [5.66 , 26.34]
Fort 2016	150.3403	91.2766	64	55.98	62.15	36	3.5%	94.36 [64.16 , 124.56]
Greer 1981	95.08	21.42	9	52.26	22.62	9	4.4%	42.82 [22.47 , 63.17]
Greer 1989	92.3	29.6	19	58.7	24.8	19	4.6%	33.60 [16.24 , 50.96]
Hanson 2011	57.7	17.5	25	44.4	11.7	25	5.3%	13.30 [5.05 , 21.55]
Hibbs 2018	82.37	18.49	125	79.88	18.49	122	5.5%	2.49 [-2.12 , 7.10]
Jensen 2016	100.62	15.6592	11	82.49	15.9271	11	5.0%	18.13 [4.93 , 31.33]
Manaseki-Holland 2012	104.9	90.6918	141	52.9	45.6462	141	4.7%	52.00 [35.24 , 68.76]
Marchisio 2013	90.36	21.22	58	46.48	14.72	58	5.4%	43.88 [37.23 , 50.53]
Moodley 2015	91.1	26.0044	11	68.39	18.8437	10	4.5%	22.71 [3.41 , 42.01]
Ponnapakkam 2010	114.5329	14.0483	17	107.53	7.56	8	5.3%	7.00 [-1.48 , 15.49]
Principi 2013	96.35	21.22	59	46.48	14.72	57	5.4%	49.87 [43.24 , 56.50]
Rianthavorn 2013	76.88	45.8	4	54.66	13.06	2	2.2%	22.22 [-26.18 , 70.62]
Rueter 2019	93.1	28.7	73	82	27.9	68	5.3%	11.10 [1.76 , 20.44]
Saleem 2018	99.4	39.7	93	46	14.1	92	5.3%	53.40 [44.83 , 61.97]
Sánchez-Armendáriz 2018	167.14	49.48	11	68.67	23.21	10	3.3%	98.47 [65.88 , 131.06]
Shedeed 2012	82.09	11.73	42	36.54	15.97	38	5.4%	45.55 [39.36 , 51.74]
Singh 2018a	75.4	45.7	49	67.1	40.4	48	4.7%	8.30 [-8.86 , 25.46]
Tang 2019	68.53	16.16	5	39.48	16.22	7	4.5%	29.05 [10.48 , 47.62]
Trilok-Kumar 2011	55	22.5	216	36	25.5	237	5.5%	19.00 [14.58 , 23.42]
Total (95% CI)			**1107**			**1095**	**100.0%**	**30.91 [21.82 , 40.00]**

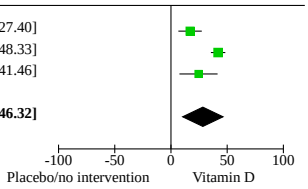
Heterogeneity: Tau² = 385.01; Chi² = 369.62, df = 20 (P < 0.00001); I² = 95%
Test for overall effect: Z = 6.66 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 11: Change in 25(OH)D levels (nmol/L)

Study or Subgroup	Vitamin D Mean [nmol/L]	Vitamin D SD [nmol/L]	Vitamin D Total	Placebo/no intervention Mean [nmol/L]	Placebo/no intervention SD [nmol/L]	Placebo/no intervention Total	Weight	Mean Difference IV, Random, 95% CI [nmol/L]
Gupta 2016	17.5	46.9	144	0.5	42.2	138	34.3%	17.00 [6.60 , 27.40]
Marchisio 2013	24.21	19.47	58	-17.72	15.48	58	36.9%	41.93 [35.53 , 48.33]
Singh 2018a	36.7	44.9112	49	12.2	40.2246	48	28.8%	24.50 [7.54 , 41.46]
Total (95% CI)			**251**			**244**	**100.0%**	**28.36 [10.41 , 46.32]**

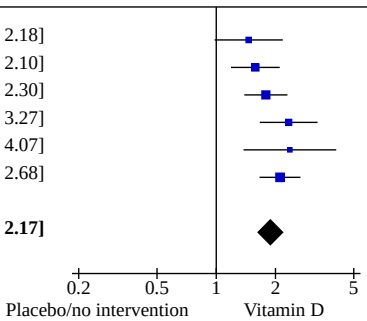
Heterogeneity: Tau² = 216.66; Chi² = 17.35, df = 2 (P = 0.0002); I² = 88%
Test for overall effect: Z = 3.10 (P = 0.002)
Test for subgroup differences: Not applicable



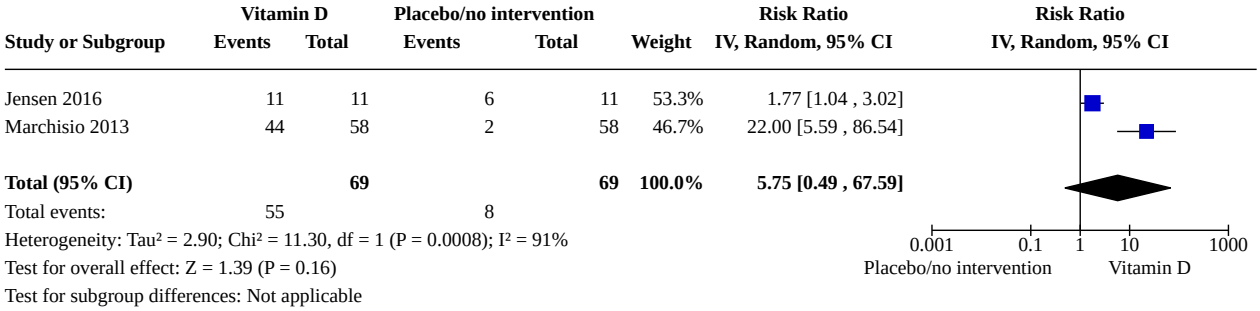
Analysis 1.12. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 12: Vitamin D sufficiency (≥ 50 nmol/L)

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo/no intervention Events	Placebo/no intervention Total	Weight	Risk Ratio IV, Random, 95% CI
Chandy 2016	28	47	22	54	11.2%	1.46 [0.98 , 2.18]
Fort 2016	59	64	21	36	19.4%	1.58 [1.19 , 2.10]
Manaseki-Holland 2012	79	84	30	57	23.3%	1.79 [1.39 , 2.30]
Saleem 2018	45	45	19	45	14.7%	2.33 [1.66 , 3.27]
Singh 2018a	29	49	12	48	6.4%	2.37 [1.38 , 4.07]
Trilok-Kumar 2011	123	216	64	237	25.0%	2.11 [1.66 , 2.68]
Total (95% CI)		**505**		**477**	**100.0%**	**1.88 [1.63 , 2.17]**
Total events:	363		168			

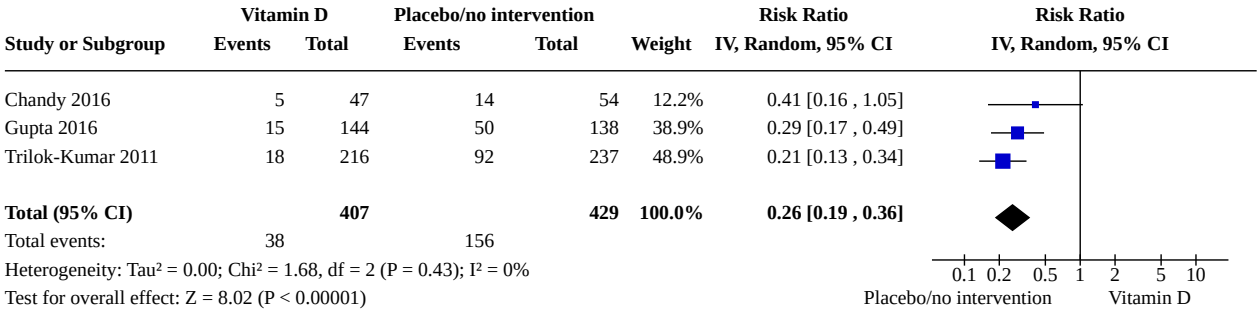
Heterogeneity: Tau² = 0.01; Chi² = 6.25, df = 5 (P = 0.28); I² = 20%
Test for overall effect: Z = 8.67 (P < 0.00001)
Test for subgroup differences: Not applicable



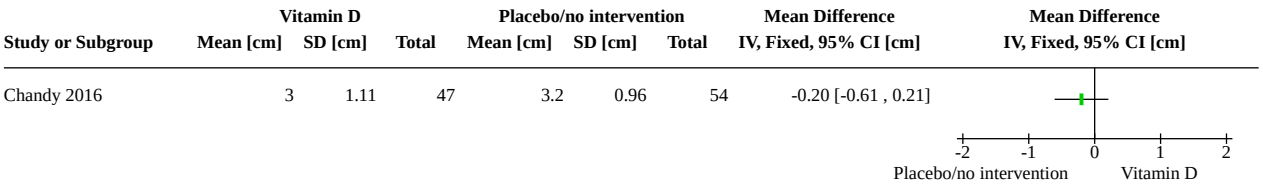
Analysis 1.13. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 13: Vitamin D sufficiency (≥ 75 nmol/L)



Analysis 1.14. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 14: Vitamin D severe deficiency (< 25 to 30 nmol/L)



Analysis 1.15. Comparison 1: Vitamin D versus placebo or no intervention, Outcome 15: Rickets (continuous)



Comparison 2. Vitamin D (higher dose) versus vitamin D (lower dose)

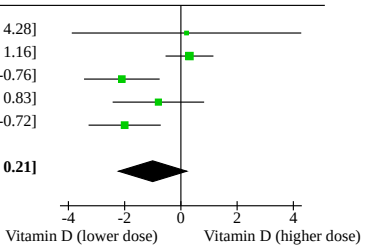
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Linear growth	5	283	Mean Difference (IV, Random, 95% CI)	-1.00 [-2.22, 0.21]
2.2 Length/height-for-age	2	105	Mean Difference (IV, Random, 95% CI)	0.40 [-0.06, 0.86]
2.3 Adverse effect: hypercalciuria	6	554	Risk Ratio (IV, Random, 95% CI)	1.16 [1.00, 1.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Adverse effect: hypercalcaemia	5	986	Risk Ratio (IV, Random, 95% CI)	1.39 [0.89, 2.18]
2.5 Linear growth: gain in length	3	378	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.02, 0.00]
2.6 Weight-for-age	2	103	Mean Difference (IV, Random, 95% CI)	0.07 [-0.44, 0.58]
2.7 Weight-for-length/height	1	53	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.74, 0.37]
2.8 Serum 25-hydroxyvitamin D	20	2765	Mean Difference (IV, Random, 95% CI)	16.13 [7.11, 25.15]
2.9 Change in 25(OH)D (nmol/L)	3	142	Mean Difference (IV, Random, 95% CI)	4.12 [-5.82, 14.07]
2.10 Vitamin D sufficiency (≥ 50 nmol/L)	12	1735	Risk Ratio (IV, Random, 95% CI)	1.04 [1.00, 1.08]
2.11 Vitamin D sufficiency (≥ 75 nmol/L)	6	1172	Risk Ratio (IV, Random, 95% CI)	1.31 [1.19, 1.45]
2.12 Vitamin D severe deficiency (< 25 to 30 nmol/L)	1	142	Risk Ratio (IV, Fixed, 95% CI)	0.14 [0.02, 1.35]
2.13 Rickets (dichotomous)	4	212	Risk Ratio (IV, Random, 95% CI)	0.64 [0.46, 0.90]

