Enteral Vitamin D Supplementation in Preterm or Low Birth Weight Infants: A Systematic Review and Meta-analysis

Mohan Kumar, MD,[a] Saijuddin Shaikh, MD,[a] Bireshwar Sinha, MD,[a,b] Ravi Prakash Upadhyay, MD,[a,b] Tarun Shankar Choudhary, MD,[a,c] Temsunaro Rongsen Chandola, PhD,[a] Sarmila Mazumder, PhD,[a] Sunita Taneja, PhD,[a] Nita Bhandari, PhD,[a] Ranadip Chowdhury, PhD[a,b]

abstract

BACKGROUND AND OBJECTIVES: Many preterm and low birth weight (LBW) infants have low vitamin D stores. The objective of this study was to assess effects of enteral vitamin D supplementation compared with no vitamin D supplementation in human milk fed preterm or LBW infants.

METHODS: Data sources include Cochrane Central Register of Controlled Trials, Medline, and Embase from inception to March 16, 2021. The study selection included randomized trials. Data were extracted and pooled with fixed and random-effects models.

RESULTS: We found 3 trials (2479 participants) that compared vitamin D to no vitamin D. At 6 months, there was increase in weight-for-age z-scores (mean difference 0.12, 95% confidence interval [CI] 0.01 to 0.22, 1 trial, 1273 participants), height-for-age z-scores (mean difference 0.12, 95% CI 0.02 to 0.21, 1 trial, 1258 participants); at 3 months there was decrease in vitamin D deficiency (risk ratio 0.58, 95% CI 0.49 to 0.68, $I^2=58\%$, 2 trials, 504 participants) in vitamin D supplementation groups. However, there was little or no effect on mortality, any serious morbidity, hospitalization, head circumference, growth to 6 years and neurodevelopment. The certainty of evidence ranged from very low to moderate. Fourteen trials (1969 participants) assessed dose and reported no effect on mortality, morbidity, growth, or neurodevelopment, except on parathyroid hormone and vitamin D status. No studies assessed timing. Limitations include heterogeneity and small sample size in included studies.

CONCLUSIONS: Enteral vitamin D supplementation improves growth and vitamin D status in preterm and LBW infants.

[a]*Centre for Health Research and Development, Society for Applied Studies, New Delhi, India;* [b]*DBT and Wellcome India Alliance Clinical and Public Health Fellow, Hyderabad, India and* [c]*Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway*

Drs Kumar, Shaikh, and Chowdhury conceptualized and designed the study and drafted the initial manuscript; Drs Kumar and Chowdhury designed the data collection instruments, collected data, conducted the initial analyses, and reviewed and revised the manuscript; and all authors coordinated and supervised data collection, critically reviewed the manuscript for important intellectual content, and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This trial is registered at PROSPERO 2021 (identifier, CRD42021238989).

DOI: https://doi.org/2022057092K

Accepted for publication May 16, 2022

Address correspondence to Ranadip Chowdhury, PhD, Centre for Health Research and Development, Society for Applied Studies, Number 45, Kalu Sarai, New Delhi, India, 110016. E-mail: ranadip.chowdhury@sas.org.in

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Many preterm and low birth weight (LBW) infants have low vitamin D stores because of insufficient accretion during gestation. Postnatally, intake from mother's milk or from sunlight may not be sufficient to maintain or increase vitamin D stores in preterm and LBW infants.[1,2] Preterm infants also have immature intestinal vitamin D absorption and metabolism.[3,4]

Vitamin D increases intestinal absorption of calcium and phosphorus and enhances bone mineralization.[5] Vitamin D deficiency is associated with increased risk of hypocalcaemic seizures, irritability rickets, bone fractures, osteopenia, metabolic bone disease, and respiratory and diarrheal disease.[6,7] Vitamin D deficiency is also associated with pulmonary function deficits,[8] impaired neurodevelopment,[9,10] and reduction of bone mass in children and young adults, resulting in early development of osteoporosis.[11,12] In the neonate, low vitamin D levels are also associated with impaired immune function.[13]

A systematic review published in 2020 reported improvements in vitamin D biomarkers (vitamin D levels, calcium levels, and parathyroid hormone) in preterm infants who received vitamin D supplementation.[14] An ongoing Cochrane systematic review is assessing the effect of any formulation (oral or parenteral) of vitamin D at a daily cumulative dose at 200 IU compared with no supplementation or placebo in preterm or LBW infants.[15]

Our primary objective was to assess the effect of enteral vitamin D supplementation compared with no vitamin D supplementation on mortality, morbidity, growth, and neurodevelopment in preterm or LBW infants who are fed their mother's own milk or donor human milk. We also assessed effects on biomarkers (vitamin D, calcium, phosphorous, alkaline phosphatase, and parathyroid hormone levels). The secondary objectives were to determine the optimal time of initiation, dose, and duration of vitamin D supplementation.

