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

Thangaraj Abiramalatha^{1,2}, Viraraghavan Vadakkencherry Ramaswamy³, Sivam Thanigainathan⁴, Bharti Yadav⁵, Tapas Bandyopadhyay⁵, Nasreen Banu Shaik³, Usha Devi⁶, Abdul Kareem Pullattayil⁷, Rohit Sasidharan⁸ and Neeraj Gupta⁹*

 1 KMCH Institute of Health Sciences and Research (KMCHIHSR), Coimbatore, Tamil Nadu, India 2 KMCH Research Foundation, Coimbatore, Tamil Nadu, India

³Department of Neonatology, Ankura Hospital for Women and Children, Hyderabad, India

⁴Department of Neonatology, All India Institute of Medical Sciences, Bibinagar, India

⁵Department of Neonatology, Dr Ram Manohar Lohia Hospital & Post Graduate Institute of Medical Education and Research, New Delhi, India

⁶Department of Neonatology, All India Institute of Medical Sciences, Bhubaneswar, India ⁷Queen's University, Kingston, Canada

⁸Department of Neonatology, All India Institute of Medical Sciences, Guwahati, India ⁹Department of Neonatology, All India Institute of Medical Sciences, Jodhpur, India

(Submitted 3 January 2024 - Final revision received 28 May 2024 - Accepted 1 July 2024 - First published online 16 September 2024)

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.

^{*} **Corresponding author:** Dr Neeraj Gupta, email neerajpgi@yahoo.co.in **PROSPERO registration number:** CRD42022360454

441

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 healthyterm 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 prioridecided 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 $2 \cdot 0^{(34)}$. 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

442

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 O-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
2 3	Alonso 2011 Atas 2013	Spain Turkey	high income upper middle income	400day/Control less250day/400day	41/47 75/64	2 weeks to 1 year Birth to 4 mon	Term Term	Mixed Breastfeeding	Electrochemiluminescent assay High-performance liquid chromatography
4 5 6	Chandy 2016 Feliciano 1994 Gallo 2013, Wicklow 2015, Weiler 2022	India China Canada	lower middle income upper middle income high income	400day/Control less250day/400day 400day/800day/ 1200dav/1600day	47/54 85/85 39/39/38/16	2–4 days to 9 mon 3–5 days to 6 mon Within 1 mon to 12 mon	Both Term Term	Mixed Mixed Mixed	Radioimmunoassay Not mentioned Radioimmunoassay
7	Greer 1981, Greer 1982	USA	high income	400day/Control	09-/09	2-3 weeks to 12 weeks	Term	Breastfeeding	Competitive protein-binding assav
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 11	Huynh 2016 Kumar 2011, Trilok-kumar 2015	Australia India	High income lower middle income	400day/50000single 1400week/Control	36/34 1039/1040, 446/466	Birth to 4 mon 7 days to 6 mon	Term Term	Mixed Mixed	Chemiluminescent immunoassay Radioimmunoassay
12 13	Lin 2022 Madar 2008	China Norway	upper middle income High income	400day/Control 400day/Control	46/46 22/29	10 days to 4 mon 6 weeks to 7 weeks after initiation	Term Not given	Breastfeeding Mixed	Chemiluminescence 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 16	Pacheco-Acosta 2020 Ponnapakkam 2010	Chile USA	High income High income	1lacsingle/400day less250day/Control	36/29 08-/09	single dose at 1 mon Birth to 6 mon	Term Term	Breastfeeding Breastfeeding	Radioimmunoassay Immuno Diagnostic Systems (immunoassay)
17 18	Razaghi 2022 Rosendahl 2018, Rosendahl 2019, Hauta-Alus 2020, Sandboge 2023	Canada Finland	high income High income	1000day/400day 400day/1200day	49/49 489/486, 402/	1 mon till 12 mon 241w0e (eHkasutoa- 2Alyuesa2rs020)	Term Term	Breastfeeding Mixed	Chemiluminescent immunoassay 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 22	Rueter 2018 Shakiba 2010	Australia Iran	high income lower middle income	400day/Control less250day/400day/ 50000_2mon	97/98 19/26/30	Within 28 days to 6 mon 15–30 d after birth to 6 mon	Term Term	Mixed Breastfeeding	Chemiluminescent immunoassay Chemiluminescent immunoassay
23 24	Siafarikas 2010 Specker 1992	Germany China	high income upper middle income	less250day/500day less250day/400day	14/14 99/88	Birth to 6 weeks 3–5 days to 6 mon	Term Term	Breastfeeding Mixed	Radioimmunoassay Competitive protein-binding assay
25 26 27 28	Trilok-kumar 2012 Tuovinen 2021 Yadav 2022 Zeghoud 1994	India Finland India Algeria	lower middle income high income lower middle income lower middle income	1400week/Control 400day/1200day 400day/800day 6lac_single/2lac_single/ 1lac_3mon	164/187 404/397 50/49 30/15/15	7 days to 6 mon 2 weeks to 24 mon 3–5 days to 14 weeks Once at birth	Term Term Term Term	Mixed Breastfeeding Breastfeeding Not mentioned	Radioimmunoassay Fully automated immunoassay Chemiluminescent immunoassay 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

444 T. Abiramalatha et al. (A) Net plot 1600day 1lac_single 1400week 400day 2 (B) NMA Forest plot 1200da Mean difference (95% Crl) 50000_2mon Compared with control 1000day 18. (7.0, 28.) 1200day 34. (23., 44.) 1000day 1400week 7.6 (-4.9, 20.) 48· (37·, 59·) 1600day 14. (0.37, 28.) 50000 single 1lac_single 400day -0-15. (10., 20.) 50000_2mon 30. (15., 44.) less250day 50000_single 8.9 (-1.0, 19.) 500day 11. (-13., 35.) 500day 18. (5.7, 31.) 600day 800day -0 22. (13., 30.) Control less250day 6.5 (-1.9, 15.) 600day 1 800day -ż0 60 Ó (C) SUCRA 1.00 0.75 SUCRA 0.20 0.25 0.00 5000 2000 5000 single 1855250day 1180 single AOONEEX 1600day 1200day 10000000 800484 600084 400dat 500027 control

Treatment

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)

https://doi.org/10.1017/S0007114524001685 Published online by Cambridge University Press

NS British Journal of Nutrition

Nutrition
of
Journal
British
X

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

Vitamin D prophylaxis

445

https://doi.org/10.1017/S0007114524001685 Published online by Cambridge University Press

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 metaanalyses 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⁾

(Y)

