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Comparative efficacies of vitamin D supplementation regimens in infants: a systematic review and network meta-analysis

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Abstract

Vitamin D deficiency in infants is widely prevalent. Most paediatric professional associations recommend routine vitamin D prophylaxis for infants. However, the optimal dose and duration of supplementation are still debated. We aimed to compare the efficacy and safety of different vitamin D supplementation regimens in term and late preterm neonates. For this systematic review and network meta-analysis, we searched MEDLINE, the Cochrane Central Register of Controlled Trials and Embase. Randomised and quasi-randomised clinical trials that evaluated any enteral vitamin D supplementation regimen initiated within 6 weeks of life were included. Two researchers independently extracted data on study characteristics and outcomes and assessed quality of included studies. A network meta-analysis with a Bayesian random-effects model was used for data synthesis. Certainty of evidence (CoE) was assessed using GRADE. Primary outcomes were mean serum vitamin D concentrations and the proportion of infants with vitamin D insufficiency (VDI). We included twenty-nine trials that evaluated fourteen different regimens of vitamin D supplementation. While all dosage regimens of ≥400 IU/d increased the mean 25(OH)D levels compared with no treatment, supplementation of ≤250 IU/d and 1400 IU/week did not. The CoE varied from very low to high. Low CoE indicated that 1600 IU/d, compared with lower dosages, reduced the proportion of infants with VDI. However, our results indicated that any dosage of ≥800 IU/d increased the risk of hypervitaminosis D and hypercalcaemia. Data on major clinical outcomes were sparse. Vitamin D supplementation of 400–600 IU/d may be the most effective and safest in infants.

Keywords: Vitamin D deficiency: Vitamin D supplementation: Infants: Neonates: Network meta-analysis: Systematic review

Vitamin D plays a vital role in bone mineralisation and regulates multiple other physiological pathways among infants[1]. Vitamin D deficiency (VDD) in infants commonly results in nutritional rickets, resulting in growth failure and skeletal deformity[2]. It can also result in seizures secondary to hypocalcaemia, myopathy due to hypophosphatemia, delayed motor development, defective enamel formation and risk of fractures[3].

VDD is a worldwide problem[4]. The reported prevalence of VDD in the Asian and African populations is very high[5,6]. Recent reports have suggested that the prevalence of VDD among pregnant women in Asia, Africa, the Middle East and Latin America is anywhere between 50 and 100 %[7]. This translated to low vitamin D stores in the neonates at birth and a lesser vitamin D concentration in the mother's milk[8,9]. The reported prevalence of

Abbreviations: CoE, certainty of evidence; NMA, network meta-analysis; SUCRA, surface under cumulative ranking curve; VDD, vitamin D deficiency; VDI, vitamin D insufficiency.

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VDD in early infancy in developing countries varied from 40 to 83 % among term-breastfed infants who were not on any vitamin D supplementation[10–12]. Clinical or radiological rickets have been reported in almost one-third of infants with serum 25-hydroxy vitamin D (25(OH)D) levels of less than 10 ng/ml[12,13]. Oral vitamin D supplementation is the current standard of care for exclusively breastfed infants. Most paediatric professional associations recommend 400 IU/d of oral vitamin D supplementation for breastfed infants[14–19]. However, studies worldwide have shown that this dose might be insufficient to maintain adequate serum 25(OH)D levels and bone mineral content in term healthy infants[20]. Hence, professional associations from countries like France and Finland recommend routine supplementation of more than 1000 IU/d of oral vitamin D to term healthy infants[21,22].

Addressing the issue of maternal VDD is very important, and vitamin D requirement for the neonate can vary on basis of maternal vitamin D status. The ideal vitamin D regimen for a neonate born to a mother with VCC may not be the same as compared with that of a neonate born to a mother with normal vitamin D levels. Various studies comparing different dosages and different regimens of oral vitamin D supplements to pregnant or lactating mothers, and infants have demonstrated inconsistent results[23–26]. A Cochrane review evaluated the effect of oral vitamin D supplementation on healthy-term breastfed infants or their lactating mothers. This review reported that oral vitamin D supplementation of 400 IU/d to infants may increase the serum 25(OH)D levels and may reduce the incidence of vitamin D insufficiency[27]. This review did not find studies that evaluated dosages of >400 IU/d of vitamin D supplementation. Besides, there is a rising concern in relation to vitamin D toxicity with higher dosage regimens[28]. Brustard and colleagues, in a systematic review, evaluated the safety of high-dose vitamin D supplementation in children aged 0–6 years. High dose was defined as greater than 1000 IU/d for infants (0–1 year) and greater than 2000 IU/d for children aged 1–6 years[29]. Though they reported significantly higher incidence of 25(OH)D levels >100 ng/ml in the high-dose group compared with placebo or ≤400 IU/d, there was no significant difference in serious clinical adverse events like hospitalisation and death or hypercalcaemia. The main limitation of these systematic reviews, which utilised pairwise meta-analyses, is that simultaneous comparisons of multiple regimens could not be performed. Hence, the best regimen of vitamin D supplementation in infants is still not well explored. By evaluating these different doses and regimens of vitamin D supplementation in a network meta-analysis (NMA), we can assess the effectiveness and safety of multiple regimens. Further, for those comparisons for which randomised controlled trials are unavailable, an NMA makes it possible to derive evidence from indirect comparisons. Hence, we conducted this systematic review and NMA to compare the efficacy and safety of the various vitamin D supplementation regimens and identify the optimal regimen of vitamin D supplementation in term and late preterm neonates.

Methods

The systematic review was registered in PROSPERO (CRD42022360454)[30]. The results of the NMA are reported according to preferred reporting of items of systematic review and meta-analysis-NMA guidelines[31].

Population, interventions and outcomes

Randomised and quasi-randomised controlled trials on term and late preterm infants were included. Any enteral vitamin D supplementation regimen to the infant initiated within one month of life was eligible for inclusion in this review. Trials that evaluated maternal vitamin D supplementation were excluded.

The primary outcomes were (1) mean serum vitamin D concentrations at 0–6 months and (2) the proportion of infants with VDI (defined as serum vitamin D concentration <30 ng/ml) at 0–6 months of life[32]. Although VDD was the only a priori-decided primary outcome, the mean vitamin D concentration was also added due to the availability of maximum data on mean vitamin D concentrations.

The secondary outcomes included proportion of infants with VDD (serum vitamin D concentration <20 ng/ml), severe VDD (serum vitamin D concentration <10–15 ng/ml), adverse effects such as hypervitaminosis D (serum (25(OH) vitamin D > 100 ng/ml or 250 nmol/l), hypercalcaemia (total Ca >12 mg/dl or 2·62 mmol/l), hypercalciuria (calcium: creatinine >0·3 (mg/mg)), bone mineral density, clinical rickets, all the above-mentioned similar outcomes assessed at 7–12 months, growth, neuro-developmental outcomes, and the incidence of infection episodes and allergic conditions.

Literature search and risk of bias assessment

Medline, Embase, CENTRAL and CINAHL were searched from inception until 4 March 2024 (online Supplementary eTable 1 in the supplement). There were no language restrictions. The preferred reporting of items of systematic review and meta-analysis flow is given in online Supplementary eFigure 1 in the supplement. Only published literature was included.

Two authors independently screened the results using Rayyan-QCRI software and independently assessed the full-text articles for potentially relevant trials[33]. Two authors independently evaluated the risk of bias in all included trials using the Cochrane Risk-of-Bias tool, version 2·0[34]. Disagreements were resolved by consensus.