METHODS

Registration

The protocol for this review was registered in PROSPERO (PROSPERO 2021 CRD42021238989).[16]

Inclusion Criteria

We selected studies that were either randomized controlled trials (RCTs) and nonrandomized trials (quasi-randomized) in which preterm or LBW infants fed their mother's own milk or donor human milk were either allocated to receive enteral vitamin D supplementation or compared with a control group (placebo or no drug). Data comparing dosage, duration, and timing of initiation were also included. Studies in which enteral vitamin D supplementation was provided for treatment of any disease were excluded.

Search and Extraction

A comprehensive search (Appendix 1) strategy was developed and reviewed by all authors. The search was conducted from the inception of each database to the date of search (16th March 2021) and included the Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 2), Medline via PubMed, and Embase. There were no language restrictions.

Two review authors (M.K., S.S.) screened the titles and abstracts and extracted data using standard methods.[17] Disagreements were resolved by discussion or referring to a third review author (R.C.). Screening and full text screening were done using the web-based software, Covidence.18 A modified version of the Cochrane Effective Practice and Organization of Care Group data collection checklist was used (Cochrane EPOC Group 2017).[19]

Risk of Bias

Two review authors (M.K., S.S.) independently assessed the risk of bias of all included trials using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[20] We planned to use funnel plots and Egger's tests for all outcomes with more than 10 studies.[21]

Statistical Analysis

The outcomes for this review were categorized into primary and secondary (Appendix 2). For each outcome, studies were pooled at latest follow-up if more than 1 study was available. If a single study reported an outcome, the individual study effect size was reported. The unit of analysis was the infant.

We used relative risk (RR) and mean difference (MD) as outcome estimate measures for categorical and continuous outcomes, respectively and used adjusted RR or MD where reported. For studies with multiple treatment groups of the same intervention (eg, different doses of vitamin D), we pooled the 2 treatment arms. Mean (standard deviation [SD]) and RR were calculated after combining the estimates and events in the intervention group.[17]

We used fixed-effect meta-analysis (inverse variance method) to pool data when it was reasonable to assume that studies were estimating the same underlying treatment effects. Pooled estimates of outcomes variables showing $I2 > 50\%$ were calculated using random effects using Restricted Maximum Likelihood Method models.[22]

We conducted subgroup analyses based on gestational age, birth weight, and income level of the country (high income, middle income, and low income) for the primary outcomes.

The certainty of the evidence for each outcome was assessed independently by 2 review authors using the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[23] We used GRADEPro GDT, a web-based tool to create a "Summary of Findings" table to report the certainty of the evidence.[24]

RESULTS

We found 577 studies (see PRISMA flowchart, Appendix 3). After removing duplicates, title, abstract and full text screening, we included 16 trials (20 reports),[25–44] from 8 countries (Canada, Egypt, Finland, India, Iran, Israel, Turkey, and USA) reporting on 4348 infants (Appendix 5).[25–44] Overall, 20% studies had low risk of bias, 25% some concerns and 55% high risk of bias (Appendix 4). A total of 62 studies were excluded in this review (Appendix 6).

Primary Comparison (vitamin D supplementation versus no vitamin D supplementation)

There were 3 trials (5 reports) including 2479 infants from India and USA that compared vitamin D supplementation to no supplementation (Appendix 5). One trial included 2079 infants (84%) from India. The dose of vitamin D supplementation ranged from 200 IU to 800 IU per day in these trials. Vitamin D supplementation commenced between birth to 7 days postnatal age. The mean duration of supplementation was 17.2 (SD 12.0) weeks, the median was 26 (inter quartile range [IQR] 4 to 26) weeks. The comparator group was placebo for all trials. In 1 trial the babies received additional multivitamins in both arms.