T. Abiramalatha et al.

Table 2. GRADE certainty of evidence for primary outcomes

Comparison of evidence Cut ovidence Vtamin D levels 0-6 months		Direct ovidence – cortainty	Indiract avidance –	Network meta-a	nalysis RR (Crl)	Cortainty of
Vibania Diversis USEN LOW:1 - 245 -<	Comparison	of evidence	certainty of evidence	RR	Crl	evidence
1000day v. 400day VERV LOW:1 - 2.45 -6.69, 1160 HIGH Hae, single v. 400day VERV LOW:1, + - -0.9 -12.49, 113.4 VERV LOW:1, + 1200day v. 400day VERV LOW:1, + - 4.61 -17.19, 27.36 VERV LOW:1, + 1200day v. 400day MODEFATES HIGH 185.5 100, 27.06 VERV LOW:1, + 1200day v. 400day MODEFATES HIGH 13.45 3.80, 42.27 HIGH 1000day v. 600day MODEFATES HIGH 13.45 3.80, 42.27 HIGH 400day v. 500do, Yon MODEFATES HIGH -665 -13.45, 03.2 HIGH 400day v. 500do, Zroon LOWI,1 HODEFATE 14.88 2.72.69, 14.27 LOWI 400day v. 500do, Xino LOWI,1 LOWI,1 -14.88 2.82, 12.62 HIGH 400day v. 500do, Xino LOWI,1 LOWI,1 -14.88 2.42, 12.62 HIGH 400day v. 500do, Xino LOWI,1 LOWI,1 -14.88 2.42, 12.62 HIGH 400day v. 500do, Xino	Vitamin D levels 0–6 month	18				
1400week v. Confrol HIGH - 76 -098 -1284 1134 VERY LOW1; 1 Stoday v. Lesz50day VERY LOW1; 2 - 481 -1718 27.08 VERY LOW1; 1 Stoday v. 400day MODEFATES HIGH 1851 10.27.08 VERY LOW1; 1 1800day v. 400day MODEFATES HIGH 38.48 23.08 23.08 23.08 23.08 23.08 23.08 23.08 23.08 23.08 10.01 36.39 LOW1 400day v. 400day MODEFATES HIGH -668 -13.45 0.22 HIGH 400day v. 500day LOW1 LOW1 -14.89 -27.89 -1.27 LOW1 400day v. 500day LOW1 MODEFATES 86.99 2.15.55 MODEFATES 23.48 LOW1 10.04 19.43 19.42 11.04 19.43 10.43 19.43 10.04 19.43 10.04 19.43 10.04 19.43 10.04 19.43 10.04 19.43 10.04 19.43 10.04 19.43	1000day <i>v</i> . 400day	VERY LOW*,†	-	2.45	-6·59, 11·59	VERY LOW*,†
Iale_single x 400day VERY LOW1; ± - -09 -1294.11.34 VERY LOW1; ± 1200day x 400day MODERATES HIGH 1851 10.27.06 HIGH 1200day x 400day MODERATES HIGH 1385 338.24.27 HIGH 1600day x 400day MODERATES HIGH 1385 338.24.27 HIGH 1600day x 1200day MODERATES HIGH 246 124.51.33 HIGH 1600day x 1200day MODERATES HIGH 246 124.51.33 HIGH 400day x 50000_amon LOW1 LOW1 1548 124.51.55 MODERATES 200day x 50000_amon LOW1 LOW1 148.3 234.21.62 LOW5; 1 400day x 50000_amon LOW1 LOW1, 1 148.8 24.82.8 LOW5; 1 200day x 50000_amon LOW1, 1 LOW1, 1 -148.8 LOW5; 1 HIGH 200day x 50000_amon LOW1, 1 LOW1, 1 -148.8 LOW5; 1 HIGH 200day x 50000_amon LOW1, 1 LOW1, 1 -148.	1400week v. Control	HIGH	_	7.6	-0.98, 16.07	HIGH
500day v. EleszSoday VERY LOW1; + - 4.81 -17.9.27.06 VERY LOW1; + 1600day v. 400day MODERATES HIGH 32.46 23.06.22.88 HIGH 600day v. 400day MODERATES HIGH 32.46 23.06.22.88 HIGH 600day v. 200day MODERATES HIGH 32.46 23.06.39 LOW1 600day v. 200day LOW1 LOW1 23.18 10.01.36.39 LOW1 600day v. 500day HIGH LOW1 23.16 10.42,19.15 MODERATE' 600day v. 100day v. 500doy HIGH LOW1 -4.48,58.28 LOW5,* 1200day v. 600day VERV LOW1,** LOW1 -1.48,58.24.22 HIGH 1200day v. 600day WODERATEI A.63,16.67 MODERATES 1200day v. 600day MODERATEI A.63,16.67 MODERATES 1200day v. 1200day HIGH HIGH 14.83 5.67,2371 MODERATES 1200day v. 1200day - VERV LOW1,* -16.84 5.67,2371 MODERATES 1200day v. 120	1lac_single v. 400day	VERY LOW†,‡	_	-0.9	–12.94, 11.34	VERY LOW†,‡
1200day & 400day HIGH HIGH 1351 10.2706 HIGH 1600day & 400day MODERATES HIGH 1395 388.247 HIGH 1600day & 1200day MODERATES HIGH 1395 388.247 HIGH 400day & 200day HIGH HIGH 1001.3639 LOWt LOWt 400day & 200day HIGH HIGH 168 -134.032 HIGH 400day & 200day HIGH HIGH -668 -134.032 HIGH 400day & 200day HIGH HIGH -148 -269.147 LOWS 400day & 200day HIGH HIGH -335 -144.768 LOWS 400day & 200day HIGH HIGH -335 -144.1768 LOWS 50000_single Control LOWI,** MODERATES 24.88 124.371 MODERATES 50000_single Control LOWI,** MODERATES 24.89 144.1165 100049 100049 100049 100049 100049 144.4116 100049	500day v. less250day	VERY LOW†,‡	-	4.81	-17·19, 27·36	VERY LOW†,‡
BODDay V. 400day MODERATES HIGH 32.46 23.06.228 HIGH BODDay V. BODDAY LOW1 LOW1 23.95 3.88,24.27 HIGH BODDAY V. BOSZBOAD LOW1 LOW1 23.95 3.88,24.27 HIGH BODDAY V. Control HIGH HIGH 15.69 10.01,19.69 HIGH BODDAY V. Control HIGH LOW1 LOW1 HIGH 16.69 10.01,19.69 HIGH BODDAY V. Control LOW1 LOW1 HIGH 11.89 24.32,14.2 HIGH BODDAY V. BODDAY LOW1 LOW1 HIGH 11.88 2.34.2 HIGH 200day V. BODDAY HIGH HIGH 11.88 2.34.2 HIGH 200day V. BODDAY MODERATEI 6.32 -4.03.16.67 MODERATES 200day V. BODDAY HIGH HIGH 11.88 2.34.2 HIGH 1000day V. BODDAY HIGH HIGH 13.8 HIGH 14.84 MODERATES 1000day V. BODDAY HIGH <td< td=""><td>1200day v. 400day</td><td>HIGH</td><td>HIGH</td><td>18.51</td><td>10, 27.06</td><td>HIGH</td></td<>	1200day v. 400day	HIGH	HIGH	18.51	10, 27.06	HIGH
160day N200ERATES HIGH 1955 38.8 (24.77 HIGH 400day K80day HIGH -666 -13.45 0.20 HIGH 400day LOWL 15.18 10.49, 10.81 10.49, 10.81 HIGH 400day LOWL MODERATE* 8.68 2.15.55 MODERATE* 400day LOWL* VERV LOWL** -11.82 20.63.22.49 LOWS* 800day VERV LOWL** LOWL* -14.44, 766 LOWS* HIGH 400day VERV LOWL** LOWL* WERV LOWS* HIGH 11.88 2.43, 216.2 LOWS* 500day JEONAY VERV LOWL** LOWL* MODERATE 8.38 14.44, 766 LOWS* 500day JEONAY LOWL** MODERATE 8.38 14.47, 766 LOWS* 500day JEONAY MODERATE LOWL** 4.63 5.67, 2.271 MODERATE 500day JEONAY JEONAY MODERATE 14.463 5.64, 3.3 VERY LOWS* <	1600day <i>v</i> . 400day	MODERATE§	HIGH	32.46	23.06, 42.28	HIGH
50000_zmon v. less250day LOW1 LOW1 23.18 100.19.86.39 LOW1 400day v. Control HIGH LOW1,1 15.18 10.49.19.81 HIGH 400day v. Control LOW1,1 LOW1,1 LOW1,1 15.18 10.49.19.81 HIGH 400day v. S0000, 2mon LOW1,1 LOW1,1 LOW1,1 11.82 27.55.2 LOW1,1 400day v. S0000, 2mon LOW1,1 LOW1,1 11.82 0.63, 23.49 LOW1,1 120058/s0504 LOW1,1 HIGH <	1600day v. 1200day	MODERATE§	HIGH	13.95	3.88, 24.27	HIGH
400day k 200day HIGH HIGH -6.66 -13.46, 0.32 HIGH 400day k 1ess250day LOWI,1 MODERATE** 8.69 2, 15.55 MODERATE* 400day k 1ess250day LOWI,1 MODERATE** 8.69 2, 15.55 MODERATE* 800day k 1ess250day LOWI,** 11.82 0.63, 22.44 LOWI,** 1200day k 1ess250day LOWI,** 13.82 0.43, 22.42 LOWI,** 1200day k 1ess250day LOWI,** HIGH 11.82 0.43, 22.42 LOWI,** 1200day k 1000ERATEI HIGH 11.82 24.56 13.83, 35.62 HIGH 1200day k 1000ERATEI MODERATE 14.63 567, 23.71 MODERATE 1000day k 1000day HIGH MODERATE* 14.63 567, 33.71 MODERATE 1000day k 1000day LOWI,** MODERATE* 14.43 564, 43.93 VERY LOW*,* 1000day k 1000day LOWI,** 14.64 HIGH 10.03 -3.14, 2.24 VERY LOW*,* 1000day k 1000day 10.000day k 1000day -	50000_2mon v. less250day	LOW‡	LOW‡	23.18	10.01, 36.39	LOW‡
400day V. Control HIGH LOWI,1 15-18 10-49, 19-81 HIGH 400day V. Gartol LOW1 MODERATE** 8-99 2, 15-55 MODERATE* 400day V. 50000.2mon LOW1 VERY LOW1,** 11-32 0-53, 22-49 LOW1 400day V. SESCOBY LOW1 VERY LOW1,** 1-33 -1-44.8 828 LOW5,*† 400day V. SESCOBY VERY LOW1,** LOW1 -333 -1-44.4 7.66 HONF** 400day V. 50000.single MODERATEII MODERATES 24-48 136, 35-62 HIGH MODERATES 24-48 136, 35-62 HIGH MODERATES 24-58 136, 35-62 HIGH HODERATE* LOW1,1 14-63 5-67, 23-71 MODERATE* LOW1,1 14-64 -44-41, 156 LOW5,1* LOW1,1 14-64 4-44, 4, 84 VERY LOW1,1 10-03 -314, 42.4 VERY LOW1,1 10-03 -314, 43, 44 VERY LOW1,1 10-03 -314, 84.4 VERY LOW1,1 1000day V.	400day <i>v</i> . 800day	HIGH	HIGH	-6.66	–13·45, 0·32	HIGH
400day (: ises250day LOWI,1 MODERATE** 8-99 2.1555 MODERATE* 800day (: ises250day LOWI,** LOWI,** 14-86 -27.69, -12.7 LOWI,** 800day (: ises250day LOWI,** VERY LOW1,** 13-82 0-44.56, 82.8 LOWI,** 1200day (: ises250day MODERATE*I 13-88 2-14.45, 82.8 LOWI,** 1200day (: ises250day MODERATE*I -33.2 -14.44, 76.6 MODERATE*I 800day (: ises250day MODERATE*I LOWI,** -33.8 -14.44, 76.6 MODERATE*I 800day (: ises250day MODERATE*I LOWI,** -14.83 56.7 2.77.8 800day (: ises250day MODERATE** LOWI,** -16.08 -28.47.1 MODERATE*I 800day (: ises250day MODERATE** LOWI,** -16.08 -36.47.24 VERY LOW;* 1000day (: ises250day MODERATE*I LOWI,** -14.83 56.7.28 VERY LOW;* 1000day (: ises250day -27.69, -12.67.23 MODERATE*I 10.03 -3.14.234 VERY LOW;* <	400day v. Control	HIGH	LOWII,¶	15.18	10·49, 19·81	HIGH
400day v. 50000_2mon LOW‡ LOW‡ — 14-58 — 27-69127 LOW‡ 500day v. 800day VERY LOW†," LOWN," — 332 — 14-85 52.84 LOWS,"† 500day v. 800day VERY LOW†," LOWN," — 332 — 14-85 52.84 LOWS,"† 400day v. 600day VERY LOW†," LOWN," — 333 — 14-48, 56.87 LOWS,"† 400day v. 600day VERY LOWT," LOWN," MODERATEI 632 -403, 16.67 MODERATES 400day v. 500day HGM MODERATES 24.86 138, 352.42 HGM NOPERATES 500day v. Isas250day MODERATES 44.68 136, 353.43 VERY LOW; T 1003 — 344.34 VERY LOW; T 1003 — 344.34 VERY LOW; T 10004ay v. 50000_2mon — VERY LOW; T 10004ay v. 50000_2mon — VERY LOW; T 33 — 148.1854 VERY LOW; T 10004ay v. 50000_2mon — VERY LOW; T -153.87.84 VERY LOW; T 10004ay v. 50000_2mon — VERY LOW; T -16.81.74.31.84 VERY LOW; T 100004ay v. 50000_2mon — VERY LOW; T	400day <i>v</i> . less250day	LOWII,¶	MODERATE**	8.59	2, 15.55	MODERATE*†
BODday V. Iess250day LOWI," VERY LOW1," 1192 0-68, 23-49 LOWS,"† 1200day V. 800day VERY LOW1," -33 -1445, 628 LOWS,"† 1200day V. 800day VERY LOW1," LOWII," -338 -1444, 766 LOWS,"† 400day V. 50000_single MODERATEII MODERATEII 632 -403, 1667 MODERATES 1600day V. 800day HIGH MODERATEII 632 -467, 1944 MODERATES* 1600day V. 800day HIGH MODERATES* 24.88 138, 35.62 HIGH 1600day V. 800day VERY LOW1,* LOWII,1 -66 -147, 194.44 MODERATES* 1600day V. 1602day - VERY LOW1,* 1003 -314, 234 VERY LOW1,* 1000day V. 1602day - VERY LOW1,* 30.64 10.88, 39 VERV LOW1,* 1000day V. 1602day - VERY LOW1,* 32.67 VERV LOW1,* 10.00000000000000000000000000000000000	400day v. 50000_2mon	LOW‡	LOW‡	-14.58	–27·69, –1·27	LOW‡