Data extraction and data synthesis

Two authors independently extracted data from the included trials in duplicate using a structured proforma. A Bayesian NMA was performed using the R-software (R Foundation for Statistical Computing, Vienna, Austria)[35]. Markov chain Monte Carlo simulation using vague priors with four chains, burn-in of 50 000 iterations, followed by 1 000 000 iterations and 10 000 adaptations, was used. Model convergence was assessed using Gelman-Rubin Potential Scale Reduction Factor, trace and density plots. Leverage plots, total residual deviance and deviance information criterion were evaluated to confirm model convergence. Intransitivity was assessed by comparing the characteristics of included trials and inconsistency by node splitting. A pair-wise meta-analysis of the trials was also performed. Sensitivity analysis was performed for both the primary outcomes based on baseline vitamin D status of the study infants, VDI (vitamin D < 30 ng/ml) *v.* VDD (vitamin D < 20 ng/ml). The effect estimates of the NMA were reported as risk ratio or mean difference with a 95 % credible interval. While the NMA estimates were illustrated with matrix plots, direct evidence from randomised controlled trials was depicted using forest plots. Surface under the cumulative ranking curve (SUCRA) was used to depict the ranking of the interventions[36]. SUCRA values when expressed as percentage can range from 0 % to 100 %. The higher the SUCRA value, the better the ranking of the intervention. SUCRA values are prone to misinterpretation; the value needs to be interpreted along with the certainty of evidence for any intervention. In addition, SUCRA can vary for an intervention for different outcomes. Although an intervention may be ranked higher for its improved outcomes, it could be ranked down for its adverse effect profile. Other factors need to be considered by the clinician while interpreting SUCRA and before adopting any intervention to practice. If there are more than ten studies for direct comparison in any of the interventions, it was planned to assess for publication bias using a funnel plot.

Certainty of evidence

The certainty of evidence (CoE) for the NMA effect estimates for the primary outcomes was assessed according to GRADE recommendations[37].

Results

After removal of duplicates, 4093 titles and abstracts were screened. Of these, 261 full texts were retrieved and assessed for inclusion. Twenty-nine trials (thirty-seven reports) were included in the systematic review (online Supplementary eFigure 1)[13,23,38–72]. The characteristics of the included studies are given in Table 1. Seventeen studies were form high-income countries, six were from upper middle-income countries and the rest were from low- and middle-income countries. We evaluated fourteen different regimens of vitamin D supplementation in the NMA: daily doses of ≤250 (less 250day), 400 (400day), 500 (500day), 600 (600day), 800 (800day), 1000 (1000day), 1200 (1200 day) and 1600 IU (1600day), weekly doses of 1400 IU (1400week), 50 000 IU as single (50000_single) and bimonthly doses (50000_2mon), and one lakh IU as single dose (1lac_single), two lakh IU as a single dose (2lac_single), six lakh IU as a single dose (6lac_single) along with no supplementation (control) group. Baseline vitamin D status was in deficiency range in nine trials and in insufficiency range in eight trials, while the baseline status was not reported in twelve trials. The method used for the assay of 25(OH) vitamin D levels is depicted in Table 1.

Risk of bias in included trials

Two independent authors assessed the risk of bias in the included studies using the ROB.2 tool (online Supplementary eTable 2). Among the twenty-nine included trials, nine trials had low risk of overall bias, while seven trials had some concerns and thirteen trials had a high risk of overall bias. Among the latter, two trials had high risk of bias for the domain ‘randomisation process’[51,62], two had high risk of bias for the domain ‘missing outcome data’[61,63] and one had high risk of bias for the domain ‘measurement of outcome’[54].

Primary outcomes

Mean serum vitamin D concentrations at 0–6 months. Twenty-four trials that included 4026 infants and evaluated fourteen vitamin D supplementation regimens reported this outcome. Almost all trials (except three)[55,58,62] have assessed the vitamin D concentration between 3 and 6 months of age. Figure 1 shows the network, NMA forest, and SUCRA plots with the control group as the common comparator. Figure 2 shows the league plot that depicts the network estimates for various comparisons. No inconsistency was found in the node-splitting analysis (online Supplementary eFigure 2). Forest plots for the direct evidence are provided in online Supplementary eFigure 3. The certainty of evidence assessment for primary outcomes is listed in Table 2.

Several dosage regimens such as 400day (mean difference 15·18 (95 % credible interval 10·49, 19·81); High CoE), 600day (18·53 (6·57, 30·35); Very low CoE), 800day (21·85 (13·45, 29·97); High CoE), 1000day (17·6 (7·58, 27·86); Very low CoE), 1200day (11·88 (2·34, 21·62); Very Low CoE), 1600day (47·67 (37·19, 58·51); Moderate CoE) and 50000_2mon (29·71 (15·75, 43·56); Low CoE) resulted in greater vitamin D concentrations at 0–6 months compared with no supplementation. Two regimens less250day (6·6 (-1·56, 14·41)) and 1400week (7·6 (-0·98, 16·07)) did not result in a significant increase in vitamin D concentration when compared with no supplementation.

Comparisons of the various vitamin D supplementation regimens among themselves showed that multiple other regimens were better in increasing serum vitamin D concentrations when compared to less250day and 1400week. Similarly, the regimen 1600day resulted in greater vitamin D concentrations compared with many other regimens (Fig. 2). SUCRA ranked 1600day (SUCRA value 99·8 %) as the best intervention to increase serum vitamin D concentration, followed by 1200day (88·4 %) and 50000_2mon (81·8 %).

Sensitivity analysis based on baseline vitamin D status for the outcome ‘serum’ vitamin D concentrations at 0–6 months’. Among the twenty-four trials that reported this outcome, baseline vitamin D status of the study infants was in insufficiency range (20–30 ng/ml) in five trials, deficiency range (<20 ng/ml) in eight trials and not reported in eleven trials. The sensitivity analysis was performed comparing the trials with baseline vitamin D status in insufficiency range *v.* those with baseline status in deficiency range. When compared with the no supplementation group, the increase in vitamin D concentrations after supplementation with multiple regimens was greater in trials where baseline vitamin D status was deficient, than those where the infants’ baseline status was insufficient (online Supplementary eFigure 4).

One trial evaluating 2lac_single *v.* 6lac_single did not connect with the other trials in the network[69]. The trial did not find a significant difference in serum vitamin D concentrations between the two groups (–3·4 (–11·14; 4·34)) (online Supplementary eFigure 3V).