Analysis 2.1. Comparison 2: Vitamin D (higher dose) versus vitamin D (lower dose), Outcome 1: Linear growth

Study or Subgroup	Vitamin D (higher dose) Mean [cm]	SD [cm]	Total	Vitamin D (lower dose) Mean [cm]	SD [cm]	Total	Weight	Mean Difference IV, Random, 95% CI [cm]
Backström 1999b	48.9	4	11	48.7	4.8	8	6.9%	0.20 [-3.88 , 4.28]
Holmlund-Suila 2012	61.2056	1.902	72	60.9	2.2	35	27.2%	0.31 [-0.55 , 1.16]
Huynh 2017	61.7	2.6	26	63.8	2.2	23	22.6%	-2.10 [-3.44 , -0.76]
Natarajan 2014	57	3.4	40	57.8	4	40	20.1%	-0.80 [-2.43 , 0.83]
Siafarikas 2011	56	1.732	14	58	1.732	14	23.2%	-2.00 [-3.28 , -0.72]
Total (95% CI)			**163**			**120**	**100.0%**	**-1.00 [-2.22 , 0.21]**

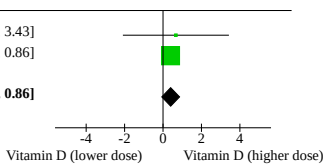
Heterogeneity: Tau² = 1.22; Chi² = 13.64, df = 4 (P = 0.009); I² = 71%
Test for overall effect: Z = 1.62 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Vitamin D (higher dose) versus vitamin D (lower dose), Outcome 2: Length/height-for-age

Study or Subgroup	Vitamin D (higher dose) Mean [z-score]	SD [z-score]	Total	Vitamin D (lower dose) Mean [z-score]	SD [z-score]	Total	Weight	Mean Difference IV, Random, 95% CI [z-score]
Gallo 2013a	0.79	5.15	26	0.12	4.801	24	2.8%	0.67 [-2.09 , 3.43]
Gallo 2013b	0.2	1.0362	36	-0.19	0.72	19	97.2%	0.39 [-0.08 , 0.86]
Total (95% CI)			**62**			**43**	**100.0%**	**0.40 [-0.06 , 0.86]**

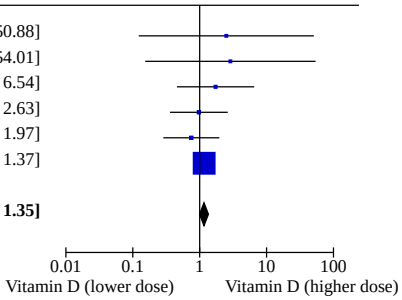
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 1.69 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Vitamin D (higher dose) versus vitamin D (lower dose), Outcome 3: Adverse effect: hypercalciuria

Study or Subgroup	Vitamin D (higher dose) Events	Total	Vitamin D (lower dose) Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bozkurt 2017	2	81	0	40	0.3%	2.50 [0.12 , 50.88]
Gallo 2013b	3	72	0	29	0.3%	2.88 [0.15 , 54.01]
Harnot 2017	5	27	3	28	1.3%	1.73 [0.46 , 6.54]
Holmlund-Suila 2012	10	72	5	35	2.4%	0.97 [0.36 , 2.63]
Natarajan 2014	6	40	8	40	2.5%	0.75 [0.29 , 1.97]
Shajari 2009	28	30	48	60	93.2%	1.17 [1.00 , 1.37]
Total (95% CI)		**322**		**232**	**100.0%**	**1.16 [1.00 , 1.35]**
Total events:	54		64			

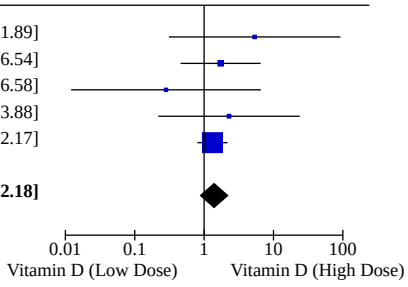
Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 5 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.90 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Vitamin D (higher dose) versus vitamin D (lower dose), Outcome 4: Adverse effect: hypercalcaemia

Study or Subgroup	Vitamin D (High Dose) Events	Total	Vitamin D (Low Dose) Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Gallo 2013b	6	72	0	29	2.5%	5.34 [0.31 , 91.89]
Harnot 2017	5	27	3	28	11.3%	1.73 [0.46 , 6.54]
Huynh 2017	0	25	1	21	2.0%	0.28 [0.01 , 6.58]
Mittal 2014	2	28	1	32	3.6%	2.29 [0.22 , 23.88]
Rosendahl 2018	33	362	25	362	80.5%	1.32 [0.80 , 2.17]
Total (95% CI)		**514**		**472**	**100.0%**	**1.39 [0.89 , 2.18]**
Total events:	46		30			

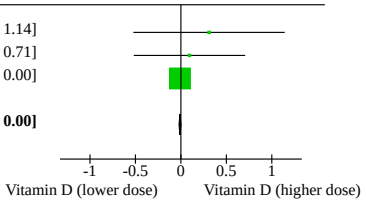
Heterogeneity: Tau² = 0.00; Chi² = 2.16, df = 4 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Vitamin D (higher dose) versus vitamin D (lower dose), Outcome 5: Linear growth: gain in length

Study or Subgroup	Vitamin D (higher dose) Mean [cm]	SD [cm]	Total	Vitamin D (lower dose) Mean [cm]	SD [cm]	Total	Weight	Mean Difference IV, Random, 95% CI [cm]
Feliciano 1994	17.5085	2.7925	129	17.1986	2.8983	70	0.0%	0.31 [-0.52 , 1.14]
Holmlund-Suila 2012	10.7944	1.5515	72	10.7	1.5	35	0.0%	0.09 [-0.52 , 0.71]
Ziegler 2014	0.14	0.0196	52	0.15	0.02	20	100.0%	-0.01 [-0.02 , 0.00]
Total (95% CI)			**253**			**125**	**100.0%**	**-0.01 [-0.02 , 0.00]**

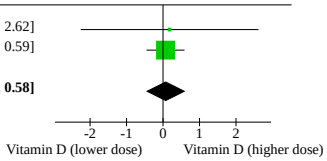
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.90 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Vitamin D (higher dose) versus vitamin D (lower dose), Outcome 6: Weight-for-age

Study or Subgroup	Vitamin D (higher dose) Mean [z-score]	SD [z-score]	Total	Vitamin D (lower dose) Mean [z-score]	SD [z-score]	Total	Weight	Mean Difference IV, Random, 95% CI [z-score]
Gallo 2013a	0.25	3.4673	26	0.07	5.0949	24	4.4%	0.18 [-2.26 , 2.62]
Gallo 2013b	0.1082	0.9551	34	0.04	0.91	19	95.6%	0.07 [-0.45 , 0.59]
Total (95% CI)			**60**			**43**	**100.0%**	**0.07 [-0.44 , 0.58]**

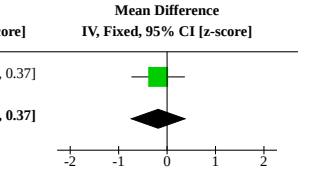
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Vitamin D (higher dose) versus vitamin D (lower dose), Outcome 7: Weight-for-length/height

Study or Subgroup	Vitamin D (higher dose) Mean [z-score]	SD [z-score]	Total	Vitamin D (lower dose) Mean [z-score]	SD [z-score]	Total	Weight	Mean Difference IV, Fixed, 95% CI [z-score]
Gallo 2013b	0.0959	0.9875	34	0.28	0.98	19	100.0%	-0.18 [-0.74 , 0.37]
Total (95% CI)			**34**			**19**	**100.0%**	**-0.18 [-0.74 , 0.37]**

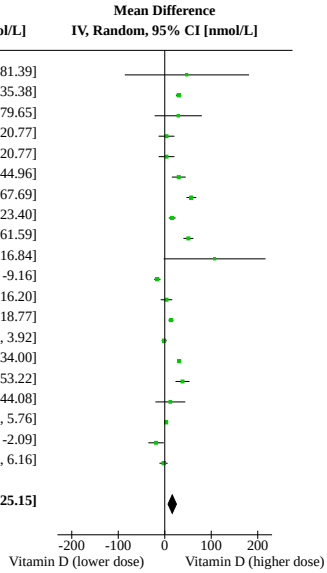
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2: Vitamin D (higher dose) versus vitamin D (lower dose), Outcome 8: Serum 25-hydroxyvitamin D

Study or Subgroup	Vitamin D (higher dose) Mean [nmol/L]	SD [nmol/L]	Total	Vitamin D (lower dose) Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Random, 95% CI [nmol/L]
Abdel-Hady 2019	184.5	92.6	2	136.8	87.6	21	0.4%	47.70 [-85.99 , 181.39]
Aglipay 2017	121.6	42.7429	349	91.9	33.4834	354	6.2%	29.70 [24.02 , 35.38]
Anderson-Berry 2017	164	73.1	16	135	73.1	16	2.1%	29.00 [-21.65 , 79.65]
Backström 1999a	90.2	26.8	16	86.4	23.9	19	5.2%	3.80 [-13.17 , 20.77]
Backström 1999b	90.2	26.8	16	86.4	23.9	19	5.2%	3.80 [-13.17 , 20.77]
Bozkurt 2017	103.5037	50.2602	81	73.4	32.4	40	5.4%	30.10 [15.25 , 44.96]
Gallo 2013a	76.8	17.4	26	19.6	20.2	24	5.9%	57.20 [46.71 , 67.69]
Gallo 2013b	87.871	23.4263	67	71.83	13.1	29	6.1%	16.04 [8.68 , 23.40]
Holmlund-Suila 2012	138.9028	38.1484	72	88	18	34	5.8%	50.90 [40.21 , 61.59]
Holst-Gemeiner 1978	259.6	172.2	11	152.3	65.4	10	0.6%	107.30 [-2.24 , 216.84]
Huynh 2017	65	14.8548	26	81	9.0217	22	6.1%	-16.00 [-22.84 , -9.16]
Mittal 2014	43.93	25.2992	28	40.19	23.6868	32	5.7%	3.74 [-8.72 , 16.20]
Natarajan 2014	72.1	12.5	40	58.7	12	40	6.2%	13.40 [8.03 , 18.77]
Robinson 1981	37.6	11	27	38.9	5.1	10	6.2%	-1.30 [-6.52 , 3.92]
Rosendahl 2018	117.71	26.11	486	86.61	19.59	489	6.3%	31.10 [28.20 , 34.00]
Shakiba 2010	116.2643	44.6013	56	78.12	21.2	19	5.4%	38.14 [23.07 , 53.22]
Siafarikas 2011	151	43.2988	14	139	43.2988	14	3.5%	12.00 [-20.08 , 44.08]
Tomimoto 2018	29	5.93	46	26	7.41	45	6.3%	3.00 [0.24 , 5.76]
Zeghoud 1994	33.5	15	15	52.2	29.2	15	5.2%	-18.70 [-35.31 , -2.09]
Ziegler 2014	85.3037	17.8192	81	87.9	24.7	38	6.0%	-2.60 [-11.36 , 6.16]
Total (95% CI)			**1475**			**1290**	**100.0%**	**16.13 [7.11 , 25.15]**