BUDday V, BUDday VEHY LOW; " LOWI," -3.82 -1.485, 5.28 LOWS," T BUDday V, BUDday VEHY LOW; " LOWI," -3.35 -1.44.7, 66 LOWS," BUDday V, S000, Single DOERATEII 6.32 -4.03, 16.67 MODERATEIS 5.23 -1.43, 16.67 MODERATES BUDday V, S000, Single LOWI," MODERATES 24.83 13.67, 55.27 HOIM BUDday V, BUDday HIGH 1.68 22.41, 21.07 HOIM ANDERATES BUDday V, S000, Single LOWI," MODERATEI 68.22 -4.03, 16.67 WOERATES BUDday V, BUDday HEY LOW, T -16.06 -2.861, -3.67 VERY LOW; T BUDday V, 1400/BUDday - VERY LOW; T 10.03 -3.14, 23.43 VERY LOW; T 1000day V, 1400/BUDO, 2000 and - VERY LOW; T -1.21 -2.784, 4.17 VERV LOW; T 1000day V, 1400/BUDO, 2000 and - VERY LOW; T -1.23, 13.38 VERY LOW; T 1000day V, 1400/BUDO, 2000 and - VERY LOW; T -1.68, 31.78 VERY LOW; T	600day v. less250day	LOWII,**	VERY LOW†,**	11.92	0.63, 23.49	LOW§,*†
12008ay V 8008ay FIGH HIGH 11.88 2.34, 21.82 FIGH 400day V 8000ay WENY LOW1," LOWIL] -3.35 -14.44, 7.66 LOWS," 400day V 8000ay MODERATEII MODERATEI 6.32 -4.03, 16.67 MODERATES 1800day V 800day HIGH MODERATES 24.48 136, 35.62 HIGH 1800day V 800day HIGH MODERATES 24.48 156, 35.62 HIGH 1800day V 800day HIGH MODERATES 24.48 156, 36.72 HIGH 1800day V 1800day - VERY LOW1,1 -166 -28.61, -357 VERY LOW1,1 1000day V 1400me4k - VERY LOW1,1 -376 -41.21.94 VERY LOW1,1 1000day V 1000day 1 - VERY LOW1,1 -767 -41.23.18 VERY LOW1,1 1000day V 1000day 1 - VERY LOW1,1 -16.23 -16.23.11.5 VERY LOW1,1 1000day V 1000day 1 - VERY LOW1,1 -4.25 -16.83.11.5 VERY LOW1,1 1000day V 1000day 1 - <td>600day v. 800day</td> <td>VERY LOW[†],**</td> <td>LOWII,**</td> <td>-3.32</td> <td>-14.85, 8.28</td> <td>LOW§,*†</td>	600day v. 800day	VERY LOW [†] ,**	LOWII,**	-3.32	-14.85, 8.28	LOW§,*†
40.039, V. 600039, Terr VEHY LDWT," LDWB," -335 -14.44, 766 LDWB," 50000_single VCONTO LOWI," MODERATEII 632 -403, 16-67 MODERATES 50000_single v. Control LOWI," MODERATEI 892 -167, 19-46 MODERATES 50000_single v. Control LOWI," MODERATES 24-58 138, 36-62 HIGH 50000_single v. Control MODERATET* LOWI," -16-66 -14-41, 156 LUWS," 10004ay v. 1200day - VERY LOW', T -16-08 -3-314, 244 VERY LOW', T 10004ay v. 1200day - VERY LOW', T 33 -11-88, 18-44 VERY LOW', T 10004ay v. 1200day - VERY LOW', T -72-75 -4-13, 21-92 VERY LOW', T 10004ay v. 50000_single - VERY LOW', T -0-92 -15-23, 13.8 VERY LOW', T 10004ay v. 100004ay v. 100004ay v. 10004ay v. 10004ay v. 10004ay v. 10004ay v.	1200day v. 800day	HIGH	HIGH	11.88	2.34, 21.62	HIGH
Budday v. Soudol. Single MODERATEII 6-32 -4-03. 16-57 MODERATES 1600day v. 800day HIGH MODERATES 24-68 138, 36-62 HIGH 1600day v. 800day HIGH MODERATES 24-68 138, 36-62 HIGH 1600day v. 168250day VERY LOW1,* LOWII,* -66 -14-41, 156 LOWS,** 1000day v. 168250day VERY LOW*,† 10-03 -314, 23-4 VERY LOW*,† 1000day v. 168250day - VERY LOW*,† 30-04 16-85, 43-39 VERY LOW*,† 1000day v. 1000day - VERY LOW*,† 12-19 -2748, 41.7 VERY LOW*,† 1000day v. 1000day v. 50000_singie - VERY LOW*,† 67.7 -16.8 7.85. 72.8 VERY LOW*,† 1000day v. 50000_singie - VERY LOW*,† 10-04.2 27.8 15.8 7.8 VERY LOW*,† 1000day v. 600day - VERY LOW*,† 17.6 7.85.27.86 VERY LOW*,† 1000day v. 600day - VERY LOW*,† 17.6 7.85.27.86 VERY LOW*,†	400day v. 600day	VERY LOWT, ^^		-3.35	-14.44, 7.66	LOW§,^^
DUDD_ENTER MODERATES 292 -167, 1946 MODERATES Broday & Booday MODERATES 2458 138, 362 HIGH Broday & Booday - VERY LOW;1 -1608 -314, 24 VERY LOW;1 1000day v. 1200day - VERY LOW;1 30-4 168, 43.9 VERY LOW;1 1000day v. 500do_zmon - VERY LOW;1 -1219 -27.84, 417 VERY LOW;1 1000day v. 500do_zmon - VERY LOW;1 -627 -413, 21.92 VERY LOW;1 1000day v. 500day - VERY LOW;1 -0.92 -153, 33.8 VERY LOW;1 1000day v. Booday - VERY LOW;1 -4425 153, 728 VERY LOW;1 1000day v. Booday - VERY LOW;1 -425 153, 728 VERY LOW;1 1000day v. Booday<	400day v. 50000_single		MODERATEI	6.32	-4.03, 16.67	MODERATES
Booday V, Booday Inisin MUDERATE' LOWIN_1 24:36 13:6, 35:62 INISIN Control V, less250day VERY LOW', 1 LOWIN_1 -6.6 -14:41, 1.66 LOWS," 1000day V, less250day VERY LOW', 1 -10.68 -28:61, -36:7 VERY LOW', 1 1000day V, less250day VERY LOW', 1 10.03 -6.68 -28:61, -36:7 VERY LOW', 1 1000day V, lacs200day - VERY LOW', 1 30:04 16:96; 43:39 VERY LOW', 1 1000day V, lacs000_smole - VERY LOW', 1 -17:19 -27:84, 417 VERV LOW', 1 1000day V, 50000_smole - VERY LOW', 1 627 -16:33, 13:8 VERV LOW', 1 1000day V, 50000_single - VERY LOW', 1 17:03 -01:2, 257 VERV LOW', 1 1000day V, 1400week - VERY LOW', 1 17:03 -01:2, 257 VERV LOW', 1 1000day V, 1400week - VERY LOW', 1 17:03 -01:2, 257 VERV LOW', 1 1000day V, 1400week / - VERY LOW', 1 17:03 -01:2, 257	1000deu u 800deu			8.92	-1.67, 19.46	MODERATES
BODDEY LISSESDIGAY MODERATE F LOWIN LOWIN LOWIN Control v. LISSESDIGAY MODERATE LOWIN CONTROL LOWIN LOWIN CONTROL LOWIN CONTROL LOWIN CONTROL <thlowin CONTROL LOWIN CONTROL</thlowin 	1600day V. 800day		MODERATES	24.58	13.8, 35.62	
Colling V, Elexaboday VERY LOW:1 -1-648 -1-648 -26461 -367 CERY LOW:1 1000day V, 1400week - VERY LOW:1 10.68 -26461 -367 VERY LOW:1 1000day V, 1400week - VERY LOW:1 10.3 -314, 234 VERY LOW:1 1000day V, 1000day - VERY LOW:1 3.3 -11.88, 1854 VERY LOW:1 1000day V, 50000_2mon - VERY LOW:1 8.75 -4.43, 21.92 VERY LOW:1 1000day V, 50000_single - VERY LOW:1 6.27 -16.8, 31.15 VERY LOW:1 1000day V, 600day - VERY LOW:1 -4.25 -15.38, 7.28 VERY LOW:1 1000day V, 600day - VERY LOW:1 17.6 7.58, 27.86 VERY LOW:1 1200day V, 1400week - VERY LOW:1 17.6 7.58, 27.86 VERY LOW:1 1200day V, 1400week - VERY LOW:1 19.41 4.44, 34.3 VERY LOW:1 1200day V, 50000_single - VERY LOW:1 17.63 2.215, 57.54 VERY LOW:1	Control v loss250day			14.63	5.07, 23.71	
1000day V. 1200day - VERT LOW;1 -16.06 -28.0136.0 VERT LOW;1 1000day V. 1000day - VERT LOW;1 30.04 16.95, 43.39 VERY LOW;1 1000day V. 1000day - VERY LOW;1 33.3 -11.88, 18.4 VERY LOW;1 1000day V. 50000_zmon - VERY LOW;1 -12.19 -27.84, 41.7 VERY LOW;1 1000day V. 50000_single - VERY LOW;1 -12.19 -27.84, 41.7 VERY LOW;1 1000day V. 500day - VERY LOW;1 -17.63 7.78.8 VERV LOW;1 1000day V. 500day - VERY LOW;1 -17.6 7.58, 27.86 VERY LOW;1 1000day V. 500day - VERY LOW;1 17.6 7.58, 27.86 VERY LOW;1 1000day V. 500day - VERY LOW;1 11.61 -0.12, 22.57 VERY LOW;1 1000day V. 500day - VERY LOW;1 11.43 44.34.34 VERY LOW;1 1200day V. 500day - VERY LOW;1 19.41 44.44.34.3 VERY LOW;1 1200day V. 500day <td>Londry v. 1000day</td> <td>VERY LOWT,</td> <td></td> <td>-0.0</td> <td>-14.41, 1.50</td> <td></td>	Londry v. 1000day	VERY LOWT,		-0.0	-14.41, 1.50	
Dioday : Houmesk Cent LOW : 1 Dioday : Dioday Cent LOW : 1 Dioday : Dioday Cent LOW : 1 Dioday : Dioday	1000day V. 1200day	-	VERTLOW, J	-10.00	-20.01, -3.07	
Houday F. Houday - VERT LOW:1 300 - Houday A: 300 - VERT LOW:1 1000day F. 50000_zmon - VERY LOW:1 -1219 -27.84.417 VERY LOW:1 1000day F. 50000_zmon - VERY LOW:1 -1219 -27.84.417 VERY LOW:1 1000day F. 500day - VERY LOW:1 -27.92 -136.31.15 VERY LOW:1 1000day F. 500day - VERY LOW:1 -0.92 -15.23.13.33 VERY LOW:1 1000day F. 500day - VERY LOW:1 -4.25 -15.83.72.8 VERY LOW:1 1000day F. 500day - VERY LOW:1 17.6 7.58.27.68 VERY LOW:1 1000day F. 500day - VERY LOW:1 17.6 7.58.27.68 VERY LOW:1 1200day F. 50000_zmon - LOW 120.44.43.43 VERY LOW:1 120.44.43.5 VERY LOW:1 1200day F. 50000_zmon - LOW 120.44.63.5 VERY LOW:1 15.18 15.9.2.87 VERY LOW:1 1200day F. 500day - VERY LOW:1 15.18 15.9.2.87 VERY LOW:1	1600day V. 1400week	-	VERTLOW, J	20.04	-3·14, 23·4	VERTLOW,
1000day v. Ida_single - VERY LOW:1 -3.5 -1186, 16.34 VERY LOW:1 1000day v. 50000_single - VERY LOW:1 -12.19 -27.84, 41.7 VERY LOW:1 1000day v. 50000_single - VERY LOW:1 -62.7 -18.6, 13.15 VERY LOW:1 1000day v. 600day - VERY LOW:1 -0.42 -15.38, 7.28 VERY LOW:1 1000day v. 600day - VERY LOW:1 17.6 7.58, 27.86 VERY LOW:1 1000day v. ises250day - VERY LOW:1 11.03 -0.12.267 VERY LOW:1 1200day v. 1400week - HIGH 26.12 13.14, 38.96 VERY LOW;1 1200day v. 1400week - LOW1;1 19.44 3.96 -11.51, 19.9 VERY LOW3;1 1200day v. 5000_single - VERY LOW1;1 19.48 19.44, 34.3 VERY LOW3;1 1200day v. 5000_single - VERY LOW1;1 19.6 VERY LOW3;1 1200day v. 500day - VERY LOW1;1 22.29 -25.3, 46.3 VERY LOW1;1 1200da	1000day V. 1000day	-		30.04	10.95, 43.39	VERTLOW,
1000day 20002_single - VERY LOW: 1 21.93 21.94 VERY LOW: 1 1000day V. S0002_single - VERY LOW: 6.75 -4.13, 21.92 VERY LOW: 1 1000day V. S0004y - VERY LOW: 1 6.75 3.87 VERY LOW: 1 1000day V. S0004y - VERY LOW: 1 7.6 7.86, 31.15 VERY LOW: 1 1000day V. S0004y - VERY LOW: 1 7.6 7.88, 27.86 VERY LOW: 1 1000day V. S00002 2mon - VERY LOW: 1 13.64, 36.96 VERY LOWS; 1 1200day V. S0000_single - VERY LOW1; 1 18.8 2.87.7 VERY LOW; 1 1200day V. S0004y - VERY LOW1; 1 18.8 2.87.7 VERY LOW1; 1 18.08, 28.77 VERY LOW1; 1 1 1.00049 VERY LOW1; 1 1.00049 VERY LOW1;	1000day V. Hac_single	-	VERTLOW, J	3·3 12 10	-11.00, 10.04	VERTLOW,
Honday V. Booday VEN LOW: 1 627 Hol 2132 VEN LOW: 1 1000day V. Booday - VERV LOW: 1 -092 -15.23, 13.38 VERV LOW: 1 1000day V. Booday - VERV LOW: 1 -4.25 -15.8, 27.86 VERV LOW: 1 1000day V. Control - VERV LOW: 1 17.6 7.58, 27.86 VERV LOW: 1 1200day V. Locotay - VERV LOW: 1 11.03 -012, 22.57 VERV LOW: 1 1200day V. Locotay - VERV LOW: 1 11.03 -012, 22.57 VERV LOW: 1 1200day V. Locotay - VERV LOW1 1 19.41 4.44, 34 VERV LOWS, I 1200day V. Soudo_single - NODERATEI 396 -11.5, 19.69 VERV LOWS, II 1200day V. Soudoay - VERV LOW1, 1 22.29 -2.53, 46.33 VERV LOWS, II 1200day V. Soudoay - VERV LOW1, 1 396 -11.5, 19.69 VERV LOWS, II 1200day V. Soudoay - VERV LOW1, 1 13.37 24.435 MODERATE'I 1200day V. Souday	1000day V. 50000_211011	_	VERTLOW, J	-12.19	-27.04, 4.17	VERYLOW , I