Proportion of infants with VDI at 0–6 months. Six trials that included 497 infants and evaluated seven vitamin D

Table 1. Characteristics of included studies

Sl.no	Study ID	Country	Income classification	Group name	Sample size	Duration and timing of supplementation	Term/ late preterm	Feeding	Assay
1	Ala-Houhala 1985	Finland	high income	400day/1000day	31/29	Birth to 20 weeks	Term	Breastfeeding	Competitive protein-binding assay
2	Alonso 2011	Spain	high income	400day/Control	41/47	2 weeks to 1 year	Term	Mixed	Electrochemiluminescent assay
3	Atas 2013	Turkey	upper middle income	less250day/400day	75/64	Birth to 4 mon	Term	Breastfeeding	High-performance liquid chromatography
4	Chandy 2016	India	lower middle income	400day/Control	47/54	2–4 days to 9 mon	Both	Mixed	Radioimmunoassay
5	Feliciano 1994	China	upper middle income	less250day/400day	85/85	3–5 days to 6 mon	Term	Mixed	Not mentioned
6	Gallo 2013, Wicklow 2015, Weiler 2022	Canada	high income	400day/800day/ 1200day/1600day	39/39/38/16	Within 1 mon to 12 mon	Term	Mixed	Radioimmunoassay
7	Greer 1981, Greer 1982	USA	high income	400day/Control	09-/09	2–3 weeks to 12 weeks	Term	Breastfeeding	Competitive protein-binding assay
8	Greer 1989	USA	high income	400day/Control	22/24	2–3 weeks to 12 weeks	Term	Breastfeeding	High-performance liquid chromatography
9	Holmlund-Suila 2012	Finland	high income	400day/1200day/ 1600day	35/35/37	2 week to 3 mon	Term	Mixed	Automated IDS-iSYS analyser (immunoassay)
10	Huynh 2016	Australia	High income	400day/50000single	36/34	Birth to 4 mon	Term	Mixed	Chemiluminescent immunoassay
11	Kumar 2011, Trilok-kumar 2015	India	lower middle income	1400week/Control	1039/1040, 446/466	7 days to 6 mon	Term	Mixed	Radioimmunoassay
12	Lin 2022	China	upper middle income	400day/Control	46/46	10 days to 4 mon	Term	Breastfeeding	Chemiluminescence
13	Madar 2008	Norway	High income	400day/Control	22/29	6 weeks to 7 weeks after initiation	Not given	Mixed	High-performance liquid chromatography
14	Moodley 2015	USA	high income	50000single/Control	27/22	only once, within 24 h of birth	Term	Mixed	Liquid chromatography tandem mass spectrometry
15	Pacheco-Acosta 2020	Chile	High income	1lacsingle/400day	36/29	single dose at 1 mon	Term	Breastfeeding	Radioimmunoassay
16	Ponnapakkam 2010	USA	High income	less250day/Control	08-/09	Birth to 6 mon	Term	Breastfeeding	Immuno Diagnostic Systems (immunoassay)
17	Razaghi 2022	Canada	high income	1000day/400day	49/49	1 mon till 12 mon	Term	Breastfeeding	Chemiluminescent immunoassay
18	Rosendahl 2018, Rosendahl 2019, Hauta-Alus 2020, Sandboge 2023	Finland	High income	400day/1200day	489/486, 402/	241w0e (eHkasutoa- 2Alyuesa2rs020)	Term	Mixed	Fully automated immunoassay
19	Rothberg 1982	South Africa	Upper middle income	400day/Control	10-/12	Birth to 6 weeks	Term	Breastfeeding	Competitive protein-binding assay
20	Ruangkit 2021	Thailand	upper middle income	400day/Control	43/44	2 mon to 6 mon	Term	Breastfeeding	Liquid chromatography tandem mass spectrometry
21	Rueter 2018	Australia	high income	400day/Control	97/98	Within 28 days to 6 mon	Term	Mixed	Chemiluminescent immunoassay
22	Shakiba 2010	Iran	lower middle income	less250day/400day/ 50000_2mon	19/26/30	15–30 d after birth to 6 mon	Term	Breastfeeding	Chemiluminescent immunoassay
23	Siafarikas 2010	Germany	high income	less250day/500day	14/14	Birth to 6 weeks	Term	Breastfeeding	Radioimmunoassay
24	Specker 1992	China	upper middle income	less250day/400day	99/88	3–5 days to 6 mon	Term	Mixed	Competitive protein-binding assay
25	Trilok-kumar 2012	India	lower middle income	1400week/Control	164/187	7 days to 6 mon	Term	Mixed	Radioimmunoassay
26	Tuovinen 2021	Finland	high income	400day/1200day	404/397	2 weeks to 24 mon	Term	Breastfeeding	Fully automated immunoassay
27	Yadav 2022	India	lower middle income	400day/800day	50/49	3–5 days to 14 weeks	Term	Breastfeeding	Chemiluminescent immunoassay
28	Zeghoud 1994	Algeria	lower middle income	6lac_single/2lac_single/ 1lac_3mon	30/15/15	Once at birth	Term	Not mentioned	Radiocompetitive protein-binding assay
29	Ziegler 2014, Ziegler 2017	USA	High income	Less250day/400day/ 600day/800day	56/60/56/41	1 mon to 9 mon	Term	Breastfeeding	Equilibrium radioimmunoassay

British Journal of Nutrition

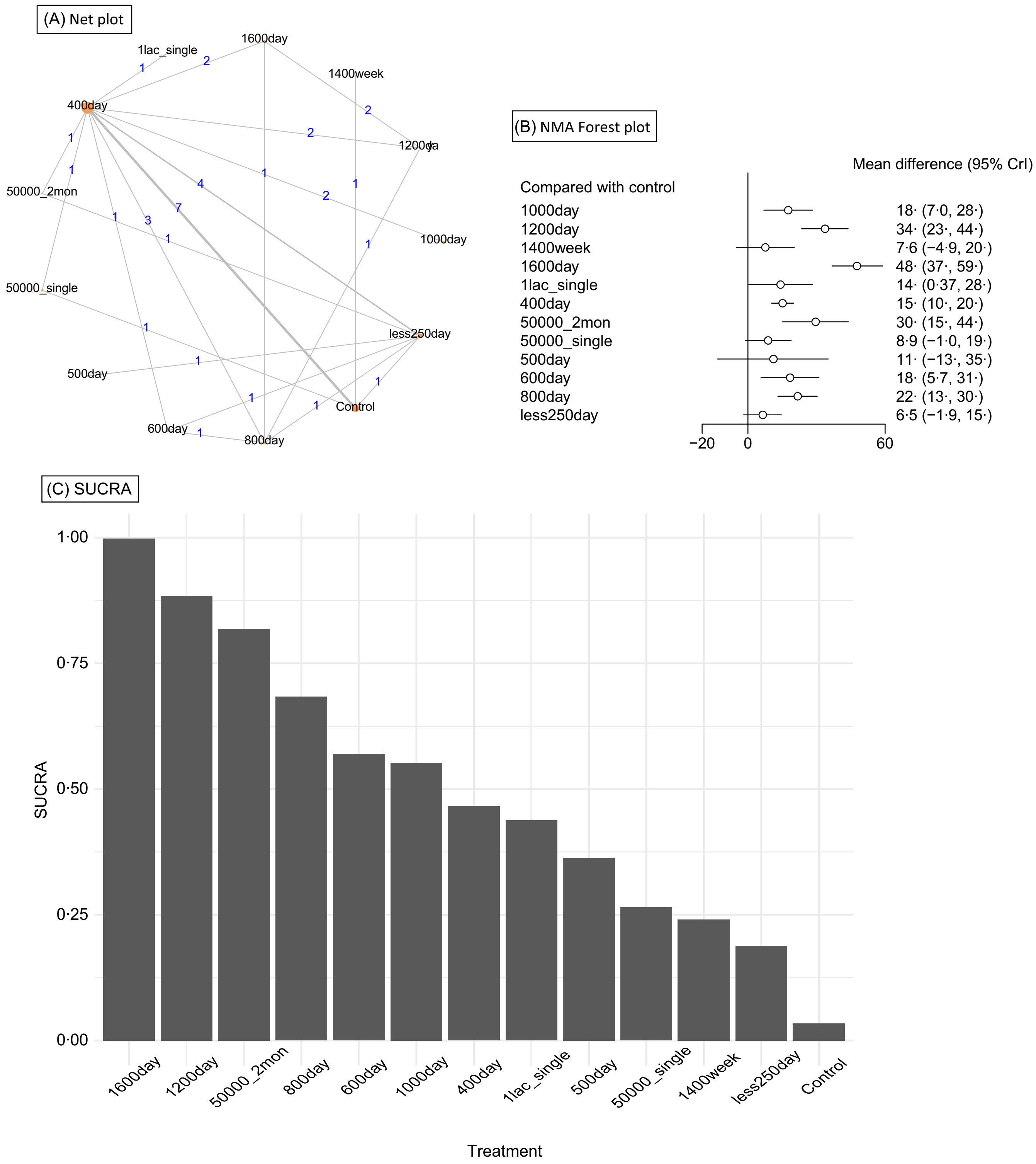

Fig. 1. Network geometry plot, NMA forest plots, and SUCRA values with the 'control group' as the common comparator for the primary outcome of mean serum vitamin concentration at 0–6 months.