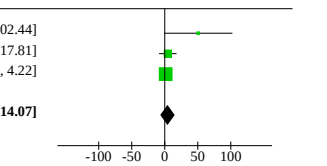
Heterogeneity: Tau² = 333.01; Chi² = 493.04, df = 19 (P < 0.00001); I² = 96%
Test for overall effect: Z = 3.50 (P = 0.0005)
Test for subgroup differences: Not applicable



Analysis 2.9. Comparison 2: Vitamin D (higher dose) versus vitamin D (lower dose), Outcome 9: Change in 25(OH)D (nmol/L)

Study or Subgroup	Vitamin D (higher dose) Mean [nmol/L]	SD [nmol/L]	Total	Vitamin D (lower dose) Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Random, 95% CI [nmol/L]
Anderson-Berry 2017	117.1	82.1	16	66.4	66.4	16	3.5%	50.70 [-1.04 , 102.44]
Gallo 2013a	22.2	20.2	26	17.6	26.7	24	31.1%	4.60 [-8.61 , 17.81]
Mittal 2014	6.69	6.112	28	5.29	4.8539	32	65.4%	1.40 [-1.42 , 4.22]
Total (95% CI)			**70**			**72**	**100.0%**	**4.12 [-5.82 , 14.07]**

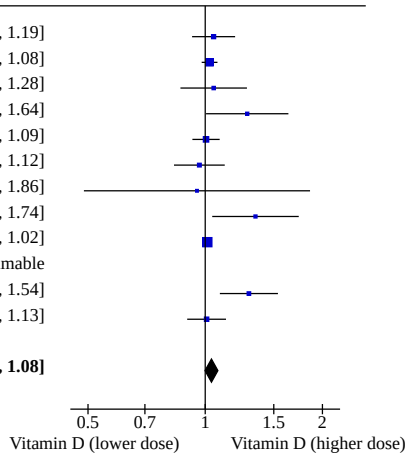
Heterogeneity: Tau² = 37.30; Chi² = 3.67, df = 2 (P = 0.16); I² = 46%
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable



Analysis 2.10. Comparison 2: Vitamin D (higher dose) versus vitamin D (lower dose), Outcome 10: Vitamin D sufficiency (≥ 50 nmol/L)

Study or Subgroup	Vitamin D (higher dose) Events	Total	Vitamin D (lower dose) Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Abdel-Hady 2019	23	23	20	21	7.0%	1.05 [0.93 , 1.19]
Atas 2013	64	64	73	75	22.0%	1.03 [0.98 , 1.08]
Bozkurt 2017	66	81	31	40	3.4%	1.05 [0.86 , 1.28]
Gallo 2013a	25	26	18	24	2.3%	1.28 [1.01 , 1.64]
Gallo 2013b	65	67	28	29	13.3%	1.00 [0.93 , 1.09]
Huynh 2017	23	25	20	21	5.4%	0.97 [0.83 , 1.12]
Mittal 2014	10	28	12	32	0.3%	0.95 [0.49 , 1.86]
Natarajan 2014	35	40	26	40	2.1%	1.35 [1.04 , 1.74]
Rosendahl 2018	410	410	399	404	31.9%	1.01 [1.00 , 1.02]
Shakiba 2010	0	19	0	56		Not estimable
Tomimoto 2018	45	46	34	45	4.3%	1.29 [1.09 , 1.54]
Ziegler 2014	35	38	74	81	8.2%	1.01 [0.90 , 1.13]
Total (95% CI)		**867**		**868**	**100.0%**	**1.04 [1.00 , 1.08]**
Total events:	801		735			

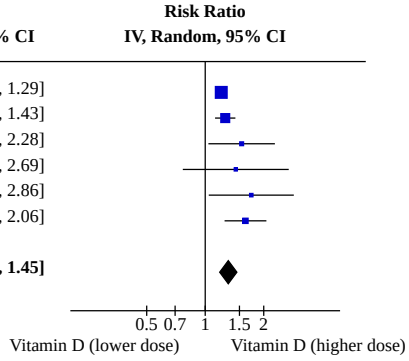
Heterogeneity: Tau² = 0.00; Chi² = 17.24, df = 10 (P = 0.07); I² = 42%
Test for overall effect: Z = 1.90 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 2.11. Comparison 2: Vitamin D (higher dose) versus vitamin D (lower dose), Outcome 11: Vitamin D sufficiency (≥ 75 nmol/L)

Study or Subgroup	Vitamin D (higher dose) Events	Total	Vitamin D (lower dose) Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Aglipay 2017	329	349	276	354	44.5%	1.21 [1.14 , 1.29]
Atas 2013	64	64	59	75	30.5%	1.27 [1.12 , 1.43]
Bozkurt 2017	53	81	17	40	5.9%	1.54 [1.04 , 2.28]
Gallo 2013a	14	26	9	24	2.5%	1.44 [0.77 , 2.69]
Gallo 2013b	36	55	11	29	3.8%	1.73 [1.04 , 2.86]
Shakiba 2010	29	30	27	45	12.8%	1.61 [1.26 , 2.06]
Total (95% CI)		**605**		**567**	**100.0%**	**1.31 [1.19 , 1.45]**
Total events:	525		399			

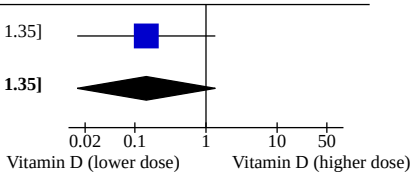
Heterogeneity: Tau² = 0.01; Chi² = 8.05, df = 5 (P = 0.15); I² = 38%
Test for overall effect: Z = 5.26 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.12. Comparison 2: Vitamin D (higher dose) versus vitamin D (lower dose), Outcome 12: Vitamin D severe deficiency (< 25 to 30 nmol/L)

Study or Subgroup	Vitamin D (higher dose) Events	Total	Vitamin D (lower dose) Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Ziegler 2014	1	99	3	43	100.0%	0.14 [0.02 , 1.35]
Total (95% CI)		**99**		**43**	**100.0%**	**0.14 [0.02 , 1.35]**
Total events:	1		3			

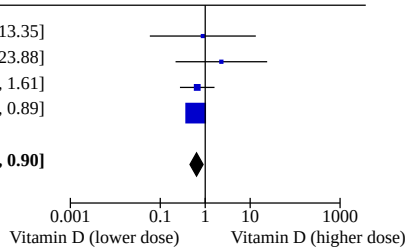
Heterogeneity: Not applicable
Test for overall effect: Z = 1.69 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 2.13. Comparison 2: Vitamin D (higher dose) versus vitamin D (lower dose), Outcome 13: Rickets (dichotomous)

Study or Subgroup	Vitamin D (higher dose) Events	Total	Vitamin D (lower dose) Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Huynh 2017	1	26	1	23	1.5%	0.88 [0.06 , 13.35]
Mittal 2014	2	28	1	32	2.0%	2.29 [0.22 , 23.88]
Morawa 1963	5	16	8	17	14.3%	0.66 [0.27 , 1.61]
Willi 1959	27	55	12	15	82.1%	0.61 [0.42 , 0.89]
Total (95% CI)		**125**		**87**	**100.0%**	**0.64 [0.46 , 0.90]**
Total events:	35		22			

Heterogeneity: Tau² = 0.00; Chi² = 1.24, df = 3 (P = 0.74); I² = 0%
Test for overall effect: Z = 2.60 (P = 0.009)
Test for subgroup differences: Not applicable



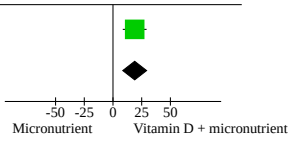
Comparison 3. Vitamin D + micronutrient(s) versus micronutrient(s) alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Serum 25-hydroxyvitamin D	1	50	Mean Difference (IV, Fixed, 95% CI)	18.90 [8.53, 29.27]
3.2 Rickets (continuous)	1	53	Mean Difference (IV, Fixed, 95% CI)	-0.94 [-2.10, 0.22]

Analysis 3.1. Comparison 3: Vitamin D + micronutrient(s) versus micronutrient(s) alone, Outcome 1: Serum 25-hydroxyvitamin D

Study or Subgroup	Vitamin D + micronutrient Mean [nmol/L]	SD [nmol/L]	Total	Micronutrient Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
Thacher 2014	56.41	18.7229	28	37.51	18.4494	22	100.0%	18.90 [8.53 , 29.27]
Total (95% CI)			**28**			**22**	**100.0%**	**18.90 [8.53 , 29.27]**

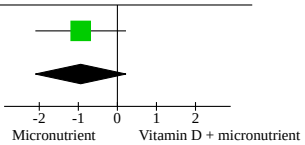
Heterogeneity: Not applicable
Test for overall effect: Z = 3.57 (P = 0.0004)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Vitamin D + micronutrient(s) versus micronutrient(s) alone, Outcome 2: Rickets (continuous)

Study or Subgroup	Vitamin D + micronutrient Mean [score]	SD [score]	Total	Micronutrient Mean [score]	SD [score]	Total	Weight	Mean Difference IV, Fixed, 95% CI [score]
Thacher 2014	1.63	2.1032	29	2.57	2.1787	24	100.0%	-0.94 [-2.10 , 0.22]
Total (95% CI)			**29**			**24**	**100.0%**	**-0.94 [-2.10 , 0.22]**

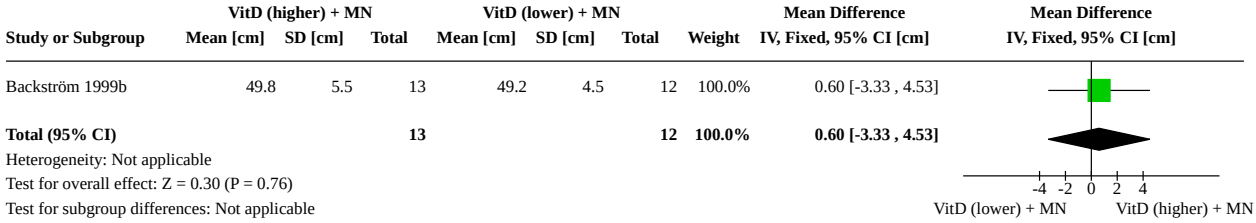
Heterogeneity: Not applicable
Test for overall effect: Z = 1.59 (P = 0.11)
Test for subgroup differences: Not applicable