Data on the effect of vitamin D compared with no vitamin D supplementation on the primary outcomes are summarized in Table 1 (also see Appendices 8–12). At latest follow-up the RR for mortality was 1.81 (95% CI 0.92 to 3.56, I^2 = 0.00%, low certainty evidence, 2 trials, 2179 participants)[33,42]; the RR for hospitalization was 0.84 (95% CI 0.42 to 1.66, I^2 = 77.9%, very low certainty evidence, 2 trials, 1468 participants)[34,38]; the RR for bronchopulmonary dysplasia (BPD) was 0.77 (1 trial, 100 participants, RR 0.77, 95% CI 0.47 to 1.27, very low certainty evidence)[32]; and the RR for any (at least 1) serious morbidity was 0.94 (95% CI 0.72 to 1.24, I^2 = 76.9%, very low certainty evidence, 2 trials, 2179 participants) (Table 1).[32,33]

At 6 months, the mean difference (MD) in weight-for-age z-scores was +0.12 z-scores (95% CI 0.01 to 0.22, moderate certainty evidence, 1 trial, 1273 participants), the MD in length-for-age z-scores was 0.12 z-scores (95% CI 0.02 to 0.21 moderate certainty evidence, 1 trial, 1258 participants), and the MD in head circumference z-scores was −0.08 (95%CI −0.17 to 0.01, low certainty evidence, 1 trial, 1259 participants).[33] At latest follow-up (3 to 6 years) the MD in weight-for-age z-scores was −0.07 z-scores (95% CI −0.18 to 0.05, low certainty evidence, 1 trial, 912 participants)[34] and the MD in height for age z-scores was 0.07 scores (95% CI −0.05 to 0.19, low certainty evidence,1 trial, 912 participants) (Table 1).[34]

At latest follow-up (104 weeks) the RR for cognitive impairment (Bayley Scales of Infant and Toddler Development, third edition <85) was 0.85 (95% CI 0.45 to 1.59, 1 trial, 70 participants, low certainty evidence),[42] and the RR for "neurodevelopmental impairment" (see Appendix 2 for definition) was 0.69 (95% CI 0.41 to 1.17, very low certainty evidence, 1 trial, 71 participants) (Table 1).[42]

At latest follow-up (mean 15, SD 15.6 weeks), the RR for vitamin D deficiency (<20 ng/mL) was 0.58 (95% CI 0.49 to 0.68, I^2 = 57.96%, moderate certainty evidence, 2 trials, 504 participants).[32,33] At 6 months the RR for serum alkaline phosphatase (IU/l) was 0.37 (95% CI 0.10 to 1.35, very low certainty evidence, 1 trial, 265 participants)[38]; at 3 and 6 months the RR for serum calcium levels >10.7 mg/dL was 0.84 (95% CI 0.46 to 1.54, very low certainty evidence, 1 trial, 269 participants) and 0.55 (95% CI 0.25 to 1.21, very low certainty evidence, 1 trial, 266 participants), respectively. There were no data on other biomarkers (ie, phosphorous or parathyroid hormone). None of the trials reported on any serious adverse events, eg, hypercalcemia, seizures, or other forms of toxicity (Appendix 7).

There was no evidence of a differential effect in the subgroup of infants <32 weeks gestational age or birth weight <1500 g (Appendices 19–21).

Other Comparisons

We included 14 trials (17 reports, 1969 participants) from 8 countries (Appendix 5) that compared high (800 IU to 1600 international units [IU]) versus low (400 IU) daily dose vitamin D supplementation to preterm or LBW infants. Sample sizes were small, and evidence was of very low certainty. No effects were seen on mortality, morbidity, or growth. There were no studies that assessed effect on neurodevelopment. At latest follow up (mean 7.6, SD 2.9 weeks) the MD in serum parathyroid hormone (pg/mL) was −15.93 (95% CI −28.11 to −3.74, 5 trials, 372 participants, low certainty evidence) and the RR for vitamin D deficiency was 0.19

TABLE 1 Summary of Findings for Critical Outcomes: Vitamin D Compared With Placebo for Preterm and/or Low Birth Weight Infants

Patient or population: preterm and/or low birth weight infants. Setting: any high, middle, or low income country at home or in the health facility. Intervention: Vitamin D. Comparison: placebo.