supplementation regimens reported this outcome. All the included trials have assessed the outcome between 3 and 6 months. Figure 3 shows the network, SUCRA, and NMA forest plots with the control group as the common comparator. online Supplementary eFigures 5–6 show the league plot and forest plots for the direct evidence.

NMA showed that the dosage regimen 1600day is more effective in reducing the proportion of infants with VDI at 0–6 months than control group (risk ratio 0 (95 % redible interval 0–0·07); Low CoE), less250day (0 (0–0); Low CoE), 400day (0 (0–0·05); Low CoE), 800 IU/d (0 (0–0·06); Low CoE), 1200day (0 (0, 0·31); Low CoE), 50000_single (0 (0–0·17); Very low CoE)

1000day	16·08 (3·67, 28·61)	-10.03 (-23.4, 3.14)	30·04 (16·95, 43·39)	-3·3 (-18·54, 11·88)	-2·45 (-11·59, 6·59)	12·19 (-4·17, 27·84)	-8·75 (-21·92, 4·13)	-6·27 (-31·15, 18·6)	0·92 (-13·38, 15·23)	4·25 (-7·28, 15·38)	-17·6 (-27·86, -7·58)	-11·03 (-22·57, 0·12)
-16·08 (-28·61, -3·67)	1200day	-26·12 (-38·96, -13·14)	13·95 (3·88, 24·27)	-19·41 (-34·3, -4·44)	-18·51 (-27·06, -10)	-3.96 (-19.69, 11.5)	-24·86 (-37·54, -12·15)	-22.29 (-46.83, 2.53)	-15·18 (-28·77, -1·59)	-11·88 (-21·62, -2·34)	-33·72 (-43·5, -24)	-27·13 (-38·08, -16·6)
10·03 (-3·14, 23·4)	26·12 (13·14, 38·96)	1400week	40·1 (26·66, 54·01)	6·72 (-8·74, 22·25)	7·61 (-2·12, 17·32)	22·11 (5·82, 38·61)	1·26 (-11·38, 13·94)	3·74 (-21·28, 29·29)	10·96 (-3·82, 25·38)	14·25 (2.2, 26·01)	-7·6 (-16·07, 0·98)	-1 (-12·86, 10·49)
-30·04 (-43·39, -16·95)	-13·95 (-24·27, -3·88)	-40·1 (-54·01, -26·66)	1600day	-33·33 (-48·89, -17·92)	-32·46 (-42·28, -23·06)	-17·91 (-34·29, -1·88)	-38·77 (-52·36, -25·69)	-36·31 (-61·62, -11·07)	-29·1 (-43·65, -15·13)	-25·82 (-36·81, -15·35)	-47·67 (-58·51, -37·19)	-41·07 (-53·08, -29·85)
3·3 (-11·88, 18·54)	19·41 (4·44, 34·3)	-6·72 (-22·25, 8·74)	33·33 (17·92, 48·89)	1lac_single	0·9 (-11·34, 12·94)	15·44 (-2·68, 33·33)	-5·48 (-20·83, 9·95)	-2·94 (-29·3, 23·02)	4·23 (-12·49, 20·73)	7·53 (-6·61, 21·34)	-14·29 (-27·31, -1·32)	-7·72 (-21·79, 5·98)
2·45 (-6·59, 11·59)	18·51 (10, 27·06)	-7·61 (-17·32, 2·12)	32·46 (23·06, 42·28)	-0·9 (-12·94, 11·34)	400day	14·58 (1·27, 27·69)	-6·33 (-15·55, 3·04)	-3·79 (-27·01, 19·74)	3·35 (-7·66, 14·44)	6·66 (-0·32, 13·45)	-15·18 (-19·81, -10·49)	-8·59 (-15·55, -2)
-12·19 (-27·84, 4·17)	3·96 (-11·5, 19·69)	-22·11 (-38·61, -5·82)	17·91 (1·88, 34·29)	-15·44 (-33·33, 2·68)	-14.58 (-27.69, -1.27)	50000_2mon	-20·9 (-36·87, -4·67)	-18·39 (-44·24, 7·86)	-11·22 (-27·81, 5·23)	-7·94 (-22·39, 6·68)	-29·71 (-43·56, -15·75)	-23·18 (-36·39, -10·01)
8·75 (-4·13, 21·92)	24·86 (12·15, 37·54)	-1·26 (-13·94, 11·38)	38·77 (25·69, 52·36)	5·48 (-9·95, 20·83)	6.33 (-3.04, 15.55)	20·9 (4·67, 36·87)	50000_single	2·51 (-22·38, 27·68)	9·64 (-4·75, 24·15)	13 (1.33, 24.33)	-8·85 (-18·45, 0·63)	-2·27 (-14·02, 8·91)
6·27 (-18·6, 31·15)	22·29 (-2·53, 46·83)	-3·74 (-29·29, 21·28)	36·31 (11·07, 61·62)	2·94 (-23·02, 29·3)	3.79 (-19.74, 27.01)	18·39 (-7·86, 44·24)	-2·51 (-27·68, 22·38)	500day	7·2 (-18·39, 31·92)	10·44 (-13·7, 34·28)	-11·39 (-35·1, 12·13)	-4·81 (-27·36, 17·19)
-0·92 (-15·23, 13·38)	15·18 (1·59, 28·77)	-10·96 (-25·38, 3·82)	29·1 (15·13, 43·65)	-4·23 (-20·73, 12·49)	-3.35 (-14.44, 7.66)	11·22 (-5·23, 27·81)	-9·64 (-24·15, 4·75)	-7·2 (-31·92, 18·39)	600day	3·32 (-8·28, 14·85)	-18·53 (-30·35, -6·57)	-11·92 (-23·49, -0·63)
-4·25 (-15·38, 7·28)	11·88 (2·34, 21·62)	-14·25 (-26·01, -2·2)	25·82 (15·35, 36·81)	-7·53 (-21·34, 6·61)	-6.66 (-13.45, 0.32)	7·94 (-6·68, 22·39)	-13 (-24·33, -1·33)	-10·44 (-34·28, 13·7)	-3·32 (-14·85, 8·28)	800day	-21·85 (-29·97, -13·45)	-15·27 (-24·1, -6·6)
17·6 (7·58, 27·86)	33·72 (24, 43·5)	7·6 (-0·98, 16·07)	47·67 (37·19, 58·51)	14·29 (1·32, 27·31)	15·18 (10·49, 19·81)	29·71 (15·75, 43·56)	8·85 (-0·63, 18·45)	11·39 (-12·13, 35·1)	18·53 (6·57, 30·35)	21·85 (13·45, 29·97)	Control	6·6 (-1·56, 14·41)
11·03 (-0·12, 22·57)	27·13 (16·6, 38·08)	1 (-10·49, 12·86)	41·07 (29·85, 53·08)	7·72 (-5·98, 21·79)	8·59 (2, 15·55)	23·18 (10·01, 36·39)	2·27 (-8·91, 14·02)	4·81 (-17·19, 27·36)	11·92 (0·63, 23·49)	15·27 (6·6, 24·1)	-6·6 (-14·41, 1·56)	Less250day