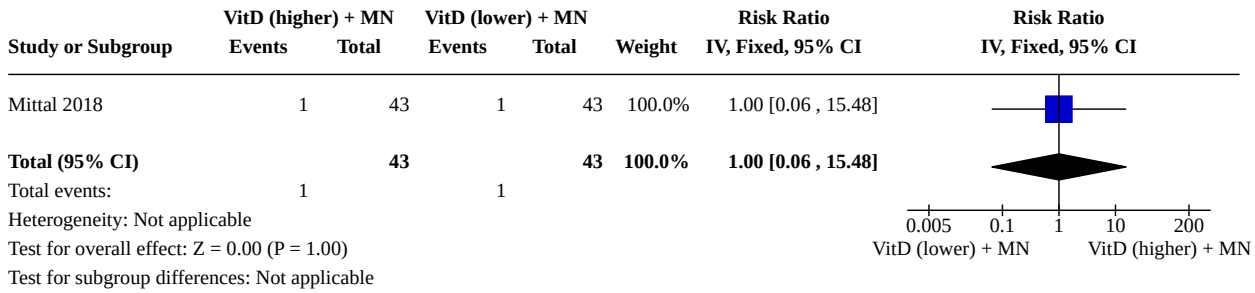
Comparison 4. Vitamin D (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Linear growth	1	25	Mean Difference (IV, Fixed, 95% CI)	0.60 [-3.33, 4.53]
4.2 Adverse effect: hypercalciuria	1	86	Risk Ratio (IV, Fixed, 95% CI)	1.00 [0.06, 15.48]
4.3 Adverse effect: hypercalcaemia	2	126	Risk Ratio (IV, Random, 95% CI)	1.00 [0.90, 1.11]
4.4 Linear growth: gain in length	1	50	Mean Difference (IV, Fixed, 95% CI)	0.73 [0.12, 1.34]
4.5 Serum 25-hydroxyvitamin D	5	325	Mean Difference (IV, Random, 95% CI)	27.94 [-2.75, 58.63]
4.6 Change in 25(OH)D (nmol/L)	1	30	Mean Difference (IV, Fixed, 95% CI)	7.19 [2.97, 11.41]
4.7 Vitamin D sufficiency (≥ 50 nmol/L)	3	225	Risk Ratio (IV, Random, 95% CI)	1.34 [0.76, 2.35]
4.8 Rickets (dichotomous)	2	153	Risk Ratio (IV, Random, 95% CI)	1.23 [0.24, 6.30]

Analysis 4.1. Comparison 4: Vitamin D (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s), Outcome 1: Linear growth



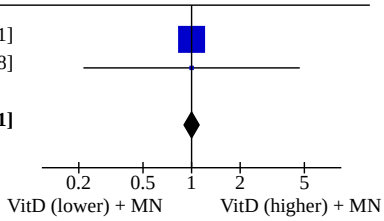
Analysis 4.2. Comparison 4: Vitamin D (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s), Outcome 2: Adverse effect: hypercalciuria



Analysis 4.3. Comparison 4: Vitamin D (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s), Outcome 3: Adverse effect: hypercalcaemia

Study or Subgroup	VitD (higher) + MN Events	Total	VitD (lower) + MN Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Gordon 2008	26	26	14	14	99.5%	1.00 [0.90 , 1.11]
Mittal 2018	3	43	3	43	0.5%	1.00 [0.21 , 4.68]
Total (95% CI)		**69**		**57**	**100.0%**	**1.00 [0.90 , 1.11]**
Total events:	29		17			

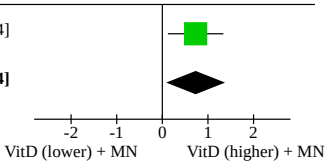
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4: Vitamin D (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s), Outcome 4: Linear growth: gain in length

Study or Subgroup	VitD (higher) + MN Mean [cm]	SD [cm]	Total	VitD (lower) + MN Mean [cm]	SD [cm]	Total	Weight	Mean Difference IV, Fixed, 95% CI [cm]
Mathur 2016	4.77	1.22	25	4.04	0.96	25	100.0%	0.73 [0.12 , 1.34]
Total (95% CI)			**25**			**25**	**100.0%**	**0.73 [0.12 , 1.34]**

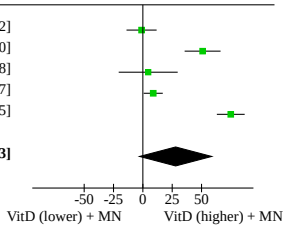
Heterogeneity: Not applicable
Test for overall effect: Z = 2.35 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 4.5. Comparison 4: Vitamin D (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s), Outcome 5: Serum 25-hydroxyvitamin D

Study or Subgroup	VitD (higher) + MN Mean [nmol/L]	SD [nmol/L]	Total	VitD (lower) + MN Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Random, 95% CI [nmol/L]
Alizadeh Taheri 2014	79.16	26.15	30	80.26	24.5	30	20.3%	-1.10 [-13.92 , 11.72]
Mathur 2016	125	27.7	25	74.1	27.5	25	20.0%	50.90 [35.60 , 66.20]
Mittal 2018	90.21	53.31	43	85.66	65	43	18.5%	4.55 [-20.58 , 29.68]
Rao 2016	127.59	4.67	15	118.76	15.39	15	20.8%	8.83 [0.69 , 16.97]
Tergestina 2016	118.5	36	51	43.6	23.1	48	20.4%	74.90 [63.05 , 86.75]
Total (95% CI)			**164**			**161**	**100.0%**	**27.94 [-2.75 , 58.63]**

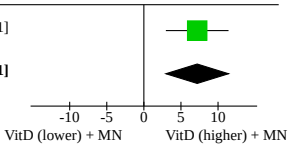
Heterogeneity: Tau² = 1163.79; Chi² = 112.69, df = 4 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.78 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 4.6. Comparison 4: Vitamin D (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s), Outcome 6: Change in 25(OH)D (nmol/L)

Study or Subgroup	VitD (higher) + MN Mean [nmol/L]	SD [nmol/L]	Total	VitD (lower) + MN Mean [nmol/L]	SD [nmol/L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [nmol/L]
Rao 2016	92	7.41	15	84.81	3.84	15	100.0%	7.19 [2.97 , 11.41]
Total (95% CI)			**15**			**15**	**100.0%**	**7.19 [2.97 , 11.41]**

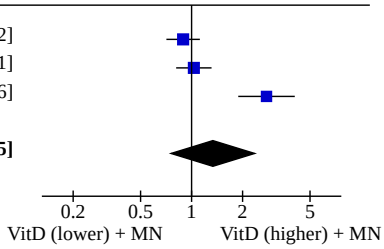
Heterogeneity: Not applicable
Test for overall effect: Z = 3.34 (P = 0.0008)
Test for subgroup differences: Not applicable



Analysis 4.7. Comparison 4: Vitamin D (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s), Outcome 7: Vitamin D sufficiency (≥ 50 nmol/L)

Study or Subgroup	VitD (higher) + MN Events	Total	VitD (lower) + MN Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Gordon 2008	12	14	25	26	34.5%	0.89 [0.71 , 1.12]
Mittal 2018	33	43	32	43	34.3%	1.03 [0.81 , 1.31]
Tergestina 2016	50	51	17	48	31.3%	2.77 [1.89 , 4.06]
Total (95% CI)		**108**		**117**	**100.0%**	**1.34 [0.76 , 2.35]**
Total events:	95		74			

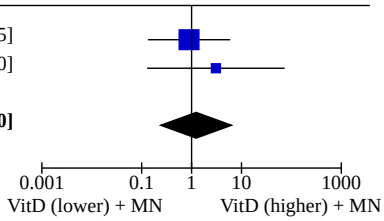
Heterogeneity: Tau² = 0.23; Chi² = 25.65, df = 2 (P < 0.00001); I² = 92%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 4.8. Comparison 4: Vitamin D (higher dose) + micronutrient(s) versus vitamin D (lower dose) + micronutrient(s), Outcome 8: Rickets (dichotomous)

Study or Subgroup	VitD (higher) + MN Events	Total	VitD (lower) + MN Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Alizadeh 2006	2	36	2	32	73.6%	0.89 [0.13 , 5.95]
Mittal 2018	1	42	0	43	26.4%	3.07 [0.13 , 73.30]
Total (95% CI)		**78**		**75**	**100.0%**	**1.23 [0.24 , 6.30]**
Total events:	3		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Intervention and comparator groups

Comparison		
Name of comparison	**Intervention group**	**Comparator group**
1. Vitamin D supplementation vs placebo or no intervention	Oral vitamin D (cholecalciferol D_3, ergocalciferol D_2, calcitriol) supplementation[a]	No intervention
		Placebo
2. Vitamin D supplementation (high dose) vs vitamin D (low dose)	Oral vitamin D (cholecalciferol D_3, ergocalciferol D_2, calcitriol) supplementation,[a] at a higher dose	Oral vitamin D (cholecalciferol D_3, ergocalciferol D_2, calcitriol) supplementation,[a] at a lower dose
3. Vitamin D supplementation + micronutrient(s) vs micronutrient(s) alone	Other micronutrient(s),[b] including oral vitamin D (cholecalciferol D_3, ergocalciferol D_2, calcitriol) supplementation[a]	Other micronutrient(s),[b] not including vitamin D
4. Vitamin D supplementation (high dose) + micronutrient(s) vs vitamin D (low dose) + micronutrient(s)	Other micronutrient(s),[b] including oral vitamin D (cholecalciferol D_3, ergocalciferol D_2, calcitriol) supplementation at a higher dose[a]	Other micronutrient(s),[b] including vitamin D at a lower dose

[a]Any formulation, including capsules, tablets, soft gels, liquids, sprays/mists, or powders.
[b]Comparisons will include intervention and comparator groups with the same combination and content of vitamin(s) and/or mineral(s) to isolate the effects of vitamin D.