				Anticipated Absolute Effects	
Outcomes	No of Participants (studies) Follow-up	Certainty of the Evidence (GRADE)	Relative Effect (95%CI)	Risk with Placebo	Risk Difference With Vitamin D
Mortality, follow-up: latest weeks, mean (SD): 60 (50.91) weeks, median (IQR): 60 (24–96) weeks	2179 (2 RCTs)	⨁⨁◯◯ Low[a]	RR 1.81 (0.92 to 3.56)	22 per 1000	18 more per 1000 (2 fewer to 57 more)
Hospitalization, follow-up: latest weeks, mean (SD): 96 (67.88) weeks, median (IQR): 96 (48–144) weeks	1468 (2 RCTs)	⨁◯◯◯ Very low[b]	RR 0.84 (0.42 to 1.66)	147 per 1000	24 fewer per 1000 (85 fewer to 97 more)
Any (at least 1) serious morbidity assessed with: any severe morbidity (hospital admission, or OP visits with diagnoses selected based on clinical judgment that represented severe illness: pneumonia, persistent diarrhea, dysentery, severe fever, severe protein energy malnutrition, ear infections, meningitis, and septicaemia), respiratory distress syndrome (RDS), Early onset sepsis (≤72 h), Late onset sepsis (>72 h) and culture positive meningitis, follow-up: latest weeks, mean (SD): 17(12.73) weeks, median (IQR): 17(8–26) weeks	2179 (2 RCTs)	⨁◯◯◯ Very low[b]	RR 0.94 (0.72 to 1.24)	193 per 1000	12 fewer per 1000 (54 fewer to 46 more)
Bronchopulmonary dysplasia (BPD) follow-up: 8 wk	100 (1 RCT)	⨁◯◯◯ Very low[d]	RR 0.77 (0.47 to 1.27)	444 per 1000	102 fewer per 1000 (236 fewer to 120 more)
Wt for age z scores follow-up: 6 mo	1273 (1 RCT)	⨁⨁⨁◯ Moderate[e]	—	The mean wt for age z scores was −1.60 (SD: 0.98) z scores	MD 0.12 z scores higher (0.01 higher to 0.22 higher)
Wt for age z scores follow-up: 3 to 6 y of age	912 (1 RCT)	⨁⨁◯◯ Low[c]	—	The mean wt for age z scores was −1.90 (SD: 0.97) z scores	MD 0.07 z scores lower (0.18 lower to 0.05 higher)
Length or height for age z scores follow-up: 6 mo	1258 (1 RCT)	⨁⨁⨁◯ Moderate[e]	—	The mean length or height for age z scores was −1.95 (SD: 0.99) z scores	MD 0.12 z scores higher (0.02 higher to 0.21 higher)
Length or height for age z scores follow-up: 3 to 6 y of age	912 (1 RCT)	⨁⨁◯◯ Low[c]	—	The mean length or height for age z scores was −1.85 (SD: 0.99) z scores	MD 0.07 z scores higher (0.05 lower to 0.19 higher)
Head or occipitofrontal circumference for age z scores follow-up: 6 mo	1259 (1 RCT)	⨁⨁◯◯ Low[c]	—	The mean head or occipitofrontal circumference for age z scores was −0.77 (SD: 0.95) z scores	MD 0.08 z scores lower (0.17 lower to 0.01 higher)
Cognitive scores assessed with: cognitive impairment was defined as a cognitive composite score on the Bayley Scales of Infant and Toddler Development, third edition (BSID III) <85 follow-up: 104 wk	70 (1 RCT)	⨁◯◯◯ Very low[g]	RR 0.85 (0.45–1.59)	393 per 1000	59 fewer per 1000 (216 fewer to 232 more)

TABLE 1 Continued

Patient or population: preterm and/or low birth weight infants. Setting: any high, middle, or low income country at home or in the health facility. Intervention: Vitamin D. Comparison: placebo.