Houday V. Sodday Chin Low 1, 1 D22 -163, 0113 VEIN LOW 1, 1 1000day V. Bodday - VERY LOW", 1 -0.92 -1523, 13.38 VERY LOW", 1 1000day V. Bodday - VERY LOW", 1 17.6 7.58, 72.88 VERY LOW", 1 1000day V. Control - VERY LOW", 1 17.6 7.58, 72.88 VERY LOW", 1 1200day V. Isos250day - VERY LOW", 1 17.03 -0.12, 22.57 VERY LOWS, 11 1200day V. Isos250day - VERY LOW1, 1 19.41 4.44, 38.96 VERY LOWS, 11 1200day V. Sou00_single - NODERATEII 24.86 12.15, 37.54 VERY LOWS, 11 1200day V. Sou00_single - VERY LOW1, 1 15.18 1.59, 28.77 VERY LOWS, 11 1200day V. Sou02_single - UOW1, 1 3.372 24.43.5 MODERATE1 1200day V. Sou02_single - LOW1, 1 3.372 24.43.5 MODERATE1 1200day V. Sou02_single - LOW1, 1 3.372 24.43.5 MODERATE1 120	1000day v. 500day	_	VERTLOW, J	6.75	-4.13, 21.92	VERYLOW , I
Hobday : Constant	1000day V. 500day	_	VERTLOW, J	-0.92	-15.23 13.38	VERYLOW , I
Nooday : VERY LOW",† 17.63 7.85 VERY LOW",† 1000day : Des250day - VERY LOW",† 11.03 -0.12, 22.67 VERY LOW",† 1200day : Des250day - VERY LOW",† 11.03 -0.12, 22.67 VERY LOW",† 1200day : Des250day - VERY LOW†,‡ 19.41 4.44, 34.3 VERY LOW*,1 1200day : Do00_single - VERY LOW†,‡ 19.41 4.44, 34.3 VERY LOW*,1 1200day : Do00_single - MODERATEII 24.86 12.15, 37.54 VERY LOW†,‡ 1200day : Do0day : - VERY LOW†,** 15.18 1.59, 28.77 VERY LOW†,‡ 1200day : Stoday - VERY LOW†,** 15.18 1.59, 28.77 VERY LOW†,‡ 1200day : Stoday - UOW†,** 15.18 1.59, 28.77 VERY LOW†,‡ 1200day : Stoday - UOW†,** 15.8 1.69, 28.74 VERY LOW†,‡ 1200day : Stoday -	1000day V. 800day	2	VERY LOW* +	-0.92	-15.38 7.28	VERVIOW*+
Nooday V. Joshing VERY LOW*,† 11.03 -7.05, 20.03 VERY LOW; † 1200day V. Ia00week - HIGH 26.12 13.14, 38.96 VERY LOW; † 1200day V. Ia00woek - LOW† 3.96 -11.5, 19.69 VERY LOW; 1 1200day V. 50000_single - LOW† 3.96 -11.5, 37.54 VERY LOW; 1 1200day V. 50000_single - MODERATEII 24.86 12.15, 37.54 VERY LOW†, 1 1200day V. 50004y - VERY LOW†,** 15.18 1.59, 28.77 VERY LOW†, 1 1200day V. 50004y - VERY LOW†,** 15.18 1.59, 28.77 VERY LOW†, 1 1200day V. 1400week - LOWI - -672 -22.25, 874 VERY LOW†, 1 1400week V. 11ac_single - VERY LOW†, 1 -672 -22.25, 874 VERY LOW†, 1 1400week V. 50002_mon - LOW1 -22.11 -38.61, -552 LOW‡ 1400week V. 50004y - VERY LOW†, 1 -10.49, 12.86 VERY LOW†, 1 1400week V. 50004y	1000day v. Control	<u> </u>	VERY LOW* +	17.6	7.58 27.86	VERVIOW*+
1000000000000000000000000000000000000	1000day v less250day	_	VEBY LOW* +	11.03	-0.12 22.57	VERY LOW* +
Laosay Harry Lowit, it Lowit, it <td>1200day v 1400week</td> <td>_</td> <td>HIGH</td> <td>26.12</td> <td>13.14 38.96</td> <td>VERY LOW&</td>	1200day v 1400week	_	HIGH	26.12	13.14 38.96	VERY LOW&
Lizouday v. 50000_2mon LOW‡ 3.96 -11.5, 19.69 VERY LOW\$,il 1200day v. 50000_2mon MODERATEII 24.86 12.15, 37.54 VERY LOW\$,il 1200day v. 5000day - VERY LOW1,‡ 22.29 -2.63, 46.83 VERY LOW\$,i! 1200day v. 5000day - VERY LOW1,** 15.18 1.59, 28.77 VERY LOW\$,i! 1200day v. Control - HIGH 11.88 2.34, 21.62 VERY LOW\$,i! 1200day v. Exes250day - LOWII,¶ 33.72 2.4, 43.5 MODERATE\$ 1400week v. 1400week - MODERATE\$ 40.1 2.666, 54.01 MODERATE\$ 1400week v. 50000_2mon - LOW1,* -7.61 -17.32, 212 HIGH 1400week v. 50000_single - LOW1,** -12.6 -13.94, 11.38 LOW\$; * 1400week v. 5000day - VERY LOW1,‡ -3.74 -29.29, 21.28 VERY LOW\$,‡ 1400week v. 800day - VERY LOW1,‡ -10.96 -25.38, 3.82 VERY LOW\$,‡ 1400week v. 800day - VERY LOW1,‡ 1 -10.49, 12.66 VERY LOW\$,‡ <	1200day v 1lac single	_	VEBY LOW+ +	19.41	4.44 34.3	VERY LOW&
2200day v. 50000_single - MODERATEII 24.86 12.15, 37.54 VERY LOWS,II 1200day v. 5000day - VERY LOW1,‡ 22.29 -2.53, 46.83 VERY LOW1,*1 1200day v. 600day - VERY LOW1,** 15.18 15.98, 27.7 VERY LOW1,** 1200day v. 600day - VERY LOW1,** 15.18 15.98, 27.7 VERY LOW1,** 1200day v. fooday - LOWII,¶ 33.72 24, 43.5 MODERATE¶ 1200week v. 1lac_single - VERY LOW1,** -6.72 -22.25, 8.74 VERY LOW1,* 1400week v. 5000_zmon - LOW1,# -26.6 -5.40 MODERATE¶ 1400week v. 5000ay - LOW1,* -7.61 -17.32, 2.12 HIGH 1400week v. 5000ay - LOW1,* -1.26 -13.94, 11.38 LOW3;* 1400week v. 5000day - VERY LOW1,‡ -0.96 -25.38, 382 VERY LOW1,‡ 1400week v. 600day - VERY LOW1,‡ -1.425 -26.01, -2.2 HIGH 1400week v. 600day - VERY LOW1,‡ 1.1 -10.49, 12.86 VERY LOW1,‡ </td <td>1200day v. 50000 2mon</td> <td>_</td> <td>I OW±</td> <td>3.96</td> <td>-11.5, 19.69</td> <td>VERY LOW&</td>	1200day v. 50000 2mon	_	I OW±	3.96	-11.5, 19.69	VERY LOW&
1200day Form VERY LOW1,‡ 22.29 -2.53, 46.83 VERY LOW1,‡ 1200day c600day - VERY LOW1,** 15.18 1.59, 28.77 VERY LOW1,‡ 1200day c600day - HIGH 11.88 2.34, 21.62 VERY LOW1,‡ 1200day v. less250day - LOWII,¶ 33.72 24, 43.5 MODERATE¶ 1400week v. lac_single - VERY LOW1,‡ -6.72 -22.58, 87.4 VERY LOW1,‡ 1400week v. 400day - HIGH -7.61 -17.32, 21.2 HIGH 1400week v. 5000_single - LOW1,* -1.26 -13.94, 11.38 LOW\$; + 1400week v. 5000agingle - LOW1,* -1.26 -1.394, 11.38 LOW\$; + 1400week v. 600day - VERY LOW1,‡ -3.74 -29.29, 21.28 VERY LOW+,‡ 1400week v. 800day - HIGH -14.25 -26.01, -2.2 HIGH 1400week v. 800day - VERY LOW1,‡ 1 -10.49, 12.86 VERY LOW+,‡	1200day v. 50000 single	-	MODERATEII	24.86	12.15, 37.54	VERY LOWS.
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§,II 1200day v. 1400week - MODERATE§ 40.1 26.66, 54.01 MODERATE¶ 1400week v. 400day - HIGH -7.61 -7.32, 2.12 HIGH 1400week v. 400day - HIGH -7.61 -7.32, 2.12 HIGH 1400week v. 5000_zingle - LOWI,** -1.26 -1.394,11.38 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. 600day - VERY LOW†,‡ 1 -10.49, 12.86 VERY LOW†,‡ 1400week v. 600day - VERY LOW†,‡ 33.33 17.92, 48.89 VERY LOW†,‡ 1400week v. 600day - VERY LOW†,‡ 1 1 -10.49, 12.86 VERY LOW†,‡ 1400week v. 600day - VERY LOW†,‡ 33.33 17.92, 48.89 VERY LOW†,‡ <td>1200day v. 500day</td> <td>-</td> <td>VERY LOW1.±</td> <td>22.29</td> <td>-2.53, 46.83</td> <td>VERY LOW1.1</td>	1200day v. 500day	-	VERY LOW1.±	22.29	-2.53, 46.83	VERY LOW1.1
1200day v. Control - HIGH 11.88 2.34, 21.62 VERY LOWs,II 1200day v. less250day - LOWII,¶ 33.72 24, 43.5 MODERATE¶ 1400week v. 1ac_single - WERY LOW†,‡ -6.72 -22.25, 8.74 VERY LOW†,‡ 1400week v. 400day - HIGH -7.61 -17.32, 21.2 HIGH 1400week v. 5000_single - LOW!,* -22.11 -38.61, -5.82 LOW‡ 1400week v. 5000_single - LOW!,* -1.26 -13.94, 11.38 LOW§,*† 1400week v. 5000_single - LOW!,* -1.096 -25.38, 3.82 VERY LOW†,‡ 1400week v. 600day - VERY LOW†,‡ -10.96 -25.68, 52.01, -2.2 HIGH 1400week v. less250day - VERY LOW†,‡ 1 -10.49, 12.86 VERY LOW†,‡ 1600day v. 50000_single - LOW‡ 17.91 1.48, 34.29 LOW‡ 1600day v. 50000_single - MODERATE§ 47.67 37.19, 58.51 MODERATE§ 1600day v. 50000_single - MODERATE§ 47.67 37.19, 58.51 MODERATE§ <	1200day v. 600day	_	VERY LOW1.**	15.18	1.59, 28.77	VERY LOW [†] .*†
1200day v. less250day - LOWII,¶ 33.72 24,43.5 MODERATE*† 1600day v. 1400week - MODERATE\$ 40.1 26.66,54.01 MODERATE\$ 1400week v. 1ac_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‡ -22.21,8.74 VERY LOW†,‡ 1400week v. 5000ay - LOW‡ -22.21,8.74 VERY LOW†,‡ 1400week v. 600day - LOW‡,* -1.26 -13.94,11.38 LOW\$,*† 1400week v. 600day - VERY LOW†,‡ -3.74 -29.29,21.28 VERY LOW†,‡ 1400week v. 600day - VERY LOW†,‡ -10.96 -25.38,382 VERY LOW†,‡ 1400week v. less250day - VERY LOW†,‡ 1 -10.49,12.86 VERY LOW†,‡ 1600day v. 50000_single - LOW‡ 33.33 17.92,48.89 VERY LOW†,‡ 1600day v. 50000_single - MODERATE\$ 36.31 11.07,61.62 VERY LOW†,‡ 1600day v. 600day	1200day v. Control	_	HIGH	11.88	2.34, 21.62	VERY LOWS,
1600day v. 1400week - MODERATE\$ 40.1 26.66, 54.01 MODERATE\$ 1400week v. 1lac_single - VERY LOW1,‡ -6.72 -22.25, 8.74 VERY LOW1,‡ 1400week v. 400day - HIGH -7.61 -17.32, 2.12 HIGH 1400week v. 5000_single - LOW1,* -22.11 -38.61, -5.82 LOW‡ 1400week v. 5000_single - LOW1,* -1.26 -13.94, 11.38 LOW\$;*† 1400week v. 500day - VERY LOW1,‡ -3.74 -29.29, 21.28 VERY LOW1,‡ 1400week v. 600day - VERY LOW1,‡ -10.96 -25.38, 3.82 VERY LOW1,‡ 1400week v. 600day - VERY LOW1,‡ 1 -10.49, 12.86 VERY LOW1,‡ 1400week v. 600day - VERY LOW1,‡ 33.33 17.92, 48.89 VERY LOW1,‡ 1600day v. 50000_single - VERY LOW1,‡ 36.31 11.07, 61.62 VERY LOW1,‡ 1600day v. 600day - VERY LOW1,‡ 36.31 11.07, 61.62 VERY LOW1,‡ 1600day v. 600day - VERY LOW1,‡ 29.1 15.13, 43.65 VERY	1200day v. less250day	_	LOWII,¶	33.72	24, 43.5	MODERATE*†
1400week v. 1lac_single - VERY LOW1,‡ -6.72 -22.25, 8.74 VERY LOW1,‡ 1400week v. 400day - HIGH -7.61 -17.32, 2.12 HIGH 1400week v. 5000_single - LOW1,** -1.26 -13.94, 11.38 LOW1,* 1400week v. 500day - VERY LOW1,‡ -3.74 -29.29, 21.28 VERY LOW1,‡ 1400week v. 600day - VERY LOW1,‡ -3.74 -29.29, 21.28 VERY LOW1,‡ 1400week v. 600day - VERY LOW1,‡ -10.96 -25.38, 3.82 VERY LOW1,‡ 1400week v. 800day - HIGH -14.25 -26.01, -2.2 HIGH 1400week v. less250day - VERY LOW1,‡ 33.33 17.92, 48.89 VERY LOW1,‡ 1600day v. 5000_single - MODERATEI 38.77 25.69, 52.36 MODERATE§ 1600day v. 5000a_single - MODERATE§ 47.67 37.19, 58.51 MODERATE§ 1600day v. 600day - VERY LOW1,‡ 36.31 11.07, 61.62 VERY LOW1,‡ 1600day v. 600day - MODERATE§ 47.67 37.19, 58.51 MODERA	1600day v. 1400week	_	MODERATES	40.1	26 66, 54 01	MODERATE
1400week v. 400day - HIGH -7.61 -17.32, 2.12 HIGH 1400week v. 5000_zmon - LOW‡ -22.11 -38.61, -5.82 LOW‡ 1400week v. 5000_single - LOWI,** -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. less250day - VERY LOW†,‡ 1 -10.49, 12.86 VERY LOW†,‡ 1600day v. lac_single - VERY LOW†,‡ 1 -10.49, 12.86 VERY LOW†,‡ 1600day v. 5000_zmon - LOW‡ 17.91 1.88, 34.29 LOW‡ 1600day v. 5000_zmon - LOW‡ 17.91 1.88, 34.29 LOW‡ 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. 60s00_zmon - WODERATE\$ 47.67 37.19, 58.51 MODERATE\$	1400week v. 1lac_single	-	VERY LOW [†] , [‡]	-6.72	-22·25, 8·74	VERY LOW†,‡