Fig. 2. League plot that depicts the network estimates for various comparisons for the primary outcome of mean serum vitamin D concentrations at 0–6 months.

and 1lac_single (0 (0–0·1); Very low CoE). The regimen 1600day (SUCRA value 99·4 %) was ranked as the best intervention to reduce VDI at 0–6 months.

Sensitivity analysis based on baseline vitamin D status for the outcome 'VDI at 0–6 months'. Baseline vitamin D status of the study infants was in insufficiency range in one trial, while it was in deficiency range in three trials. The baseline vitamin D status was not reported in two trials. The proportion of infants with VDI after supplementation did not differ much between the trials where baseline vitamin D status was deficient and those where the infants' baseline status was insufficient (online Supplementary eFigure 7).

Secondary outcomes

Other outcomes assessed at 0–6 months

VDD. Twelve studies evaluating ten interventions and 1341 infants reported this outcome. Three regimens 400day, 800day and 1600day were better than no supplementation in reducing VDD. 1600day was found to be better than multiple other regimens in reducing VDD (online Supplementary eFigures 8–11).

Severe VDD. Eleven studies evaluating ten interventions and 1235 infants reported this outcome. 400day and 800day were better than no supplementation in reducing severe **VDD** (online Supplementary eFigures 12–15).

Hypervitaminosis D. Six studies evaluating eight interventions and 492 infants reported this outcome (online Supplementary eFigures 16–18). The regimens 1600day, 1200day, 800day, 1lac_single and 50000_2mon were found to have a greater risk of hypervitaminosis D compared to less250day, 400day and 50000_single.

Hypercalcaemia and hypercalciuria. Four trials evaluating four vitamin D regimens and no supplementation reported hypercalcaemia at 0–6 months (online Supplementary eFigures 19–21). The 1600day, 1200day and 800day regimens had a greater risk of hypercalcaemia compared with 400day and no supplementation.

One trial evaluating hypercalciuria did not find a difference among the regimens 400day, 800day, 1200day and 1600day (online Supplementary eFigure 22)[23].

Bone mineral density. Three trials evaluating six different vitamin D regimens (less250day, 400day, 600day, 800day, 1200day and 1600day) and no supplementation group reported this outcome (online Supplementary eFigure 23). Pairwise meta-analyses did not find a clinically significant difference in bone mineral density between the groups.

Clinical rickets. Nine trials evaluating six different vitamin D regimens (less250day, 400day, 500day, 1000day and 1400week) and no supplementation group reported this outcome (online Supplementary eFigures 24–27). One trial found 800day to be better than 400day in reducing the risk of clinical rickets.[13]

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Table 2. GRADE certainty of evidence for primary outcomes

Comparison	Direct evidence – certainty of evidence	Indirect evidence – certainty of evidence	Network meta-analysis RR (CrI)		Certainty of evidence
			RR	CrI	
Vitamin D levels 0–6 months					
1000day *v.* 400day	VERY LOW*,†	–	2·45	–6·59, 11·59	VERY LOW*,†
1400week *v.* Control	HIGH	–	7·6	–0·98, 16·07	HIGH
1lac_single *v.* 400day	VERY LOW†,‡	–	–0·9	–12·94, 11·34	VERY LOW†,‡
500day *v.* less250day	VERY LOW†,‡	–	4·81	–17·19, 27·36	VERY LOW†,‡
1200day *v.* 400day	HIGH	HIGH	18·51	10, 27·06	HIGH
1600day *v.* 400day	MODERATE§	HIGH	32·46	23·06, 42·28	HIGH
1600day *v.* 1200day	MODERATE§	HIGH	13·95	3·88, 24·27	HIGH
50000_2mon *v.* less250day	LOW‡	LOW‡	23·18	10·01, 36·39	LOW‡
400day *v.* 800day	HIGH	HIGH	–6·66	–13·45, 0·32	HIGH
400day *v.* Control	HIGH	LOW‖,¶	15·18	10·49, 19·81	HIGH
400day *v.* less250day	LOW‖,¶	MODERATE**	8·59	2, 15·55	MODERATE*†
400day *v.* 50000_2mon	LOW‡	LOW‡	–14·58	–27·69, –1·27	LOW‡
600day *v.* less250day	LOW‖,**	VERY LOW†,**	11·92	0·63, 23·49	LOW§,*†
600day *v.* 800day	VERY LOW†,**	LOW‖,**	–3·32	–14·85, 8·28	LOW§,*†
1200day *v.* 800day	HIGH	HIGH	11·88	2·34, 21·62	HIGH
400day *v.* 600day	VERY LOW†,**	LOW‖,¶	–3·35	–14·44, 7·66	LOW§,**
400day *v.* 50000_single	MODERATE‖	MODERATE‖	6·32	–4·03, 16·67	MODERATE§
50000_ single *v.* Control	LOW‖,**	MODERATE‖	8·92	–1·67, 19·46	MODERATE§
1600day *v.* 800day	HIGH	MODERATE§	24·58	13·8, 35·62	HIGH
800day *v.* less250day	MODERATE**	LOW‖,¶	14·63	5·67, 23·71	MODERATE*†
Control *v.* less250day	VERY LOW†,‡	LOW‖,¶	–6·6	–14·41, 1·56	LOW§,**
1000day *v.* 1200day	–	VERY LOW*,†	–16·08	–28·61, –3·67	VERY LOW§,‖
1000day *v.* 1400week	–	VERY LOW*,†	10·03	–3·14, 23·4	VERY LOW*,†
1600day *v.* 1000day	–	VERY LOW*,†	30·04	16·95, 43·39	VERY LOW*,†
1000day *v.* 1lac_single	–	VERY LOW*,†	3·3	–11·88, 18·54	VERY LOW*,†
1000day *v.* 50000_2mon	–	VERY LOW*,†	–12·19	–27·84, 4·17	VERY LOW*,†
1000day *v.* 50000_single	–	VERY LOW*,†	8·75	–4·13, 21·92	VERY LOW*,†
1000day *v.* 500day	–	VERY LOW*,†	6·27	–18·6, 31·15	VERY LOW*,†
1000day *v.* 600day	–	VERY LOW*,†	–0·92	–15·23, 13·38	VERY LOW*,†
1000day *v.* 800day	–	VERY LOW*,†	–4·25	–15·38, 7·28	VERY LOW*,†
1000day *v.* Control	–	VERY LOW*,†	17·6	7·58, 27·86	VERY LOW*,†
1000day *v.* less250day	–	VERY LOW*,†	11·03	–0·12, 22·57	VERY LOW*,†
1200day *v.* 1400week	–	HIGH	26·12	13·14, 38·96	VERY LOW§,‖
1200day *v.* 1lac_single	–	VERY LOW†,‡	19·41	4·44, 34·3	VERY LOW§,‖
1200day *v.* 50000_2mon	–	LOW‡	3·96	–11·5, 19·69	VERY LOW§,‖
1200day *v.* 50000_single	–	MODERATE‖	24·86	12·15, 37·54	VERY LOW§,‖
1200day *v.* 500day	–	VERY LOW†,‡	22·29	–2·53, 46·83	VERY LOW†,‡
1200day *v.* 600day	–	VERY LOW†,**	15·18	1·59, 28·77	VERY LOW†,*†
1200day *v.* Control	–	HIGH	11·88	2·34, 21·62	VERY LOW§,‖
1200day *v.* less250day	–	LOW‖,¶	33·72	24, 43·5	MODERATE*†
1600day *v.* 1400week	–	MODERATE§	40·1	26·66, 54·01	MODERATE¶
1400week *v.* 1lac_single	–	VERY LOW†,‡	–6·72	–22·25, 8·74	VERY LOW†,‡
1400week *v.* 400day	–	HIGH	–7·61	–17·32, 2·12	HIGH
1400week *v.* 5000_2mon	–	LOW‡	–22·11	–38·61, –5·82	LOW‡
1400week *v.* 50000_single	–	LOW‖,**	–1·26	–13·94, 11·38	LOW§,*†
1400week *v.* 500day	–	VERY LOW†,‡	–3·74	–29·29, 21·28	VERY LOW†,‡
1400week *v.* 600day	–	VERY LOW†,‡	–10·96	–25·38, 3·82	VERY LOW†,‡
1400week *v.* 800day	–	HIGH	–14·25	–26·01, –2·2	HIGH
1400week *v.* less250day	–	VERY LOW†,‡	1	–10·49, 12·86	VERY LOW†,‡
1600day *v.* 1lac_single	–	VERY LOW†,‡	33·33	17·92, 48·89	VERY LOW†,‡
1600day *v.* 50000_2mon	–	LOW‡	17·91	1·88, 34·29	LOW‡
1600day *v.* 50000_single	–	MODERATE‖	38·77	25·69, 52·36	MODERATE§
1600day *v.* 500day	–	VERY LOW†,‡	36·31	11·07, 61·62	VERY LOW†,‡
1600day *v.* 600day	–	VERY LOW†,**	29·1	15·13, 43·65	VERY LOW†,*†
1600day *v.* Control	–	MODERATE§	47·67	37·19, 58·51	MODERATE¶
1600day *v.* less250day	–	MODERATE**	41·07	29·85, 53·08	MODERATE*†
1lac_single *v.* 50000_2mon	–	VERY LOW†,‡	–15·44	–33·33, 2·68	VERY LOW†,‡
1lac_single *v.* 50000_single	–	VERY LOW†,‡	5·48	–9·95, 20·83	VERY LOW†,‡
1lac_single *v.* 500day	–	VERY LOW†,‡	2·94	–23·02, 29·3	VERY LOW†,‡
1lac_single *v.* 600day	–	VERY LOW†,‡	–4·23	–20·73, 12·49	VERY LOW†,‡
1lac_single *v.* 800day	–	VERY LOW†,‡	–7·53	–21·34, 6·61	VERY LOW†,‡
1lac_single *v.* Control	–	VERY LOW†,‡	14·29	1·32, 27·31	VERY LOW†,‡
1lac_single *v.* less250day	–	VERY LOW†,‡	7·72	–5·98, 21·79	VERY LOW†,‡
400day *v.* 500day	–	VERY LOW†,‡	3·79	–19·74, 27·01	VERY LOW†,‡
	–	LOW‡	20·9	4·67, 36·87	LOW‡