				Anticipated Absolute Effects	
Outcomes	No of Participants (studies) Follow-up	Certainty of the Evidence (GRADE)	Relative Effect (95%CI)	Risk with Placebo	Risk Difference With Vitamin D
Neuro Developmental Impairment (NDI) assessed with: any of the following: a cognitive composite score on the BSID III <85, moderate or severe cerebral palsy with a Gross Motor Function Classification System (GMFCS) score of 2 or higher, hearing impairment, bilateral visual impairment follow-up: 104 wk	71 (1 RCT)	⨁◯◯◯ Very low[g]	RR 0.69 (0.41–1.17)	536 per 1000	166 fewer per 1000 (316 fewer to 91 more)
Serum alkaline phosphatase (IU/l) assessed with: ALP >500 U/L follow-up: 6 mo	265 (1 RCT)	⨁◯◯◯ Very low[d]	RR 0.37 (0.10–1.35)	61 per 1000	38 fewer per 1000 (55 fewer to 21 more)
Vitamin D deficiency assessed with: <20 ng/mL follow-up: latest weeks mean (SD): 15(15.56) weeks median (IQR): 15(4–26) weeks	504 (2 RCTs)	⨁⨁⨁◯ Moderate[f]	RR 0.58 (0.49–0.68)	709 per 1000	298 fewer per 1000 (362 fewer to 227 fewer)

Patient or population: preterm and/or low birth weight infants. Setting: any high, middle, or low income country at home or in the health facility. Intervention: Vitamin D. Comparison: placebo. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI). GRADE Working Group grades of evidence: High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. ALP, alkaline phosphatase; CI, confidence interval; MD, mean difference; RR, risk ratio.

[a] Downgraded 2 levels for: serious risk of bias; serious imprecision (wide confidence interval).

[b] Downgraded 3 levels for: serious risk of bias, serious inconsistency (high heterogeneity) and, serious imprecision (wide confidence interval).

[c] Downgraded 2 levels for: serious inconsistency (small number of studies) and serious imprecision (wide confidence interval).

[d] Downgraded 3levels for: serious risk of bias, serious inconsistency (small number of studies), and serious imprecision (wide confidence interval).

[e] Downgraded 1 level for: serious inconsistency (small number of studies).

[f] Downgraded 1 level for: serious risk of bias.

[g] Downgraded 3 levels for: very serious risk of bias, serious inconsistency (small number of studies), and serious imprecision (wide confidence interval).

(95% CI 0.06 to 0.63 very low certainty evidence, 3 trials, 300 participants). No effects were seen on calcium, phosphorous, and alkaline phosphatase (Appendices 13–18).

No studies were located that compared timing of initiation or duration of vitamin D supplementation.

DISCUSSION

Our systematic review found moderate certainty evidence of increase in weight, length, and reduction in vitamin D deficiency during first 6 months of life in human milk fed preterm or LBW infants who received vitamin D (200 IU to 800 IU per day). However, we did not find any effect on neurodevelopment, serious morbidities (necrotizing enterocolitis, BPD, all cause hospitalization) in the vitamin D supplementation groups. There was very low to low certainty evidence of reduction in serum parathyroid hormone and vitamin D deficiency status in the high dose vitamin D (800 to 1600 IU) supplemented groups. We also found no evidence on early versus late initiation of vitamin D supplementation on critical outcomes and serious adverse events.

Similar to our findings, a recent Cochrane review showed increase in height-for-age z-score (MD 0.11, 95% CI 0.001 to 0.22) in term infants at 6 months of age in the vitamin D supplemented groups.[45] However, another Cochrane review did not show any effect on linear growth in term breastfed infants 0 to 6 months of age.[46] There have been no published systematic reviews of the effect of vitamin D supplementation on growth among preterm or LBW infants. Similar to our findings, a systematic review in preterm infants showed that vitamin D supplementation increased vitamin D concentration (weighted mean difference: 29.4 nmol/L, 95% CI 17.9 to 41.0 nmol/L).[14] To our knowledge there has been only 1 systematic review[45] that has compared the effects of higher versus lower dose vitamin D supplementation. This review reported that higher-dose vitamin D supplementation (200 to 6000 IU daily; or up to 600 000 IU bolus at enrolment) had little to no effect on linear growth at 4 months (MD 1.00, 95% CI −2.22 to 0.21; 5 studies, 283 participants), and height for age z-scores at 7 months (MD 0.40, 95% CI −0.06 to 0.86; 2 studies, 105 participants; low-certainty evidence) compared with a lower dose of vitamin D (100 to 1000 IU daily; or up to 300 000 IU bolus at enrolment).