1400week v. 5000_źmon - LOW‡ -22:11 -38:61, -5:82 LOW‡ 1400week v. 50000_single - LOWI,** -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 - VERY LOW†,‡ 1 -10:49, 12:86 VERY LOW†,‡ 1400week v. less250day - VERY LOW†,‡ 33:33 17:92, 48:89 VERY LOW†,‡ 1600day v. 1lac_single - VERY LOW†,‡ 1 -10:49, 12:86 VERY LOW†,‡ 1600day v. 50000_zmon - LOW‡ 17:91 1.48, 34:29 LOW‡ 1600day v. 50000_single - MODERATEII 38:77 25:69, 52:36 MODERATE§ 1600day v. 600day - VERY LOW†,‡ 36:31 11:07, 61:62 VERY LOW†,‡ 1600day v. 600day - VERY LOW†,‡ 36:31 11:07, 61:62 VERY LOW†,‡ 1600day v. less250day - MODERATE§ 47:67 37:19, 58:51 MO	1400week v. 400day	-	HIGH	-7.61	-17·32, 2·12	HIGH
1400week v. 5000_single - LOWII,** -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. 5000_zmon - LOW‡ 17.91 1.88, 34.29 LOW‡ 1600day v. 5000_single - MODERATEII 38.77 25.69, 52.36 MODERATE§ 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. 50000_single - VERY LOW†,‡ -15.44 -33.33, 2.68 VERY LOW†,‡ 11ac_single v. 50000_single - VERY LOW†,‡ -4.23 -20.73, 12.49	1400week v. 5000_2mon	-	LOW‡	-22.11	-38·61, -5·82	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. flac_single - VERY LOW†,‡ 33.33 17.92, 48.89 VERY LOW†,‡ 1600day v. 50000_zmon - LOW‡ 17.91 1.88, 34.29 LOW‡ 1600day v. 50000_single - MODERATEII 38.77 25.69, 52.36 MODERATE§ 1600day v. 600day - VERY LOW†,** 29.1 15.13, 43.65 VERY LOW†,* 1600day v. Control - MODERATE§ 47.67 37.19, 58.51 MODERATE¶ 1800day v. 50000_zingle - VERY LOW†,* -15.44 -33.33, 2.68 VERY LOW†,* 11ac_single v. 5000_single - VERY LOW†,* -42.3 -20.73, 12.49 VERY LOW†,* 11ac_single v. 600day - VERY LOW†,* -7.53 -21.34, 6.61 <td>1400week v. 50000_single</td> <td>-</td> <td>LOWII,**</td> <td>-1.26</td> <td>–13·94, 11·38</td> <td>LOW§,*†</td>	1400week v. 50000_single	-	LOWII,**	-1.26	–13·94, 11·38	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†,‡ 133.33 17.92, 48.89 VERY LOW†,‡ 1600day v. 50000_2mon - LOW‡ 17.91 1.88, 34.29 LOW‡ 1600day v. 500day - MODERATEII 38.77 25.69, 52.36 MODERATE§ 1600day v. 500day - VERY LOW†,‡ 36.31 11.07, 61.62 VERY LOW†,‡ 1600day v. 6odday - VERY LOW†,** 29.1 15.13, 43.65 VERY LOW†,* 1600day v. less250day - MODERATE§ 47.67 37.19, 58.51 MODERATE¶ 1600day v. less250day - MODERATE§ 41.07 29.85, 53.08 MODERATE¶ 1600day v. less250day - VERY LOW†,‡ -15.44 -33.33, 2.68 VERY LOW†,‡ 11ac_single v. 5000_single - VERY LOW†,‡ 5.48 -9.95, 20.83	1400week v. 500day	-	VERY LOW†,‡	-3.74	–29·29, 21·28	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 - MODERATEII 38:77 25:69, 52:36 MODERATE§ 1600day v. 600day - 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. less250day - MODERATE§ 47:67 37:19, 58:51 MODERATE¶ 1600day v. less250day - MODERATE** 41:07 29:85, 53:08 MODERATE¶ 11ac_single v. 50000_zmon - VERY LOW†,‡ -5:48 -9:95, 20:83 VERY LOW†,‡ 11ac_single v. 500day - VERY LOW†,‡ 2:94 -23:02, 29:3 VERY LOW†,‡ 11ac_single v. 600day - VERY LOW†,‡ 7:72 -2:0:73, 12:49	1400week v. 600day	-	VERY LOW†,‡	-10.96	–25·38, 3·82	VERY LOW†,‡
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_zmon - LOW‡ 17.91 1.88, 34.29 LOW‡ 1600day v. 50000_single - MODERATEII 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*† 11ac_single v. 50000_zmon - VERY LOW†,‡ -15.44 -33.33, 2.68 VERY LOW†,‡ 11ac_single v. 50000_single - VERY LOW†,‡ 2.94 -23.02, 29.3 VERY LOW†,‡ 11ac_single v. 500day - VERY LOW†,‡ -7.53 -21.34, 6.61 VERY LOW†,‡ 11ac_single v. 600day - VERY LOW†,‡ -7.53	1400week v. 800day	-	HIGH	-14.25	–26·01, –2·2	HIGH
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 - MODERATEII 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†,‡ 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_single - VERY LOW†,‡ -15:44 -33:33, 2:68 VERY LOW†,‡ 1lac_single v. 500day - VERY LOW†,‡ 2:94 -2:3:02, 2:9:3 VERY LOW†,‡ 1lac_single v. 600day - VERY LOW†,‡ -4:23 -20:73, 12:49 VERY LOW†,‡ 1lac_single v. 600day - VERY LOW†,‡ -7:53 -21:	1400week v. less250day	-	VERY LOW†,‡	1	–10·49, 12·86	VERY LOW†,‡
1600day v. 50000_2mon - LOW‡ 17.91 1.88, 34.29 LOW‡ 1600day v. 50000_single - MODERATEII 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_single - VERY LOW†,‡ 548 -9.95, 20.83 VERY LOW†,‡ 1lac_single v. 500day - VERY LOW†,‡ 5.48 -9.95, 20.83 VERY LOW†,‡ 1lac_single v. 600day - 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. 600day - VERY LOW†,‡ -7.53 -21.34, 6.61 VERY LOW†,‡ 1lac_single v. less250day - VERY LOW†,‡ 7.72 -5.9	1600day v. 1lac_single	-	VERY LOW†,‡	33.33	17.92, 48.89	VERY LOW†,‡
1600day v. 50000_single - MODERATEII 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*† 11ac_single v. 5000_single - VERY LOW†,‡ -15-44 -33-33, 2-68 VERY LOW†,‡ 11ac_single v. 5000_single - VERY LOW†,‡ 5-48 -9-95, 20-83 VERY LOW†,‡ 11ac_single v. 500day - VERY LOW†,‡ 2.94 -23-02, 29-3 VERY LOW†,‡ 11ac_single v. 600day - VERY LOW†,‡ -4-23 -20-73, 12-49 VERY LOW†,‡ 11ac_single v. 600day - VERY LOW†,‡ -7-53 -21-34, 6-61 VERY LOW†,‡ 11ac_single v. control - VERY LOW†,‡ 14-29 1-32, 27-31 VERY LOW†,‡ 11ac_single v. less250day - VERY LOW†,‡ 7-	1600day v. 50000_2mon	-	LOW‡	17.91	1·88, 34·29	LOW‡
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*† 11ac_single v. 5000_2mon - VERY LOW†,‡ -15·44 -33·33, 2·68 VERY LOW†,‡ 11ac_single v. 5000_single - VERY LOW†,‡ 5·48 -9·95, 20·83 VERY LOW†,‡ 11ac_single v. 500day - VERY LOW†,‡ 2.94 -23·02, 29·3 VERY LOW†,‡ 11ac_single v. 600day - VERY LOW†,‡ -4·23 -20·73, 12·49 VERY LOW†,‡ 11ac_single v. 600day - VERY LOW†,‡ -7·53 -21·34, 6·61 VERY LOW†,‡ 11ac_single v. Control - VERY LOW†,‡ 14·29 1·32, 27·31 VERY LOW†,‡ 11ac_single v. less250day - VERY LOW†,‡ 7·72 -5·98, 21·79 VERY LOW†,‡ 400day v. 500day - VERY LOW†,‡ 3·79 <td>1600day v. 50000_single</td> <td>-</td> <td>MODERATEII</td> <td>38.77</td> <td>25.69, 52.36</td> <td>MODERATE§</td>	1600day v. 50000_single	-	MODERATEII	38.77	25.69, 52.36	MODERATE§
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*† 11ac_single v. 5000_2mon - VERY LOW ⁺ , [‡] -15·44 -33·33, 2·68 VERY LOW ⁺ , [‡] 11ac_single v. 5000_single - VERY LOW ⁺ , [‡] 5·48 -9·95, 20·83 VERY LOW ⁺ , [‡] 11ac_single v. 500day - VERY LOW ⁺ , [‡] 2·94 -23·02, 29·3 VERY LOW ⁺ , [‡] 11ac_single v. 600day - VERY LOW ⁺ , [‡] -4·23 -20·73, 12·49 VERY LOW ⁺ , [‡] 11ac_single v. 600day - VERY LOW ⁺ , [‡] -7·53 -21·34, 6·61 VERY LOW ⁺ , [‡] 11ac_single v. Control - VERY LOW ⁺ , [‡] 14·29 1·32, 27·31 VERY LOW ⁺ , [‡] 11ac_single v. less250day - VERY LOW ⁺ , [‡] 7·72 -5·98, 21·79 VERY LOW ⁺ , [‡] 11ac_single v. 500day - VERY LOW ⁺ , [‡] 3·79 -19·74, 27·01 VERY LOW ⁺ , [‡] 400day v.	1600day <i>v</i> . 500day	-	VERY LOW†,‡	36-31	11·07, 61·62	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. 5000_2mon - VERY LOW†,‡ -15.44 -33.33, 2.68 VERY LOW†,‡ 1lac_single v. 5000_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. 600day - 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‡	1600day v. 600day	-	VERY LOW†,**	29.1	15·13, 43·65	VERY LOW†,*†
1600day v. less250day - MODERATE** 41.07 29.85, 53.08 MODERATE*† 1lac_single v. 50000_zmon - 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. 600day - 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†,‡ 1lac_single v. less250day - VERY LOW†,‡ 3.79 -19.74, 27.01 VERY LOW†,‡ 400day v. 500day - LOW‡ 20.9 4.67, 36.87 LOW‡	1600day v. Control	-	MODERATE§	47.67	37.19, 58.51	MODERATE¶
11ac_single v. 50000_2mon - VERY LOW†,‡ -15.44 -33.33, 2.68 VERY LOW†,‡ 11ac_single v. 5000_single - VERY LOW†,‡ 5.48 -9.95, 20.83 VERY LOW†,‡ 11ac_single v. 500day - VERY LOW†,‡ 2.94 -23.02, 29.3 VERY LOW†,‡ 11ac_single v. 600day - VERY LOW†,‡ -4.23 -20.73, 12.49 VERY LOW†,‡ 11ac_single v. 800day - VERY LOW†,‡ -7.53 -21.34, 6.61 VERY LOW†,‡ 11ac_single v. control - VERY LOW†,‡ 14.29 1.32, 27.31 VERY LOW†,‡ 11ac_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‡	1600day v. less250day	-	MODERATE**	41.07	29.85, 53.08	MODERATE*†
1lac_single v. 5000_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. 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‡	1lac_single v. 50000_2mon	-	VERY LOW†,‡	-15·44	–33·33, 2·68	VERY LOW†,‡
11ac_single v. 500day - VERY LOW†,‡ 2:94 -23:02, 29:3 VERY LOW†,‡ 11ac_single v. 600day - VERY LOW†,‡ -4:23 -20:73, 12:49 VERY LOW†,‡ 11ac_single v. 800day - VERY LOW†,‡ -7:53 -21:34, 6:61 VERY LOW†,‡ 11ac_single v. 800day - VERY LOW†,‡ 14:29 1:32, 27:31 VERY LOW†,‡ 11ac_single v. Control - VERY LOW†,‡ 7:72 -5:98, 21:79 VERY LOW†,‡ 11ac_single v. less250day - VERY LOW†,‡ 3:79 -19:74, 27:01 VERY LOW†,‡ 400day v. 500day - LOW‡ 20:9 4:67, 36:87 LOW‡	1lac_single v. 50000_single	-	VERY LOW†,‡	5.48	<i>−</i> 9·95, 20·83	VERY LOW†,‡
11ac_single v. 600day - VERY LOW†,‡ -4:23 -20:73, 12:49 VERY LOW†,‡ 11ac_single v. 800day - VERY LOW†,‡ -7:53 -21:34, 6:61 VERY LOW†,‡ 11ac_single v. Control - VERY LOW†,‡ 14:29 1:32, 27:31 VERY LOW†,‡ 11ac_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‡	1lac_single v. 500day	-	VERY LOW†,‡	2.94	-23.02, 29.3	VERY LOW†,‡
11ac_single v. 800day - VERY LOW†,‡ -7.53 -21.34, 6.61 VERY LOW†,‡ 11ac_single v. Control - VERY LOW†,‡ 14.29 1.32, 27.31 VERY LOW†,‡ 11ac_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‡	1lac_single v. 600day	_	VERY LOW†,‡	-4·23	-20.73, 12.49	VERY LOW†,‡
11ac_single v. Control - VERY LOW ⁺ , [‡] 14·29 1·32, 27·31 VERY LOW ⁺ , [‡] 11ac_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 [‡]	1lac_single v. 800day	_	VERY LOW†,‡	-7.53	-21.34, 6.61	VERY LOW†,‡
11ac_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 [‡]	1lac_single v. Control	-	VERY LOW†,‡	14.29	1.32, 27.31	VERY LOW†,‡
400day v. 500day - VERY LOW†,‡ 3.79 -19.74, 27.01 VERY LOW†,‡ - LOW‡ 20.9 4.67, 36.87 LOW‡	1lac_single v. less250day	_	VERY LOW†,‡	7.72	-5.98, 21.79	VERY LOW†,‡
– LOW‡ 20.9 4.67, 36.87 LOW‡	400day v. 500day	_	VERY LOW†,‡	3.79	-19.74, 27.01	VERY LOW†,‡
		-	LOWŢ	20.9	4.07, 36.87	LOW‡