Table 2. (*Continued*)

Comparison	Direct evidence – certainty of evidence	Indirect evidence – certainty of evidence	Network meta-analysis RR (CrI)		Certainty of evidence
			RR	CrI	
50000_2mon *v.* 50000_single					
50000_2mon *v.* 500day	–	VERY LOW†,‡	18·39	–7·86, 44·24	VERY LOW†,‡
50000_2mon *v.* 600day	–	LOW‡	11·22	–5·23, 27·81	LOW‡
50000_2mon *v.* 800day	–	LOW‡	7·94	–6·68, 22·39	LOW‡
50000_2mon *v.* Control	–	LOW‡	29·71	15·75, 43·56	LOW‡
50000_ single *v.* 500day	–	VERY LOW†,‡	–2·51	–27·68, 22·38	VERY LOW†,‡
50000_ single *v.* 600day	–	MODERATE‖	–9·64	–24·15, 4·75	MODERATE§
50000_ single *v.* 800day	–	MODERATE‖	–13	–24·33, –1·33	MODERATE§
50000_ single *v.* less250day	–	LOW‖,¶	2·27	–8·91, 14·02	LOW§,**
500day *v.* 600day	–	VERY LOW†,‡	–7·2	–31·92, 18·39	VERY LOW†,‡
500day *v.* 800day	–	VERY LOW†,‡	–10·44	–34·28, 13·7	VERY LOW†,‡
500day *v.* Control	–	VERY LOW†,‡	11·39	–12·13, 35·1	VERY LOW†,‡
600day *v.* Control	–	VERY LOW†,**	18·53	6·57, 30·35	VERY LOW†,*†
800day *v.* Control	–	HIGH	21·85	13·45, 29·97	HIGH
VDI (Vitamin D level < 30 ng/ml) at 0–6 months					
1200day *v.* 1600day	LOW†	LOW†	40362820438086·7	3·21, 1·85467118243141e+43	LOW†
1200day *v.* 400day	MODERATE*†	LOW†	0·19	0, 8·41	MODERATE*†
1200day *v.* 800day	LOW†	MODERATE*†	0·23	0, 10·04	MODERATE*†
1600day *v.* 400day	LOW†	LOW†	0	0, 0·05	LOW†
1600day *v.* 800day	LOW†	LOW†	0	0, 0·06	LOW†
1lac_single *v.* 400day	VERY LOW†,‡	–	0·83	0·01, 64·26	VERY LOW†,‡
400day *v.* 800day	MODERATE*†	LOW†	1·16	0·08, 18·82	HIGH
400day *v.* Control	LOW†	–	0·94	0·02, 48·33	LOW†
400day *v.* less250day	LOW‡	–	0	0, 0·04	LOW‡
50000_single *v.* Control	VERY LOW†,**	–	0·58	0·01, 28·98	VERY LOW†,**
1200day *v.* 1lac_single	–	VERY LOW†,‡	0·23	0, 73·47	VERY LOW†,‡
1200day *v.* 50000_single	–	VERY LOW†,**	0·31	0, 278·96	VERY LOW†,**
1200day *v.* Control	–	LOW†	0·18	0, 41·7	LOW†
1200day *v.* less250day	–	LOW‡	0	0, 0·01	LOW‡
1600day *v.* 1lac_single	–	VERY LOW†,‡	0	0, 0·1	VERY LOW†,‡
1600day *v.* 50000_single	–	VERY LOW†,**	0	0, 0·17	VERY LOW†,**
1600day *v.* Control	–	LOW†	0	0, 0·07	LOW†
1600day *v.* less250day	–	LOW†	0	0, 0	LOW†
1lac_single *v.* 50000_single	–	VERY LOW†,‡	1·33	0, 1642·71	VERY LOW†,‡
1lac_single *v.* 800day	–	VERY LOW†,‡	0·96	0·01, 166·58	VERY LOW†,‡
1lac_single *v.* Control	–	VERY LOW†,‡	0·77	0, 266·79	VERY LOW†,‡
1lac_single *v.* less250day	–	VERY LOW†,‡	0	0, 0·07	VERY LOW†,‡
400day *v.* 50000_single	–	VERY LOW†,**	1·61	0·01, 476·77	VERY LOW†,**
50000_single *v.* 800day	–	VERY LOW†,**	0·72	0, 397	VERY LOW†,**
50000_single *v.* less250day	–	VERY LOW†,**	0	0, 0·07	VERY LOW†,**
800day *v.* Control	–	LOW†	0·8	0·01, 96·17	LOW†
800day *v.* less250day	–	LOW‡	0	0, 0·05	LOW‡
Control *v.* less250day	–	LOW‡	0	0, 0·08	LOW‡