Table 2. Unused methods

Data analysis	Unused method	Reason for non-use
Unit of analysis issues	**Cluster-randomised trials** Had we included cluster-randomised trials, we would have accounted for randomisation of study participant groups by conducting analyses at the cluster level. We would have calculated effect estimates (with respective standard errors (SEs)) by using the generic inverse variance method presented in Review Manager 5 (RevMan 5) (Higgins 2020b; Review Manager 2014). Depending on analyses of included studies, we would have conducted approximately correct analyses, when possible (Higgins 2020b)	No cluster-randomised trials included in review
	Cross-over trials We planned to assess data from a 2-period, 2-intervention cross-over trial by using a paired t-test to evaluate the difference between 2 measurements (subtracting the control measurement from the experimental measurement) for each study participant (Higgins 2020b). For studies with potential carry-over effects, we planned to consider only the first period of trial intervention follow-up (Higgins 2020b)	No cross-over trials included in quantitative analysis
Subgroup analysis and investigation of heterogeneity	If at least 4 studies measuring a primary outcome had reported on age at time of intervention (birth to 6 months of age vs 7 to 12 months of age, 13 to 36 months of age, 37 to 59 months of age), frequency of supplementation (daily vs intermittent vs other), serum 25(OH)D at baseline (current cutoff levels recommended by the Institute of Medicine and the Endocrine Society (Holick 2011; Institute of Medicine 2011)), geographical latitude (between Tropics of Cancer and Capricorn, compared with north of Tropic of Cancer and south of Tropic of Capricorn), season at start of study (spring, summer, fall, winter), or baseline height/length-for-age z-score, we would have performed subgroup analyses (see the protocol Yu 2017 for details). Subgroup analyses would have been undertaken in RevMan 5 (Review Manager 2014), using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020)	Not enough studies available (≤ 3)
Sensitivity analysis	If at least 10 studies measuring a primary outcome had been available to compare in terms of being published or unpublished, high risk of bias, longer intervention durations or greater sample sizes, influence of methods, and use of filters such as imputation, language of publication, source of funding, and country, we would have performed statistical tests, including Egger's test to assess asymmetry of funnel plots and as indicators of bias (Egger 1997) (see the protocol Yu 2017 for details). Sensitivity analyses would have been undertaken in RevMan 5 (Review Manager 2014), using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020)	Not enough studies available (≤ 10)
Publication bias	We searched 17 electronic databases and 2 trial registries to be as comprehensive as possible in examining all available evidence. However, we were not able to assess for publication bias using funnel plots due to lack of studies for comparison, thereby preventing us from drawing conclusions on publication bias of the included studies	Not enough studies available (≤ 10)

Table 3. Participant characteristics

Participants included	Studies included
Both infants and children	Alam 2011; Gordon 2008; Gupta 2016; Harnot 2017; Manaseki Holland 2010; Mittal 2014; Mittal 2018; Rianthavorn 2013; Sarhan 2019; Singh 2019; Thacher 2014
Children older than 1 year	Aglipay 2017; Ducharme 2019; Jensen 2016; Marchisio 2013; Principi 2013; Rao 2016; Sánchez-Armendáriz 2018; Somnath 2017; Tang 2019
Studies with extended follow-up data after no supplementation	Gallo 2013b; Greer 1981; Trilok-Kumar 2011; Ziegler 2014
Baseline health status	**Studies included**
Healthy	Aglipay 2017; Ala-Houhala 1985; Alizadeh 2006; Atas 2013; Chandy 2016; Feliciano 1994; Gallo 2013a; Gallo 2013b; Greer 1981; Greer 1989; Holmlund-Suila 2012; Holst-Gemeiner 1978; Huynh 2017; Lagomarsino 1996; Lava 2011; Manaseki-Holland 2012; Marchisio 2013; Moodley 2015; Pehlivan 2003; Ponnapakkam 2010; Rodd 2011; Rosendahl 2018; Rueter 2019; Shajari 2009; Shakiba 2010; Siafarikas 2011; Singh 2018a; Specker 1992; Stögmann 1985; Zeghoud 1994; Ziegler 2014
Vitamin D deficiency	Gordon 2008; Gupta 2016; Rao 2016; Rianthavorn 2013; Tomimoto 2018
Preterm and/or very low birth weight	Abdel-Hady 2019; Alizadeh 2006; Alizadeh Taheri 2014; Aly 2019; Anderson-Berry 2017; Backström 1999a; Backström 1999b; Bozkurt 2017; Chan 1978; Evans 1989; Fort 2016; Hanson 2011; Hibbs 2018; Kislal 2008; Mathur 2016; Morawa 1963; Natarajan 2014; Robinson 1981; Tergestina 2016; Trilok-Kumar 2011; Willi 1959
Rickets	Harnot 2017; Mittal 2014; Mittal 2018; Thacher 2014
Severe acute malnutrition	Saleem 2018
Acute or recurrent otitis media	Marchisio 2013; Principi 2013
Acute diarrhoea	Alam 2011
Bronchiolitis	Saad 2015; Sarhan 2019
Pneumonia	Choudhary 2012; Manaseki Holland 2010; Singh 2019
Upper or lower respiratory tract infection	Jensen 2016; Somnath 2017
Asthma	Ducharme 2019; Jensen 2016
Chronic kidney disease	Rianthavorn 2013
Chronic heart failure	Shedeed 2012
Juvenile idiopathic arthritis	Tang 2019
Atopic dermatitis	Sánchez-Armendáriz 2018

Table 4. Sensitivity analyses: results of analyses using fixed-effect models with ≥ 2 studies

Results of sensitivity analysis with fixed-effect model					
Comparison 1: vitamin D vs placebo or no intervention	**Number of studies**	**Mean difference (95% CI)**	**Chi²**	**P value for overall effect**	**I²(%)**
Linear growth (Analysis 1.1)	3	0.73 (0.01 to 1.45)	3.96	0.05	49
Adverse effect: hypercalciuria (Analysis 1.4)	2	2.03 (0.28 to 14.67)	0.63	0.48	0
Adverse effect: hypercalcaemia (Analysis 1.5)	2	0.79 (0.43 to 1.44)	1.93	0.44	48
Weight-for-height (z-score) (Analysis 1.8)	2	0.06 (-0.06 to 0.19)	13.61	0.33	93
Serum 25(OH)D (Analysis 1.10)	21	25.04 (23.10 to 26.98)	369.62	< 0.001	95
Change in 25(OH)D (Analysis 1.11)	3	34.09 (28.90 to 39.28)	17.35	< 0.001	88
Vitamin D sufficiency (≥ 50 nmol/L) (Analysis 1.12)	6	1.88 (1.66 to 2.14)	6.25	< 0.001	20
Vitamin D sufficiency (≥ 75 nmol/L) (Analysis 1.13)	2	2.47 (1.50 to 4.06)	11.30	0.0004	91
Vitamin D severe deficiency (Analysis 1.14)	3	0.26 (0.19 to 0.36)	1.68	< 0.001	0
Comparison 2: vitamin D (higher dose) vs vitamin D (lower dose)	**Number of studies**	**Mean difference (95% CI)**	**Chi²**	**P value for overall effect**	**I²(%)**
Linear growth (Analysis 2.1)	5	-0.75 (-1.33 to -0.17)	13.64	0.01	71
Length/height-for-age (z-score) (Analysis 2.2)	2	0.40 (-0.06 to 0.86)	0.04	0.09	0
Adverse effect: hypercalciuria (Analysis 2.3)	6	1.16 (1.00 to 1.35)	1.88	0.06	0
Adverse effect: hypercalcaemia (Analysis 2.4)	5	1.39 (0.89 to 2.18)	2.16	0.15	0
Linear growth: gain in length (Analysis 2.5)	3	-0.01 (-0.02 to 0.00)	0.68	0.06	0
Weight-for-age (z-score) (Analysis 2.6)	2	0.07 (-0.44 to 0.58)	0.01	0.78	0
Serum 25(OH)D (Analysis 2.8)	20	14.73 (13.24 to 16.22)	493.04	< 0.001	96
Change in 25(OH)D (Analysis 2.9)	3	1.68 (-1.08 to 4.43)	3.67	0.23	46
Vitamin D sufficiency (≥ 50 nmol/L) (Analysis 2.10)	12	1.02 (1.00 to 1.03)	17.24	0.008	42
Vitamin D sufficiency (≥ 75 nmol/L) (Analysis 2.11)	6	1.25 (1.18 to 1.31)	8.05	< 0.001	38

Table 4. Sensitivity analyses: results of analyses using fixed-effect models with ≥ 2 studies *(Continued)*

Rickets (Analysis 2.13)	4	0.64 (0.46 to 0.90)	1.24	0.009	0
Comparison 4: vitamin D (higher dose) + micronutrient(s) vs vitamin D (lower dose) + micronutrient(s)	**Number of studies**	**Mean difference (95% CI)**	**Chi²**	**P value for overall effect**	**I²(%)**
Adverse effect: hypercalcaemia (Analysis 4.3)	2	1.00 (0.90 to 1.11)	0	1.00	0
Serum 25(OH)D (Analysis 4.5)	5	25.91 (20.50 to 31.32)	112.69	< 0.001	96
Vitamin D sufficiency (≥ 75 nmol/L) (Analysis 4.7)	3	1.13 (0.97 to 1.31)	25.65	0.12	92
Rickets (Analysis 4.8)	2	1.23 (0.24 to 6.30)	0.43	0.80	0

CI: confidence interval.
Serum 25(OH)D: serum 25-hydroxyvitamin D.

Table 5. Sensitivity analysis: outcome 1.10

Serum 25(OH)D (nmol/L) (Analysis 1.10)						
Category	**Number of studies**	**Mean difference (95% CI)**	**Tau²**	**Chi²**	**P value**	**I²(%)**
All studies	20	30.91 (21.82 to 40.00)	385.01	369.62	< 0.001	95
Physiological doses only	15	31.00 (20.31 to 41.68)	388.92	306.64	< 0.001	95
Infants only	14	27.95 (17.36 to 38.54)	357.03	240.76	< 0.001	95
Children only (> 1 year)	5	42.50 (20.85 to 64.15)	460.98	31.74	< 0.001	87

CI: confidence interval.

Table 6. Sensitivity analysis: outcome 2.8

Serum 25(OH)D (nmol/L) (Analysis 2.8)						
Category	**Number of studies**	**Mean difference (95% CI)**	**Tau²**	**Chi²**	**P value**	**I²(%)**
All studies	20	16.13 (7.11 to 25.15)	333.01	493.04	< 0.001	96
Physiological doses only	14	18.62 (8.86 to 28.39)	268.61	243.46	< 0.001	95
Infants only	18	16.02 (6.16 to 25.87)	352.80	461.94	< 0.001	96
Preterm only	9	12.96 (2.23 to 23.68)	183.61	72.17	< 0.001	89

CI: confidence interval.