Table 2. (Continued)

	Direct evidence – certainty	Indirect evidence –	Network meta-	analysis RR (Crl)	Certainty of
Comparison	of evidence	certainty of evidence	RR	Crl	evidence
50000_2mon <i>v</i> .					
50000 2mon v 500dav	_	VERY LOW1.1	18.39	-7.86, 44.24	VEBY LOW1.1
50000 2mon v. 600day	_	I OW±	11.22	-5.23, 27.81	I OW±
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 500 dav	_	VEBY LOW+ +	-2.51	-27.68 22.38	VEBY LOW++
50000 single v 600 day	_	MODEBATEII	-9.64	-24.15 4.75	MODEBATE8
50000 single v 800day	_	MODEBATEII	-13	-24.33 -1.33	MODERATES
50000_ single v. less250day	-	LOWII,¶	2.27	-8.91, 14.02	LOW§,**
$500 \text{day} \times 600 \text{day}$	_	VEBY LOW+ +	_7.2	-31.92 18.39	VEBY LOW++
500day v. 800day	_	VEBY LOW+ +	-10.44	-34.28 13.7	VERY LOW++
500day v. Control		VERYLOW++	11.39	-12.13 35.1	VERVIOW++
600day v. Control		VERY LOW+ **	18.53	6.57 30.35	VERVIOW+*+
800day v. Control			21.85	13.45 20.07	
VDI (Vitamin D level < 30 n	g/ml) at 0_6 months	That	21.05	10.40, 20.01	man
1200day v. 1600day	LOW†	LOW†	40362820438086.7	3·21, 1.85467118243141e+	LOW†
				43	
1200day v 400day	MODEBATE*+	LOW+	0.19	0 8.41	MODEBATE*+
1200day v. 800day	LOW+	MODEBATE*+	0.23	0, 10,04	MODERATE*+
1600day v 400day	LOW ⁺	LOW+	0	0,0.05	LOW+
1600day v. 800day	LOW ⁺	LOWT	0	0,0.06	LOW+
1 ac single v 400dav	VEBY LOW+ +	-	0.83	0.01 64.26	VEBY LOW++
400day v 800day	MODEBATE*+	LOW+	1,16	0.08 18.82	
400day v. Control	LOW+	-	0.94	0.02 48.33	I OW+
400day v less250day	LOW+	_	0	0.02, 40.00	
50000 single v Control	VEBY LOW+ **	_	0.58	0.01 28.98	VEBY LOW+ **
1200day v 1lac single	-	VEBY LOW++	0.23	0 73.47	VERVIOW++
1200day v. 50000 single	_	VEBY LOW+ **	0.31	0 278.96	VERVIOW+**
1200day v. Control	_		0.18	0, 210,00	
1200day v. loss250day		LOW+	0	0, 417	
1600day v. 1lac single			0	0,0.01	
1600day v. 50000 single	_	VEBY LOW+ **	0	0,0.17	VERVIOW+**
1600day v. Control	_		0	0,0.07	
1600day v. loss250day	_		0	0,007	
1 ac single v 50000 single	_	VEBY LOW++	1.33	0, 16/2,71	
1 lac single v. 800day	_	VEBY LOW+ +	0.96	0.01 166.58	VERVIOW++
1 ac single v. Control			0.30	0.266.70	
1 ac_single v. loss250day			0.77	0, 20079	
400day y 50000 single	_		1.61	0,0.07	
50000 single v 800dav			0.72	0.307	VERVIOWI,
50000_single v. 5000ay	-		0.72	0,007	VERV LOWF **
less250day	-	VENTLOWI,	0	0, 0.07	VENT LOWI,
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.