* Downgraded by one level for risk of bias due to some concerns in one of the two included studies and high risk of bias in the other study.
† Downgraded by two levels for very serious imprecision due to small sample size and confidence interval crossing the line of no difference.
‡ Downgraded by two levels for high risk of bias in the only included study.
§ Downgraded by one level for high risk of bias in one of the two included studies.
‖ Downgraded by one level for serious imprecision due to confidence interval crossing the line of no clinical significance (5 ng/ml).
¶ Downgraded by one level for risk of bias due to high risk of bias in studies contributing to more than 50 % weightage.
** Downgraded by one level for risk of bias due to 'some concerns' in the only included study.
*† Downgraded by one level for serious imprecision due to small sample size.

None of the babies in either group in other trials was diagnosed with rickets, except for one baby in the control group in one trial[49].

Mortality. One trial that compared 1400week *v.* control found no difference in mortality until 6 months between the groups[49].

Outcomes assessed at 7–12 months

Mean serum vitamin D concentrations. Six trials, including 2845 infants, evaluated this outcome. Five dosage regimens were evaluated: less250day, 400day, 600day, 800day and 1200day along with control group. None of the dosage regimens was better compared to no supplementation or other regimens (online Supplementary eFigures 29–32).

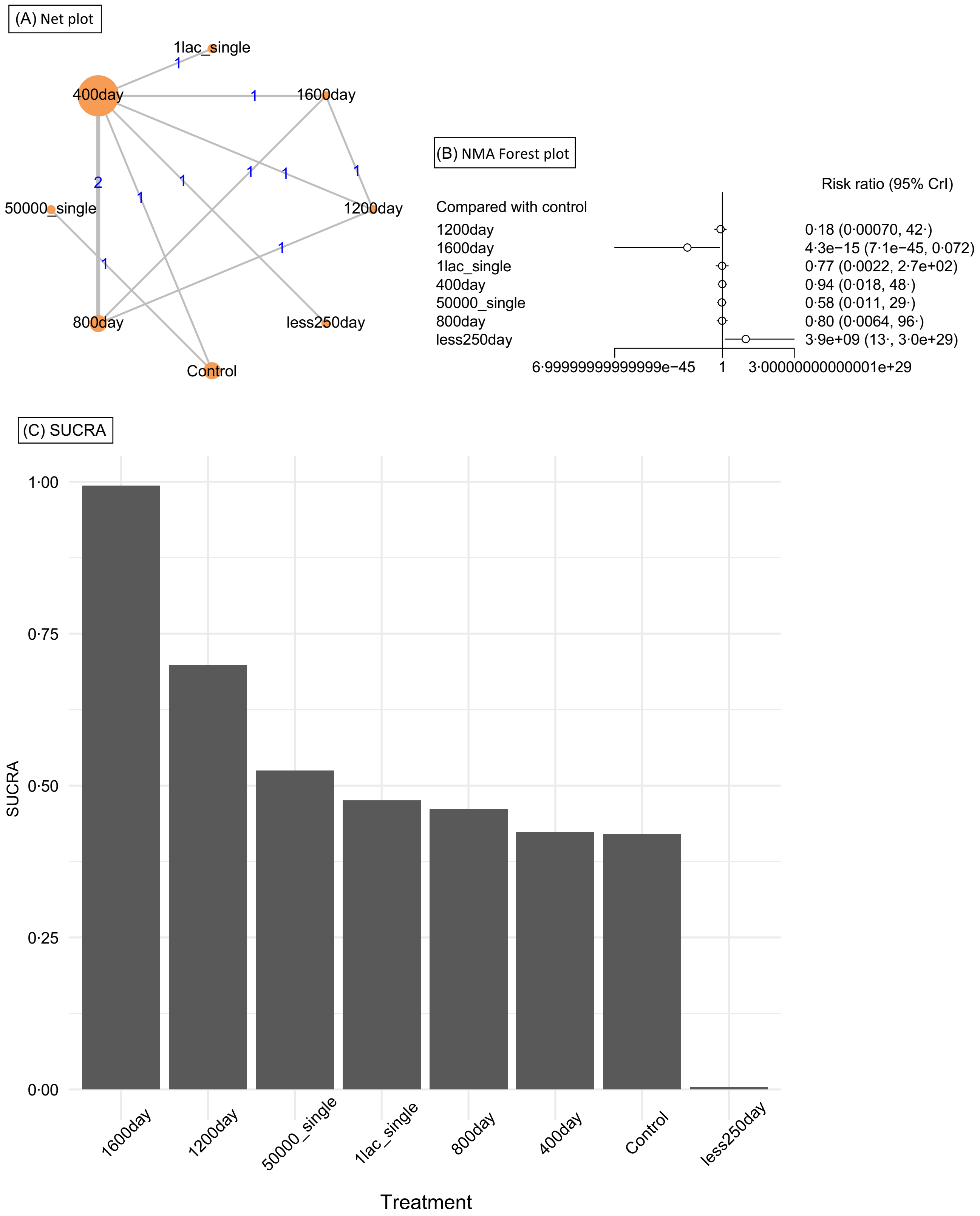

Fig. 3. Network geometry plot, NMA forest plots, and SUCRA values with the 'control group' as the common comparator for the primary outcome of the proportion of infants with vitamin D insufficiency at 0–6 months.

VDI. Only one trial reported this outcome[57]. 1200day was better than 400day in reducing the proportion of infants with VDI at 7–12 months (online Supplementary eFigure 33).

VDD. Three trials evaluating five vitamin D regimens reported this outcome (online Supplementary eFigures 34–36). 800day and 1200day were better than 400day and less250day in reducing VDD at 7–12 months.

Severe VDD. Two trials evaluating five interventions reported this outcome (online Supplementary eFigures 37–38). None of the babies in any trial had severe VDD.

Hypercalcaemia. One trial comparing 400day *v.* 1200day did not find a difference in hypercalcaemia between the groups (online Supplementary eFigure 39)[57].

BMD. One trial comparing less250day, 400day, 600day and 800day did not find a difference in BMD between the groups (online Supplementary eFigure 40)[72].

Clinical rickets. One trial comparing 400day *v.* control did not find a difference in rickets between the groups (online Supplementary eFigure 41)[39].

Other outcomes

Neurodevelopmental outcomes. Two trials comparing 1400week *v.* control and 400day *v.* 1200day found no difference in the outcome between the groups (online Supplementary eFigure 42)[65,70].