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library

Searched 14 March 2018 (2169 records)
Searched 11 December 2019 (8 records)

IDSearch
#1(("Vitamin D" OR "Vitamin D deficiency" OR "Vitamin D*" OR ergocalciferol* OR cholecalciferol* OR calcifediol* OR calcitriol* OR dihydrotachysterol* OR "hydroxyvitamin D*" OR alfacalcidol* OR "alpha- calcidol*" OR colecalciferol*)):ti,ab,kw (Word variations have been searched)
#2("Dietary supplements" OR supplement* OR capsul* OR gel OR liquid OR powder* OR tablet* OR syrup OR drop* OR spray* OR mist* OR pill*)
#3#1 AND #2
#4(infant OR child)
#5(Infant* OR baby OR babies OR newborn* OR neonat* OR toddler* OR child* OR preschool* OR schoolchild* OR boy* OR girl* OR pre-school*)
#6#4 OR #5
#7#3 AND #6

PubMed (MEDLINE)

Searched 14 March 2018 (1564 records)
Searched 11 December 2019 (146 records)

SearchAdd to builderQueryItems
#10AddSearch (#8 NOT #9)
#9AddSearch (Animals [mh] NOT humans [mh])
#8AddSearch (#3 AND #6 AND #7)
#7AddSearch (Randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR randomised [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab])
#6AddSearch (#4 OR #5)
#5AddSearch (Infant*[tiab] OR baby[tiab] OR babies[tiab] OR newborn*[tiab] OR neonat*[tiab] OR toddler*[tiab] OR child*[tiab] OR preschool*[tiab] OR schoolchild*[tiab] OR boy*[tiab] OR girl*[tiab] OR pre-school*[tiab])
#4AddSearch (Infant[mh] OR child[mh])
#3AddSearch (#1 AND #2)
#2AddSearch (Dietary supplements[mh] OR supplement*[tiab] OR capsul*[tiab] OR gel[tiab] OR liquid[tiab] OR powder* [tiab] OR tablet*[tiab] OR syrup[tiab] OR drop*[tiab] OR spray*[tiab] OR mist*[tiab] OR pill*[tiab])
#1AddSearch (Vitamin D[mh] OR Vitamin D deficiency [mh] OR Vitamin D*[tiab] OR ergocalciferol*[tiab] OR cholecalciferol*[tiab] OR calcifediol*[tiab] OR calcitriol*[tiab] OR dihydrotachysterol*[tiab] OR hydroxyvitamin D*[tiab] OR alfacalcidol*[tiab] OR alpha-calcidol*[tiab] OR colecalciferol*[tiab])

Embase (OVID)

Searched 14 March 2018 (1632 records)
Searched 11 December 2019 (102 records)

1 Vitamin D/ or Vitamin D deficiency/ or Vitamin D*.mp. or ergocalciferol*.mp. or cholecalciferol*.mp. or calcifediol*.mp. or calcitriol*.mp. or dihydrotachysterol*.mp. or hydroxyvitamin D*.mp. or alfacalcidol*.mp. or alpha- calcidol*.mp. or colecalciferol*.mp.
2 Dietary supplements/ or supplement*.mp. or capsul*.mp. or gel.mp. or liquid.mp. or powder*.mp. or tablet*.mp. or syrup.mp. or drop*.mp. or spray*.mp. or mist*.mp. or pill*.mp.
3 1 and 2
4 infant/ or child/
5 (Infant* or baby or babies or newborn* or neonat* or toddler* or child* or preschool* or schoolchild* or boy* or girl* or pre-school*).mp.
6 4 or 5
7 crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ or (random* or factorial* or crossover* or cross over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).mp.
8 3 and 6 and 7
9 animals/ not humans/

10 8 not 9

Notes: Line 7 contains the search terms suggested in Lefebvre 2020 for the identification of RCTs in Embase.

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO)

Searched 14 March 2018 (146 records)
Searched 11 December 2019 (509 records)

S11(MH "animals") NOT (MH "humans")
S10S3 AND S6 AND S9
S9S7 OR S8
S8"Infant*" OR "baby" OR "babies" OR "newborn*" OR "neonat*" OR "toddler*" OR "child*" OR "preschool*" OR "schoolchild*" OR "boy*" OR "girl*" OR "pre-school*"
S7(MH "infant") OR (MH "child")Limiters - Published Date: -20191231
S6S4 OR S5Limiters - Published Date: -20191231
S5"supplement*" OR "capsul*" OR "gel" OR "liquid" OR "powder*" OR "tablet*" OR "syrup" OR "drop*" OR "spray*" OR "mist*" OR "pill*"Limiters - Published Date: -20191231
S4MH "Dietary supplements"Limiters - Published Date: -20191231
S3S1 OR S2Limiters - Published Date: -20191231
S2"Vitamin D*" OR "ergocalciferol*" OR "cholecalciferol*" OR "calcifediol*" OR "calcitriol*" OR "dihydrotachysterol*" OR "hydroxyvitamin D*" OR "alfacalcidol*" OR "alpha- calcidol*" OR "colecalciferol*"Limiters - Published Date: -20191231
S1(MH "Vitamin D") OR (MH "Vitamin D deficiency")

Centre for Agriculture and Biosciences (CAB) Abstracts & Web of Science Core Collection databases

Web of Science CAB Abstracts

Searched 14 March 2018 (1371 records)
Searched 11 December 2019 (229 records)

# 10#8 NOT #9
Indexes=CAB Abstracts
# 9TS=(animals NOT humans)
Indexes=CAB Abstracts
# 8#3 AND #6 AND #7
Indexes=CAB Abstracts
# 7TS=("randomised controlled trial" OR "controlled clinical trial" OR randomized OR randomised OR placebo OR "drug therapy" OR randomly OR trial OR groups)
Indexes=CAB Abstracts
# 6#4 OR #5
Indexes=CAB Abstracts
# 5TS=(Infant* OR baby OR babies OR newborn* OR neonat* OR toddler* OR child* OR preschool* OR schoolchild* OR boy* OR girl* OR pre-school*)
Indexes=CAB Abstracts
# 4TS=(infant OR child)
Indexes=CAB Abstracts
# #1 AND #2
Indexes=CAB Abstracts
# 2TS=("Dietary supplements" OR supplement* OR capsul* OR gel OR liquid OR powder* OR tablet* OR syrup OR drop* OR spray* OR mist* OR pill*)
Indexes=CAB Abstracts
# 1TS=("Vitamin D" OR "Vitamin D deficiency" OR "Vitamin D*" OR ergocalciferol* OR cholecalciferol* OR calcifediol* OR calcitriol* OR dihydrotachysterol* OR "hydroxyvitamin D*" OR alfacalcidol* OR alpha- calcidol* OR colecalciferol*)
Indexes=CAB Abstracts

Web of Science Core Collection

Searched 14 March 2018 (1850 records)
Searched 11 December 2019 (512 records)

# 10#8 NOT #9
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED
# 9TS=(animals NOT humans)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED

# 8#7 AND #6 AND #3
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED
# 7TS=("randomised controlled trial" OR "controlled clinical trial" OR randomized OR randomised OR placebo OR "drug therapy" OR randomly OR trial OR groups)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED
# 6#5 OR #4
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED
# 5TS=(Infant* OR baby OR babies OR newborn* OR neonat* OR toddler* OR child* OR preschool* OR schoolchild* OR boy* OR girl* OR pre-school*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED
# 4TS=(infant OR child)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED
# 3#2 AND #1
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED
# 2TS=("Dietary supplements" OR supplement* OR capsul* OR gel OR liquid OR powder* OR tablet* OR syrup OR drop* OR spray* OR mist* OR pill*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED
# 1TS=("Vitamin D" OR "Vitamin D deficiency" OR "Vitamin D*" OR ergocalciferol* OR cholecalciferol* OR calcifediol* OR calcitriol* OR dihydrotachysterol* OR "hydroxyvitamin D*" OR alfacalcidol* OR alpha- calcidol* OR colecalciferol*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED

Notes: Web of Science Core Collection includes: Science Citation Index Expanded (SCI-EXPANDED, 1900-11 December 2019), Social Sciences Citation Index (SSCI, 1900-11 December 2019), Arts & Humanities Citation Index (A&HCI, 1975-11 December 2019), Conference Proceedings Citation Index- Science (CPCI-S, 1990-11 December 2019), Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH, 1990-11 December 2019), Book Citation Index-Science (BKCI-S, 2005-11 December 2019), Book Citation Index-Social Sciences & Humanities (BKCI-SSH, 2005-11 December 2019), Emerging Sources Citation Index (ESCI, 2015-11 December 2019), Current Chemical Reactions (CCR-Expanded, 1985-11 December 2019), Index Chemicus (IC, 1993-11 December 2019).

Cochrane Database of Systematic Reviews (CDSR), in the Cochrane Library

Searched 14 March 2018 (2169 records)
Searched 11 December 2019 (8 records)

IDSearch
#1(("Vitamin D" OR "Vitamin D deficiency" OR "Vitamin D*" OR ergocalciferol* OR cholecalciferol* OR calcifediol* OR calcitriol* OR dihydrotachysterol* OR "hydroxyvitamin D*" OR alfacalcidol* OR "alpha- calcidol*" OR colecalciferol*)):ti,ab,kw (Word variations have been searched) with Cochrane Library publication date to Dec
#2("Dietary supplements" OR supplement* OR capsul* OR gel OR liquid OR powder* OR tablet* OR syrup OR drop* OR spray* OR mist* OR pill*) with Cochrane Library publication date to Dec 2019 (Word variations have been searched)
#3#1 AND #2 with Cochrane Library publication date to Dec 2019 (Word variations have been searched)
#4(infant OR child) with Cochrane Library publication date to Jan 2019 (Word variations have been searched)
#5(Infant* OR baby OR babies OR newborn* OR neonat* OR toddler* OR child* OR preschool* OR schoolchild* OR boy* OR girl* OR pre-school*) with Cochrane Library publication date to Dec 2019 (Word variations have been searched)
#6#4 OR #5 with Cochrane Library publication date to Dec 2019 (Word variations have been searched)
#7#3 AND #6 with Cochrane Library publication date to Dec 2019 (Word variations have been searched)
#8(animals NOT humans) with Cochrane Library publication date to Dec 2019 (Word variations have been searched)
#9#7 NOT #8 with Cochrane Library publication date to Dec 2019 (Word variations have been searched)

Database of Abstracts of Reviews of Effects (DARE) (www.crd.york.ac.uk/CRDWeb)

Searched 14 March 2018 (7 records)

#11 5 AND 8 AND 10
#10 8 NOT 9
#9 (Animals) NOT (humans)
#8 6 OR 7
#7 (Infant* OR baby OR babies OR newborn* OR neonat* OR toddler* OR child* OR preschool* OR schoolchild* OR boy* OR girl* OR (pre-school*)):TI
#6 (MeSH DESCRIPTOR Infant) OR (MeSH DESCRIPTOR Child)
#5 4 AND 3
#4 ((Dietary supplements) OR supplement* OR capsul* OR gel OR liquid OR powder* OR tablet* OR syrup OR drop* OR spray* OR mist* OR pill*):TI
#3 1 OR 2
#2 (MeSH DESCRIPTOR Vitamin D) OR (MeSH DESCRIPTOR Vitamin D deficiency)

#1 ((Vitamin D*) OR ergocalciferol* OR cholecalciferol* OR calcifediol* OR calcitriol* OR dihydrotachysterol* OR (hydroxyvitamin D) OR alfacalcidol* OR alphacalcidol* OR colecalciferol*):TI

Notes: The DARE database was not updated after 14 March 2018 and therefore omitted from the 11 December 2019 search.