I Downgraded by one level for serious imprecision due to confidence interval crossing the line of no clinical significance (5 ng/ml).

I 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

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).

groups⁽⁴⁹⁾.







NS British Journal of Nutrition

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 evidencebased practice guidelines to inform public policy. No evidencebased 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.

449

450

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 \leq 250 IU/d and 1400 IU/week may not increase vitamin D concentrations and hence may not be recommended. Any dosage regimen \geq 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.

Acknowledgements

The authors declare no acknowledgments.

The authors declare no funding.

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

References

- 1. Holick MF (2007) Vitamin D deficiency. NEngl J Med 357, 266-281.
- Creo AL, Thacher TD, Pettifor JM, *et al.* (2017) Nutritional rickets around the world: an update. *Paediatr Int Child Health* 37, 84–98.
- Li R, Han A, Hu Q, *et al.* (2023) Relationship between vitamin D deficiency and neonatal hypocalcemia: a meta-analysis. *J Pediatr Endocrinol Metab* 36, 909–916.
- Amrein K, Scherkl M, Hoffmann M, *et al.* (2020) Vitamin D deficiency 2.0: an update on the current status worldwide. *EurJ Clin Nutr* 74, 1498–1513.
- Jiang Z, Pu R, Li N, *et al.* (2023) High prevalence of vitamin D deficiency in Asia: a systematic review and meta-analysis. *Crit Rev Food Sci Nutr* 63, 3602–3611.
- Mogire RM, Mutua A, Kimita W, *et al.* (2020) Prevalence of vitamin D deficiency in Africa: a systematic review and meta-analysis. *Lancet Glob Health* **8**, e134–42.
- 7. Van der Pligt P, Willcox J, Szymlek-Gay EA, *et al.* (2018) Associations of maternal vitamin D deficiency with pregnancy and neonatal complications in developing countries: a systematic review. *Nutrients* **10**, 640.
- Jan Mohamed HJ, Rowan A, Fong B, *et al.* (2014) Maternal serum and breast milk vitamin D levels: findings from the Universiti Sains Malaysia pregnancy cohort study. *PLOS ONE* 9, e100705.
- 9. Dawodu A & Tsang RC (2012) Maternal vitamin D status: effect on milk vitamin D content and vitamin D status of breastfeeding infants. *Adv Nutr* **3**, 353–361.
- Salameh K, Al-Janahi NSA, Reedy AM, *et al.* (2016) Prevalence and risk factors for low vitamin D status among breastfeeding mother–infant dyads in an environment with abundant sunshine. *Int J Womens Health* **8**, 529–535.
- Jain V, Gupta N, Kalaivani M, *et al.* (2011) Vitamin D deficiency in healthy breastfed term infants at 3 months & their mothers in India: seasonal variation & determinants. *na J Med Res* **133**, 267–273.
- Chacham S, Rajput S, Gurnurkar S, *et al.* (2020) Prevalence of vitamin D deficiency among infants in Northern India: a hospital based prospective study. *Cureus* 12, e11353.

Vitamin D prophylaxis

- Yadav B, Gupta N, Sasidharan R, *et al.* (2022) 800 IU versus 400 IU per day of vitamin D3 in term breastfed infants: a randomized controlled trial from an LMIC. *Eur J Pediatr* 181, 3473–3482.
- 14. WHO (2023) Vitamin D Supplementation in Infants. Geneva: WHO.
- EFSA Panel on Dietetic Products N, Allergies (NDA) (2016) Dietary reference values for vitamin D. *EFSA J* 14, e04547.
- Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium (2011) *Dietary Reference Intakes for Calcium and Vitamin D.* Washington (DC): National Academies Press (US).
- Munns CF, Shaw N, Kiely M, *et al.* (2016) Global consensus recommendations on prevention and management of nutritional rickets. *J Clin Endocrinol Metab* **101**, 394–415.
- Wagner CL, Greer FR, American Academy of Pediatrics Section on Breastfeeding, *et al.* (2008) Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatr* 122, 1142–1152.
- Misra M, Pacaud D, Petryk A, *et al.* (2008) Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatr* **122**, 398–417.
- Priyadarshi M, Sankar MJ, Gupta N, *et al.* (2018) Efficacy of daily supplementation of 800 IU vitamin D on vitamin D status at 6 months of age in term healthy Indian infants. *J Perinatol* 38, 1566–1572.
- 21. Vidailhet M, Mallet E, Bocquet A, *et al.* (2012) Vitamin D: still a topical matter in children and adolescents. A position paper by the committee on nutrition of the french society of paediatrics. *Arch Pédiatrie* **19**, 316–328.
- 22. Papadimitriou DT (2017) The big vitamin D mistake. *J Prev Med Pub Health* **50**, 278.
- Gallo S, Comeau K, Vanstone C, *et al.* (2013) Effect of different dosages of oral vitamin D supplementation on vitamin D status in healthy, breastfed infants: a randomized trial. *Jama* **309**, 1785–1792.
- Grant CC, Stewart AW, Scragg R, *et al.* (2014) Vitamin D during pregnancy and infancy and infant serum 25-hydroxyvitamin D concentration. *Pediatr* 133, e143–53.
- Roth DE, Morris SK, Zlotkin S, *et al.* (2018) Vitamin D supplementation in pregnancy and lactation and infant growth. *N Engl J Med* **379**, 535–546.
- Cooper C, Harvey NC, Bishop NJ, et al. (2016) Maternal gestational vitamin D supplementation and offspring bone health (MAVIDOS): a multicentre, double-blind, randomised placebo-controlled trial. Lancet Diabetes Endocrinol 4, 393–402.
- Tan ML, Abrams SA & Osborn DA (2020) Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health. *Cochrane Database Syst Rev* 12, CD013046.
- Bilbao NA (2017) Vitamin D toxicity in young breastfed infants: report of 2 cases. *Glob Pediatr Health* 4, 2333794X17731695.
- Brustad N, Yousef S, Stokholm J, *et al.* (2022) Safety of high-dose vitamin D supplementation among children aged 0–6 years: a systematic review and meta-analysis. *JAMA Netw Open* 5, e227410–e227410.
- Thankaraj A, Gupta N, Ramaswamy VV, *et al.* (2022) Different strategies of vitamin D supplementation in term, late preterm infants - A systematic review, network meta-analysis PROSPERO 2022 CRD42022360454. https://www.crd.york.a c.uk/prospero/display_record.php?RecordID=360454 (accessed November 2023).
- 31. Hutton B, Salanti G, Caldwell DM, *et al.* (2015) The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care

interventions: checklist and explanations. Ann Intern Med 162, 777–784.

- Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 96, 1911–1930.
- Rayyan (2021) AI Powered Tool for Systematic Literature Reviews. https://www.rayyan.ai/ (accessed September 2023).
- Sterne JA, Savović J, Page MJ, et al. (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366, 14898.
- 35. R Core Team (2020) *R: A Language and Environment for Statistical Computing.* Vienna, Austria: R Foundation for Statistical Computing.
- 36. Rücker G & Schwarzer G (2015) Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol* **15**, 1–9.
- 37. Izcovich A, Chu DK, Mustafa RA, *et al.* (2023) A guide and pragmatic considerations for applying GRADE to network meta-analysis. *BMJ* **381**, e074495.
- Ala-Houhala M (1985) 25-Hydroxyvitamin D levels during breast-feeding with or without maternal or infantile supplementation of vitamin D. *J Pediatr Gastroenterol Nutr* 4, 220–226.
- Alonso A, Rodríguez J, Carvajal I, *et al.* (2011) Prophylactic vitamin D in healthy infants: assessing the need. *Metab* 60, 1719–1725.
- 40. Atas E, Karademir F, Ersen A, *et al.* (2013) Comparison between daily supplementation doses of 200 versus 400 IU of vitamin D in infants. *Eur J Pediatr* **172**, 1039–1042.
- Chandy DD, Kare J, Singh SN, *et al.* (2016) Effect of vitamin D supplementation, directly or via breast milk for term infants, on serum 25 hydroxyvitamin D and related biochemistry, and propensity to infection: a randomised placebo-controlled trial. *Br J Nutr* **116**, 52–58.
- 42. Feliciano ES, Ho ML, Specker BL, *et al.* (1994) Seasonal and geographical variations in the growth rate of infants in China receiving increasing dosages of vitamin D supplements. *J Trop Pediatr* **40**, 162–165.
- 43. Greer FR & Marshall S (1989) Bone mineral content, serum vitamin D metabolite concentrations, and ultraviolet B light exposure in infants fed human milk with and without vitamin D₂ supplements. *J Pediatr* **114**, 204–212.
- Greer FR, Searcy JE, Levin RS, *et al.* (1981) Bone mineral content and serum 25-hydroxyvitamin D concentration in breast-fed infants with and without supplemental vitamin D. *J Pediatr* **98**, 696–701.
- 45. Greer FR, Searcy JE, Levin RS, *et al.* (1982) Bone mineral content and serum 25-hydroxyvitamin D concentrations in breast-fed infants with and without supplemental vitamin D: one-year follow-up. *J Pediatr* **100**, 919–922.
- 46. Hauta-Alus HH, Holmlund-Suila EM, Kajantie E, *et al.* (2021) The effects of vitamin D supplementation during infancy on growth during the first 2 years of life. *J Clin Endocrinol Metab* **106**, e1140–55.
- Holmlund-Suila E, Viljakainen H, Hytinantti T, *et al.* (2012) High-dose vitamin D intervention in infants—effects on vitamin D status, calcium homeostasis, and bone strength. *J Clin Endocrinol Metab* **97**, 4139–4147.
- Huynh J, Lu T, Liew D, et al. (2017) Vitamin D in newborns. A randomised controlled trial comparing daily and single oral bolus vitamin D in infants. J Paediatr Child Health 53, 163–169.
- 49. Kumar GT, Sachdev HS, Chellani H, *et al.* (2011) Effect of weekly vitamin D supplements on mortality, morbidity, and growth of low birthweight term infants in India up to age 6 months: randomised controlled trial. *BMJ* **342**, d2975.

451

Ŷ

T. Abiramalatha et al.

- Lin C, Lin C, Sung Y, *et al.* (2022) Effect of oral vitamin D₃ supplementation in exclusively breastfed newborns: prospective, randomized, double-blind, placebo-controlled trial. *J Bone Miner Res* **37**, 786–793.
- Madar AA, Klepp KI & Meyer HE (2009) Effect of free vitamin D2 drops on serum 25-hydroxyvitamin D in infants with immigrant origin: a cluster randomized controlled trial. *Eur J Clin Nutr* 63, 478–484.
- Moodley A & Spector SA (2015) Single high-dose vitamin D at birth corrects vitamin D deficiency in infants in Mexico. *Int J Food Sci Nutr* 66, 336–341.
- Pacheco-Acosta J & Pizarro F (2020) Effect of vitamin D supplementation as a single dose on the nutritional status of vitamin D. *Rev Chil Pediatr* **91**, 684–690.
- Ponnapakkam T, Bradford E & Gensure R (2010) A treatment trial of vitamin D supplementation in breast-fed infants: universal supplementation is not necessary for rickets prevention in southern Louisiana. *Clin Pediatr (Phila)* 49, 1053–1060.
- 55. Razaghi M, Gharibeh N, Vanstone CA, *et al.* (2022) Correction of neonatal vitamin D status using 1000 IU vitamin D/d increased lean body mass by 12 months of age compared with 400 IU/d: a randomized controlled trial. *Am J Clin Nutr* **115**, 1612–1625.
- Rosendahl J, Pelkonen AS, Helve O, *et al.* (2019) High-dose vitamin D supplementation does not prevent allergic sensitization of infants. *J Pediatr* 209, 139–145.
- 57. Rosendahl J, Valkama S, Holmlund-Suila E, *et al.* (2018) Effect of higher vs standard dosage of vitamin D3 supplementation on bone strength and infection in healthy infants: a randomized clinical trial. *JAMA Pediatr* **172**, 646–654.
- Rothberg AD, Pettifor JM, Cohen DF, et al. (1982) Maternalinfant vitamin D relationships during breast-feeding. J Pediatr 101, 500–503.
- Ruangkit C, Suwannachat S, Wantanakorn P, et al. (2021) Vitamin D status in full-term exclusively breastfed infants versus full-term breastfed infants receiving vitamin D supplementation in Thailand: a randomized controlled trial. BMC Pediatr 21, 1–10.
- Rueter K, Jones AP, Siafarikas A, et al. (2019) Direct infant UV light exposure is associated with eczema and immune development. J Allergy Clin Immunol 143, 1012–1020.
- 61. Shakiba M, Sadr S, Nefei Z, *et al.* (2010) Combination of bolus dose vitamin D with routine vaccination in infants: a randomised trial. *Singap Med J* **51**, 440.
- 62. Siafarikas A, Piazena H, Feister U, *et al.* (2011) Randomised controlled trial analysing supplementation with 250 versus 500 units of vitamin D₃, sun exposure and surrounding factors in breastfed infants. *Arch Dis Child* **96**, 91–95.
- Specker BL, Ho ML, Oestreich A, *et al.* (1992) Prospective study of vitamin D supplementation and rickets in China. *J Pediatr* **120**, 733–739.

- 64. Trilok-Kumar G, Arora H, Rajput M, *et al.* (2012) Effect of vitamin D supplementation of low birth weight term Indian infants from birth on cytokine production at 6 months. *Eur J Clin Nutr* **66**, 746–750.
- 65. Trilok-Kumar G, Kaur M, Rehman AM, et al. (2015) Effects of vitamin D supplementation in infancy on growth, bone parameters, body composition and gross motor development at age 3–6 years: follow-up of a randomized controlled trial. *Int J Epidemiol* 44, 894–905.
- 66. Tuovinen S, Räikkönen K, Holmlund-Suila E, *et al.* (2021) Effect of high-dose vs standard-dose vitamin D supplementation on neurodevelopment of healthy term infants: a randomized clinical trial. *JAMA Netw Open* 4, e2124493.
- 67. Weiler HA, Hazell TJ, Majnemer A, *et al.* (2022) Vitamin D supplementation and gross motor development: a 3-year follow-up of a randomized trial. *Early Hum Dev* **171**, 105615.
- 68. Wicklow B, Gallo S, Majnemer A, *et al.* (2016) Impact of vitamin D supplementation on gross motor development of healthy term infants: a randomized dose-response trial. *Phys Occup Ther Pediatr* **36**, 330–342.
- Zeghoud F, Ben-Mekhbi H, Djeghri N, *et al.* (1994) Vitamin D prophylaxis during infancy: comparison of the long-term effects of three intermittent doses (15, 5, or 2.5 mg) on 25-hydroxyvitamin D concentrations. *Am J Clin Nutr* **60**, 393–396.
- Zhou J, Du J, Huang L, *et al.* (2018) Preventive effects of vitamin D on seasonal influenza A in infants: a multicenter, randomized, open, controlled clinical trial. *Pediatr Infect Dis J* 37, 749–754.
- Ziegler EE, Nelson SE & Jeter JM (2014) Vitamin D supplementation of breastfed infants: a randomized dose–response trial. *Pediatr Res* 76, 177–183.
- Ziegler EE, Koo WW, Nelson SE, *et al.* (2017) Lack of effect of graded doses of vitamin D on bone metabolism of breastfed infants. *J Clin Nutr Metab* 1, 105.
- Randev S, Kumar P & Guglani V (2018) Vitamin D supplementation in childhood–a review of guidelines. *na J Pediatr*85, 194–201.
- Giustina A, Bouillon R, Binkley N, *et al.* (2020) Controversies in vitamin D: a statement from the third international conference. *JBMR Plus* 4, e10417.
- Bouillon R (2017) Comparative analysis of nutritional guidelines for vitamin D. *Nat Rev Endocrinol* 13, 466–479.
- Zittermann A, Pilz S & Berthold HK (2020) Serum 25-hydroxyvitamin D response to vitamin D supplementation in infants: a systematic review and meta-analysis of clinical intervention trials. *Eur J Nutr* **59**, 359–369.
- 77. Beauchesne AR, Cara KC, Krobath DM, *et al.* (2022) Vitamin D intakes and health outcomes in infants and preschool children: summary of an evidence report. *Ann Med* 54, 2277–2300.

452