Infection episodes. Five trials evaluating 400day, 1200day and control groups found no difference in the incidence of pneumonia, diarrheal illness, duration of hospitalisation or antibiotics use between the groups[39,41,57,60,70].

Allergies. One trial comparing 400day *v.* 1200day did not find a significant difference between the groups in food or aero-allergen sensitisation or wheezing[56]. Cow's milk protein allergy was higher in 1200day group. Another trial comparing 400day *v.* control did not find a difference in eczema or wheezing between the groups[60].

Discussion

The comparison of various infant vitamin D supplementation regimens during lactation is important in seeking best evidence-based practice guidelines to inform public policy. No evidence-based consensus exists on the optimal dosage and duration of vitamin D supplementation in infants[73–75]. This systematic review and NMA included twenty-nine trials and evaluated the efficacy and safety of fourteen different strategies of vitamin D supplementation in term and late preterm infants.

Zittermann and colleagues in a systematic review had reported increased serum vitamin D concentrations from baseline among infants with daily vitamin D supplementation ranging from as low as 100 IU to as high as 1600 IU[76]. Tan and colleagues in a Cochrane review concluded that vitamin D at 400 IU/d may increase the mean vitamin D concentrations[27]. Beauchesne and colleagues in a complex systematic review including both randomised controlled trials and observational studies showed a dose-dependent increase in vitamin D concentrations with daily supplementation, with the evidence certainty being moderate. The results of this review showed that every 100 IU/d increase in daily dose increased the mean vitamin D concentrations by 0·768 ng/ml[77].

Our systematic review utilised an NMA to study the efficacy and safety of different dosage regimens. Wherever the network was not connected, we had reported the direct evidence from pairwise meta-analyses. We found that most daily vitamin D regimens (400 IU, 600 IU, 800 IU, 1000 IU, 1200 IU and 1600 IU) and 50 000 IU/dose for 2 months significantly improved the mean serum vitamin D concentrations at 0–6 months compared with no treatment group, though the certainty of evidence varied from very low to high.

The Cochrane review reported that though vitamin D supplementation in term breastfed infants may significantly reduce the incidence of VDI (<20 ng/ml), there was insufficient evidence for its effect on the outcome of VDD (<12 ng/ml)[27]. We found low certainty evidence for daily supplementation of vitamin D at 1600 IU/d in decreasing the proportion of infants with VDI (defined as <30 ng/ml) at 0–6 months when compared with no treatment. Similarly, daily supplementation of 1600 IU/d also decreased the proportion of infants with VDD (defined as <20 ng/ml).

We found only limited data on the effect of vitamin D supplementation on clinically important outcomes such as bone mineral density, clinical rickets and hypocalcaemia. Similarly, the data on mortality and neurodevelopmental outcomes were sparse. A few trials evaluating allergies and infection episodes did not find a significant effect of vitamin D supplementation.

Whenever a drug or treatment regimen is being evaluated, one should also look into the possible adverse events. Zitterman and colleagues concluded that hypervitaminosis D (25(OH) D > 100 ng/ml) was seen in less than 2·5 % of infants with daily vitamin D at doses between 200 and 1200 IU/d[76]. However, vitamin D supplementation at 1600 IU/d was associated with a higher incidence of hypervitaminosis D. Similarly, Brustard and colleagues in their systematic review reported a significantly increased risk of hypervitaminosis (>100 ng/ml) in the high daily vitamin D supplementation group (>1000 IU/d) compared with 400 IU/d or placebo groups[29]. Most of the previous reviews did not find a significant increase in hypercalcaemia with any of the vitamin D supplementation regimens. In our NMA, vitamin D regimens of 1600 IU/d, 1200 IU/d, 800 IU/d, 100 000 IU single dosage and 50 000 IU/ dose for two consecutive months were found to increase the risk of hypervitaminosis D. Similarly, the daily regimens of 1600 IU, 1200 IU and 800 IU increased the risk of hypercalcaemia. Hence, though SUCRA ranked 1600 IU/d as the best intervention to increase serum vitamin D concentrations and reduce VDI and VDD, any dosage ≥800 IU/d may not be recommended due to the risk of hypervitaminosis D and hypercalcaemia. In specific scenarios, a higher dosage of ≥800 IU/d may be warranted. In such situations, we advise to periodically monitor for hypervitaminosis and hypercalcaemia.

Though routine supplementation among infants has been shown to increase vitamin D levels, there is a lack of evidence as to whether it prevents adverse clinical outcomes such as clinical rickets. In our review, all except one study reported zero incidence of clinical rickets in both the control and intervention groups. Only one case of clinical rickets was reported in the control group of a study that evaluated weekly supplementation of vitamin D[49]. This is in line with the results of previously published reviews in the literature[27,76].

The baseline status of maternal vitamin D affects the baseline vitamin D status of the neonate and also the vitamin D content of the breast milk of a lactating mother. Vitamin D as a preprohormone starts variably in neonates based on maternal vitamin D status during pregnancy with the superimposed status of that mother during lactation. It may be logical to assume that an infant born to a mother with VDD, might require higher doses of daily vitamin D supplementation than a mother with vitamin D replete stores. If we addressed the inherent problem first in the mother and achieved global maternal sufficiency, then infant supplementation would no longer be necessary. However, very few studies have looked into the baseline maternal vitamin D status and correlated with the optimal vitamin D supplementation regimen for their infants. To test, this hypothesis, we did a post hoc sensitivity analysis based on the baseline neonatal vitamin D status. Interestingly, infants with baseline Vitamin D levels in the deficiency range (<20 ng/ml) had a greater mean vitamin D level with all supplementation regimens compared with those with insufficiency range (<30 ng/ml) with the different supplementation regimens.

Our study had several limitations. First, several effect modifiers could have affected our estimates. These include vitamin D status of mother, antenatal and postnatal vitamin D supplementation to mother, baseline level of vitamin D in the infant, exclusive breastfeeding or formula feeding, timing of introduction of complementary feeding, type of complementary feeds and the duration of exposure to sunlight. We could not adjust for the effect of these as the included studies had not uniformly reported on these parameters. Second, studies have shown that the method used to measure vitamin D can also affect the results of vitamin D concentrations, which was not evaluated in this NMA. Finally, we did not analyse some of the a-priori decided secondary outcomes because of limited data.

In conclusion, supplementation at ≤250 IU/d and 1400 IU/week may not increase vitamin D concentrations and hence may not be recommended. Any dosage regimen ≥400 IU/d may increase the serum vitamin D concentration compared to no treatment. A dosage of 800–1600 IU/d may result in hypervitaminosis D and hypercalcaemia. Hence, a dosage regimen of 400 to 600 IU/d may be the most appropriate when considering the risk–benefit aspect. We would like to caution the readership that the conclusions derived from this NMA are predominantly based on serum vitamin D concentrations, hypervitaminosis and hypercalciuria as the available data on clinical outcomes is sparse. We need adequately powered trials evaluating clinical outcomes.

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N. G., T. A., V. R., S. T. and B. Y. conceptualised and prepared the study protocol. A. K. P., T. A., S. T., B. Y., T. B., N. B. S. and U. D. searched the literature and extracted relevant information. T. A. and V. R. curated the data and did the statistical analysis. T. A., R. S., B. Y. and N. G. synthesizsed the data and developed the initial draft of the manuscript. All authors revised successive drafts of the paper and approved the final draft. N. G. supervised the overall study and is the guarantor of the review.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114524001685

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