Spanish Bibliographic Index of the Health Sciences (IBECS)/Latin American & Caribbean Health Sciences Literature (LILACS)/Pan American Health Organization (PAHO)/WHO Library Database (WHOLIS)

Searched 11 December 2019 (all years; 547 records total)

Search strategy was identical for these 4 databases:

Search on :((Vitamin D$) OR (Vitamin D deficiency) OR ergocalciferol$ OR cholecalciferol$ OR calcifediol$ OR calcitriol$ OR dihydrotachysterol$ OR (hydroxyvitamin D) OR alfacalcidol$ OR alphacalcidol$ OR colecalciferol$) [Words] and ((Dietary supplements) OR supplement$ OR capsul$ OR gel OR liquid OR powder$ OR tablet$ OR syrup OR drop$ OR spray$ OR mist$ OR pill$) [Words] and (Infant$ OR child OR baby OR babies OR newborn$ OR neonat$ OR toddler$ OR child$ OR preschool$ OR schoolchild$ OR boy$ OR girl$ OR (pre-school$)) [Words]

Database: PAHO
References found:16

Database: LILACS
References found:366

Database: WHOLIS
References found:22

Database: IBECS
References found:143

SciELO (Scientific Electronic Library Online)

Searched 14 March 2018 (231 records)
Searched 11 December 2019 (4 records)

#4Expression: (#1 AND #2 AND #3)
Filters:4Add item to search field Edit search expression Remove from list
#3Expression: (ti: (Infant* OR baby OR babies OR newborn* OR neonat* OR toddler* OR child* OR preschool* OR schoolchild* OR boy* OR girl* OR (pre-school*))) OR (ab: (Infant* OR baby OR babies OR newborn* OR neonat* OR toddler* OR child* OR preschool* OR schoolchild* OR boy* OR girl* OR (pre-school*)))
Filters:302Add item to search field Edit search expression Remove from list
#2Expression: (ti: ((Dietary supplements) OR supplement* OR capsul* OR gel OR liquid OR powder* OR tablet* OR syrup OR drop* OR spray* OR mist* OR pill*)) OR (ab:((Dietary supplements) OR supplement* OR capsul* OR gel OR liquid OR powder* OR tablet* OR syrup OR drop* OR spray* OR mist* OR pill*))
Filters:43.982Add item to search field Edit search expression Remove from list
#1Expression: (ti: ((Vitamin D*) OR (Vitamin D Deficiency) OR ergocalciferol* OR cholecalciferol* OR calcifediol* OR calcitriol* OR dihydrotachysterol* OR (hydroxyvitamin D) OR alfacalcidol* OR alphacalcidol* OR colecalciferol*)) OR (ab: ((Vitamin D*) OR (Vitamin D Deficiency) OR ergocalciferol* OR cholecalciferol* OR calcifediol* OR calcitriol* OR dihydrotachysterol* OR (hydroxyvitamin D) OR alfacalcidol* OR alphacalcidol* OR colecalciferol*))

Western Pacific Region Index Medicus (WPRIM)

Searched 14 March 2018 (1731 records)
Searched 11 December 2019 (25 records)

#1. Search All:Vitamin D OR All:Vitamin D Deficiency OR All:ergocalciferol OR All:cholecalciferol OR All:calcifediol OR All:calcitriol OR All:dihydrotachysterol OR All:hydroxyvitamin D OR All:alfacalcidol or All:alphacalcidol

IndMED (Indian Medical Journals)

Searched 14 March 2018 (360 records)

#4 1 OR 2 AND 3
#3 Infant OR baby OR babies OR newborn OR neonatal OR toddler OR child OR preschool OR schoolchild OR boy OR girl OR pre-school
#2 Supplement OR capsule OR gel OR liquid OR powder OR tablet OR syrup OR drop OR spray OR mist OR pill
#1 Vitamin D OR Vitamin D deficiency OR ergocalciferol OR cholecalciferol OR calcifediol OR calcitriol OR dihydrotachysterol OR hydroxyvitamin D OR alfacalcidol OR alphacalcidol OR colecalciferol

Note: Database was no longer available at time of 11 December 2019 search

WHO International Clinical Trials Registry Platform (ICTRP)

Searched 14 March 2018 (91 records)

Intervention AND Condition

Condition: Vitamin D OR Vitamin D deficiency OR Vitamin D* OR ergocalciferol* OR cholecalciferol* OR calcifediol* OR calcitriol* OR dihydrotachysterol* OR hydroxyvitamin D OR alfacalcidol* OR alphacalcidol* OR colecalciferol*

Intervention: Dietary supplements OR supplement* OR capsul* OR gel OR liquid OR powder* OR tablet* OR syrup OR drop* OR spray* OR mist* OR pill*

Notes: Selected "search for clinical trials in children" and "recruitment status ALL." ICTRP records are now added to CENTRAL, so a separate search of the WHO website was not performed

Epistemonikos

Searched 14 March 2018 (92 records)
Searched 11 December 2019 (61 records)

Full query:(title:((title:(Animals NOT humans) OR abstract:(Animals NOT humans))) OR abstract:((title:(Animals NOT humans) OR abstract:(Animals NOT humans))))
1)(title:((title:(Animals NOT humans) OR abstract:(Animals NOT humans))) OR abstract:((title:(Animals NOT humans) OR abstract:(Animals NOT humans))))

Scopus

Searched 14 March 2018 (4891 records)
Searched 11 December 2019 (226 records)

5
((TITLE-ABS-KEY ("Vitamin D*" OR ergocalciferol* OR cholecalciferol* OR calcifediol* OR calcitriol* OR dihydrotachysterol* OR "hydroxyvitamin D" OR alfacalcidol* OR alphacalcidol* OR colecalciferol*)) AND (TITLE-ABS-KEY ("Dietary supplements" OR supplement*or AND capsul* OR gel OR liquid OR powder* OR tablet* OR syrup OR drop* OR spray* OR mist* OR pill*))) AND ((infant OR child) OR (TITLE-ABS-KEY (infant* OR baby OR babies OR newborn* OR neonat* OR toddler* OR child* OR preschool* OR schoolchild* OR boy* OR girl* OR "pre-school*"))) AND (((INDEXTERMS ("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials" OR "random allocation" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "multicenter study" OR "double blind procedure" OR "single blind procedure" OR "crossover procedure" OR "clinical trial" OR "controlled study" OR "randomization" OR "placebo")) OR (TITLE-ABS-KEY (("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials as Topic" OR "random allocation" OR "randomly allocated" OR "allocated randomly" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "cross-over trial" OR "single blind" OR "double blind" OR "factorial design" OR "factorial trial"))) OR (TITLE-ABS (clinical AND trial* OR trial* OR rct* OR random* OR blind*))) AND NOT (KEY (animals AND NOT humans)))

4
((INDEXTERMS ("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials" OR "random allocation" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "multicenter study" OR "double blind procedure" OR "single blind procedure" OR "crossover procedure" OR "clinical trial" OR "controlled study" OR "randomization" OR "placebo")) OR (TITLE-ABS-KEY (("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials as Topic" OR "random allocation" OR "randomly allocated" OR "allocated randomly" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "cross-over trial" OR "single blind" OR "double blind" OR "factorial design" OR "factorial trial"))) OR (TITLE-ABS (clinical AND trial* OR trial* OR rct* OR random* OR blind*))) AND NOT (KEY (animals AND NOT humans))

3
KEY (animals AND NOT humans)

2
(INDEXTERMS ("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials" OR "random allocation" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "multicenter study" OR "double blind procedure" OR "single blind procedure" OR "crossover procedure" OR "clinical trial" OR "controlled study" OR "randomization" OR "placebo")) OR (TITLE-ABS-KEY (("clinical trials" OR "clinical

trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials as Topic" OR "random allocation" OR "randomly allocated" OR "allocated randomly" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "cross-over trial" OR "single blind" OR "double blind" OR "factorial design" OR "factorial trial"))) OR (TITLE-ABS (clinical AND trial* OR trial* OR rct* OR random* OR blind*))

1
(infant OR child) OR (TITLE-ABS-KEY (infant* OR baby OR babies OR newborn* OR neonat* OR toddler* OR child* OR preschool* OR schoolchild* OR boy* OR girl* OR "pre-school*")) AND (EXCLUDE (PUBYEAR, 2020))

European Union Clinical Trials Register (EUCTR)

Searched 11 December 2019 (6 records; all years)

((Vitamin D OR Vitamin D deficiency OR Vitamin D OR ergocalciferol OR cholecalciferol OR calcifediol OR calcitriol OR dihydrotachysterol OR hydroxyvitamin D OR alfacalcidol OR alpha-calcidol OR colecalciferol) AND (Dietary supplements OR supplement OR capsule OR capsules OR gel OR liquid OR powder OR tablet OR tablets OR syrup OR drop OR drops OR spray OR mist OR pill OR pills)) AND ((Infant OR child) OR (Infant OR baby OR babies OR newborn OR newborns OR neonate OR neonates OR toddler OR toddlers OR child OR children OR preschool OR schoolchild OR schoolchildren OR boy OR girl OR pre-school)) NOT (Animals NOT humans)

Appendix 2. Criteria for assessing risk of bias

Sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence. We assessed the method as follows.

1. Low risk of bias: any truly random process (e.g. random number table, computer random number generator, stratified or block randomisation, low-tech methods (coin toss, shuffling cards or envelopes, throwing dice, drawing lots)).
2. High risk of bias: any non-random process (e.g. sequence based on date of birth, week of month, even or odd days, case record number, date of presentation, alternate allocation, non-random or choice of clinician or participant, based on test results or availability).
3. Unclear risk of bias: insufficient information to facilitate a judgement of low or high risk of bias; or study authors state that they randomly allocated participants but do not describe how they generated the randomisation sequence.

Allocation concealment (checking for possible selection bias)

For each included study, we described the method used to conceal the allocation sequence (when applicable) and assessed whether the intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We assessed the method as follows.

1. Low risk of bias: concealed allocation using, for example, central allocation done by a third party or by use of consecutively numbered, sealed, opaque envelopes or drug containers (or equivalent).
2. High risk of bias: allocation based on, for example, open random allocation, unsealed or non-opaque envelopes; or if the random sequence is known to staff in advance; or if sequence generation was considered at high risk of bias.
3. Unclear risk of bias: insufficient information (no description of how interventions were indistinguishable) to facilitate a judgement of low or high risk of bias.

Blinding of participants and personnel (checking for possible performance bias)

For each included study, we described the methods used to blind performance. We described the methods used, if any, for blinding study participants and personnel from knowledge of the allocated intervention during the study.

1. Low risk of bias: both participants and personnel are blinded and the outcome is unlikely to have been influenced; or no blinding or incomplete blinding but outcome is unlikely to have been influenced.
2. High risk of bias: no, incomplete, or broken blinding and outcome is likely to be have been influenced.
3. Unclear risk of bias: insufficient information (blinding of participants or personnel, or both, is not described) to facilitate a judgement of low or high risk of bias.

Blinding of outcome assessors (checking for possible detection bias)

For each included study, we described methods used to blind outcome assessors. We described the methods used, if any, for blinding outcome assessors from knowledge of the allocated intervention during the study.

1. Low risk of bias: blinded and unlikely that blinding was broken; or not blinded but measurement is unlikely to have been influenced.
2. High risk of bias: no, incomplete, or broken blinding and outcome is likely to have been influenced.
3. Unclear risk of bias: insufficient information (blinding of outcome assessors is not described) to facilitate a judgement of low or high risk of bias.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

For each included study, we described completeness of data, including attrition and exclusions from analysis, and noted if attrition levels were higher for one prespecified outcome or group of outcomes. We also noted whether missing data were imbalanced across groups, reasons for attrition or exclusions when reported, or whether data were imputed (and, if so, the methods used). We assessed the methods as follows.

1. Low risk of bias: all randomised participants completed follow-up or there were no missing data; reasons for missing data were not related to the outcome (e.g. moving away); missing data were balanced across groups and reasons were similar; the proportion of missing data was small; intention-to-treat analysis, including all participants randomised, was conducted.
2. High risk of bias: reasons for loss to follow-up (LTFU) not described or reasons for LTFU related to the outcome (e.g. recovered, adverse effects, refusal, withdrawal) and imbalanced across groups in numbers; missing data were imputed or a complete case analysis was done (omitting the missing data); no attempts were made to check if excluded participants were different than those included; intention-to-treat or per-protocol analysis was performed when non-compliers were excluded from the analysis.
3. Unclear risk of bias: insufficient information to facilitate a judgement of low or high risk of bias.

Selective reporting bias

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as follows.

1. Low risk of bias: available protocol's prespecified outcomes of interest are reported in the study in a prespecified way (this includes a published study protocol or a ClinicalTrials.gov ID that was registered before enrolment began).
2. High risk of bias: outcomes are not reported as prespecified or expected such as due to missing data, adding participants or groups, looking at subsets, or unexpected measurements or methods.
3. Unclear risk of bias: insufficient information (study protocol does not exist to compare prespecified outcomes to reported outcomes; there is no trial registration code or prepublished protocol referenced) to facilitate a judgement of low or high risk of bias.

Other sources of bias

For each included study, we described any important concerns that we had about other possible sources of bias (particularly reporting of a calculated sample size target and whether or not this target was met at randomisation and for analysis) and assessed them as follows.

1. Low risk of bias: sample size calculation reported and met at randomisation and at analysis.
2. High risk of bias: sample size calculation not reported; sample size calculation reported but number randomised or in the final analysis does not meet the sample size (so study is underpowered to analyse outcome).
3. Unclear risk of bias: insufficient information to facilitate a judgement of low or high risk of bias.

WHAT'S NEW

Date	Event	Description
18 March 2021	Amended	The GRADE judgement for the outcome Adverse events: Hypercalciuria in the comparison vitamin D versus placebo or no treatment has been ammended from high to moderate.

HISTORY

Protocol first published: Issue 11, 2017
Review first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

Samantha Huey (SLH) and Nina Archarya (NA) drafted the review. Elaine Yu (EAY) wrote an earlier draft of this review. SLH, NA, EAY, Ashley Silver (AS), and Risha Sheni (RS) performed search strategy translation and screened records. SLH, NA, and AS extracted data and assessed 'Risk of bias' in included studies. SLH and NA performed the GRADE assessment. Juan Pablo Peña-Rosas (JPP) and Saurabh Mehta (SM) revised and critically reviewed the protocol and the review, and arbitrated disagreements.

SM is the guarantor for the review.

DECLARATIONS OF INTEREST

Samantha L Huey: none known.

Nina Acharya: none known.

Ashley Silver: none known.

Risha Sheni: none known.

Elaine Yu: none known.

Juan Pablo Peña-Rosas: the WHO receives partial financial support from the Bill & Melinda Gates Foundation to support commissioning of systematic reviews of interventions for health throughout the life course. Donors do not fund specific guidelines and do not participate in any decision related to the guideline development process, including the composition of policy questions, membership of the guideline groups, the conduct and interpretation of systematic reviews, or the formulation of recommendations.

Disclaimer: Juan Peña-Rosas is a full-time staff member at the World Health Organization. The review authors alone are responsible for the views expressed in this publication, which do not necessarily represent the official position, decisions, policy, or views of the WHO.

Saurabh Mehta (SM) is an unpaid board member with an equity stake/stocks/stock options in a diagnostic start-up company, VitaScan, which is focused on developing assays for low-cost and point-of-care measurement of certain nutrients from a drop of blood, using results from his research as a faculty member at Cornell University. SM is also the principal investigator on competitive research grants from HarvestPlus/International Food Policy Research Institute to conduct efficacy trials for crops biofortified with iron, zinc, and vitamin A among children in India, for which the outcomes include child growth and nutritional status. SM was paid a consulting fee as external reviewer for the nutrition programme at New York Academy of Sciences and was paid travel and accommodation expenses by Foundation Merieux for a conference presentation on precision nutrition and gut microbiome. SM received partial financial support for this work from the WHO.

SOURCES OF SUPPORT

Internal sources

- Division of Nutritional Sciences, Cornell University, USA

  SM is faculty, and SH and EY are doctoral candidates of the Division of Nutritional Sciences at Cornell University.
- Department of Nutrition and Food Safety, World Health Organization (WHO), Switzerland

  JPP is a full-time member of staff of the Department of Nutrition and Food Safety at the WHO.

External sources

- Bill & Melinda Gates Foundation, USA

  WHO gratefully acknowledges financial support from the Bill & Melinda Gates Foundation. Donors do not fund specific guidelines and do not participate in any decision related to the guideline development process including the composition of policy questions, membership of the guideline groups, the conduct and interpretation of systematic reviews, or the formulation of recommendations.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Title. We changed the title to "Oral vitamin D supplementation on linear growth and other health outcomes among children under five years of age" to focus our review on our primary and secondary outcomes related to linear growth, including adverse effects and rickets. We made this decision after reviewing the literature and noting that many of the trials investigating non-communicable diseases, including atopy, allergy, metabolic disease, and bone health outcomes, had already been included in previous Cochrane Reviews.
2. Authorship. We added three new authors - NA, AS, and RA - for their substantial contributions to the review.
3. Description of the condition and Why it is important to do this review. We revised these sections to reflect updated estimates and statistics published since 2017.
4. Objectives. We edited our objectives to be in line with changes to the title and scope of the review (see #1 above).
5. Types of interventions. We had planned to conduct two comparisons: (1) vitamin D versus placebo or no intervention; and (2) vitamin D+micronutrient(s) versus micronutrient(s) alone. After conducting the search, we found that many studies compared higher-dose vitamin D to lower-dose vitamin D (across both arms, with or without micronutrient(s)). Upon discussion amongst all review authors, we chose to include such studies as a third and fourth comparison for the review, to more deeply describe, and to gain further clarity over, the literature base in this research area (Table 1).

6. Types of outcome measures.
   a. We added 'gain in linear growth' as a relevant secondary outcome, as two studies included from our search results included this outcome.
   b. We added 'change in vitamin D concentration' as a relevant secondary outcome, as several studies included from our search results included this outcome.
   c. We added 'underweight' and 'wasting' as relevant secondary outcomes to include these dichotomised outcomes in parallel with including 'stunting' as a primary outcome.
   d. We removed secondary outcomes #8 'Atopic diseases (i.e. asthma, including recurring wheeze, dermatitis, and/or rhinitis; as defined by trialists)' and #9, 'Other non-communicable disease outcomes (i.e. bone health, number of fractures, bone mineral density, any type of cancer, type 1 and type 2 diabetes mellitus, insulin resistance, and other autoimmune disorders; congestive heart failure; as defined by trialists)', as they are covered by previous Cochrane Reviews (Winzenberg 2011; Martineau 2016), as well as by other reviews (Pojsupap 2015), and we sought to narrow our review scope to focus on linear growth and adverse effects (see #1 above).
7. Electronic searches. Our specific changes are detailed below.
   a. PubMed.
      i. We removed quotation marks to increase sensitivity.
      ii. We added wildcard to hydroxyvitamin D*
      iii. We corrected the spelling of 'randomised controlled trial [pt]' to 'randomised controlled trial [pt]'.
   b. Scopus.
      i. We did not limit to conference papers only, thereby conducting a broader search.
   c. WPRO (WHO Western Pacific Regional Office).
      i. We corrected the name WPRO to WPRIM (Western Pacific Region Index Medicus); WPRO is the office.
   d. IMSEAR (Indian Medicus for the South East Asia Region).
      i. This database was not available at the time of searching (14 March 2018 and 11 December 2019) and therefore was not included.
   e. WHO ICTRP.
      i. In December 2019, we did not search WHO ICTRP directly because the trials records were available in CENTRAL.
   f. IndMED.
      i. We tried to access IndMED in 2019 but the database was no longer available at the last known URL, and we could not find an alternative location.
8. Data extraction and management. After piloting our data extraction forms, we found additional information to capture beyond what we had originally proposed, which included only "intervention, participants, trial identification numbers if available, results, and adverse events". We recorded this and additional details in the aforementioned section because we considered these details to be relevant in making comparisons.
9. Measures of treatment effect.
   a. After screening and extracting data, we found that many studies reported medians, ranges, interquartile ranges, and standard errors, rather than means and standard deviations, as described in our protocol (Yu 2017). Using methods in the *Cochrane Handbook for Systematic Reviews of Interventions* (Li 2020), we were able to include these data in comparisons by back-calculating means and standard deviations, when appropriate.
   b. To examine our secondary outcome 'rickets', we chose to include any study reporting on signs and symptoms of rickets as a dichotomous variable, and to combine these into one variable for meta-analysis (see Included studies > Outcomes). We analysed rickets this way due to the heterogeneity in rickets' definitions across studies reporting this outcome.
   c. We analysed two studies that reported rickets as an outcome using continuous measures, as reported in the original study (see Included studies > Outcomes). We analysed continuous data on rickets separately from categorical measures of rickets to include both types of data in our review.
10. Unit of analysis issues > Studies with more than two treatment groups.
   a. After screening and extracting data, we found that some studies assessed effects of oral vitamin D compared to a control as well as compared to other forms of vitamin D administration, such as intramuscular injection. We did not anticipate this in our protocol (Yu 2017), but we have accounted for this in the Review by extracting data only from relevant trial arms.
   b. Because we included another comparison to examine higher-dose vitamin D compared to lower-dose vitamin D (Table 1), if a study involved two or more comparison arms, we added our method to accommodate this, which was not described in our protocol (Yu 2017).
11. Assessment of reporting biases. To avoid repetition, we did not populate this section in our protocol (Yu 2017); we had explained how we would assess reporting bias under 'Selective reporting' in the 'Assessment of risk of bias' section. However, for clarity for the reader, we have explained how we assessed reporting bias in this section of the review.
12. Data synthesis. After screening and extracting data, we found that many outcomes included only one study in the analysis. For analyses including only one study, we used fixed-effect models, as they are more appropriate than the random-effects analyses originally proposed.

13. Potential biases in the review process. We searched 17 electronic databases and two trial registries to be as comprehensive as possible in examining all available evidence. However, we were not able to assess for publication bias using funnel plots due to lack of studies for comparison, thereby preventing us from drawing conclusions on publication bias of the included studies (Table 2).

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Body Height; Confidence Intervals; *Growth; Growth Disorders [epidemiology]; Hypercalcemia [etiology]; Hypercalciuria [etiology]; Micronutrients [administration & dosage]; Placebos [administration & dosage]; Randomized Controlled Trials as Topic; Vitamin D [*administration & dosage] [adverse effects]; Vitamins [*administration & dosage] [adverse effects]

MeSH check words

Child, Preschool; Humans; Infant; Infant, Newborn