Our review had some limitations. Five of the included reports had "some concerns" and 11 reports had high risk of bias because of missing outcome data and bias in measurement of outcomes. There was also marked variability in duration of vitamin D supplementation and length of follow-up, and small sample sizes in the subgroup analyses. There were only 3 studies in the primary analysis and no studies from low-income countries. No studies were located that compared timing of initiation or duration of vitamin D supplementation. Strengths of the review include the comprehensive literature search, a priori specification of subgroup variables and number of participants. The study that contributed most data to the analysis was from a middle-income country setting (India) where the prevalence of maternal undernutrition was high. Our findings on growth outcomes also have biological plausibility, vitamin D is well known to influence calcium and bone mineral density, which is highly correlated with improved linear growth.[5,6]

In conclusion, our systematic review showed moderate certainty of evidence on the effect of enteral vitamin D supplementation for preterm and LBW infants on growth and vitamin D deficiency compared with no supplementation or placebo. However, there was little or no effect on mortality, morbidity, and neurodevelopmental outcomes. More RCTs are required to understand the optimal timing of initiation, duration of treatment, and dosing of enteral vitamin D supplementation for preterm and LBW infants.

ACKNOWLEDGMENTS

The Society for Applied Studies acknowledges the core support provided by the Department of Maternal, Newborn, Child and Adolescent Health, World Health Organization, Geneva (WHO Collaborating Centre IND-158).

ABBREVIATIONS

BPD: bronchopulmonary dysplasia
BSID: Bayley Scales of Infant and Toddler Development
CI: confidence interval
GRADE: Grading of Recommendations Assessment, Development and Evaluation
IQR: interquartile range
LBW: low birth weight
MD: Mean difference
RCT: randomized controlled trials
RR: relative risk
SD: standard deviation

FUNDING: This study was funded by the Department of Maternal, Newborn, Child and Adolescent Health and Ageing, World Health Organization (WHO), Geneva, Switzerland. The WHO commissioned the review for a guideline development group meeting for development of WHO recommendations on care of the preterm or low birth weight infant. The sponsor assisted in formulating the research question and provided inputs on the synthesis of the results and manuscript.

CONFLICT OF INTEREST DISCLOSURES: The authors have indicated they have no conflicts of interest to disclose.

REFERENCES

1. Dawodu A, Tsang RC. Maternal vitamin D status: effect on milk vitamin D content and vitamin D status of breastfeeding infants. *Adv Nutr*. 2012;3(3):353–361
2. Specker B. Vitamin D requirements during pregnancy. *Am J Clin Nutr*. 2004;80(6 Suppl):1740S–1747S
3. Abitbol CL, DeFreitas MJ, Strauss J. Assessment of kidney function in preterm infants: lifelong implications. *Pediatr Nephrol*. 2016;31(12):2213–2222
4. De Curtis M, Vetrano G. Absorption of proteins, carbohydrates and fats in the preterm neonate. *Pediatr Med Chir*. 1986;8(4):437–442
5. Blunt JW, DeLuca HF, Schnoes HK. 25-hydroxycholecalciferol. a biologically active metabolite of vitamin D3. *Biochemistry*. 1968;7(10):3317–3322
6. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M; Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics*. 2008;122(2):398–417
7. Specker BL, Tsang RC, Hollis BW. Effect of race and diet on human-milk vitamin D and 25-hydroxyvitamin D. *Am J Dis Child*. 1985;139(11):1134–1137
8. Zosky GR, Hart PH, Whitehouse AJO, et al. Vitamin D deficiency at 16 to 20 weeks' gestation is associated with impaired lung function and asthma at 6 years of age. *Ann Am Thorac Soc*. 2014;11(4):571–577
9. Hart PH, Lucas RM, Walsh JP, et al. Vitamin D in fetal development: findings from a birth cohort study. *Pediatrics*. 2015;135(1):e167–e173
10. Whitehouse AJO, Holt BJ, Serralha M, Holt PG, Kusel MMH, Hart PH. Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. *Pediatrics*. 2012;129(3):485–493
11. Javaid MK, Crozier SR, Harvey NC, et al; Princess Anne Hospital Study Group. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. *Lancet*. 2006;367(9504):36–43
12. Zhu K, Whitehouse AJ, Hart PH, et al. Maternal vitamin D status during pregnancy and bone mass in offspring at 20 years of age: a prospective cohort study. *J Bone Miner Res*. 2014;29(5):1088–1095
13. Walker VP, Zhang X, Rastegar I, et al. Cord blood vitamin D status impacts innate immune responses. *J Clin Endocrinol Metab*. 2011;96(6):1835–1843
14. Zittermann A, Pilz S, Berthold HK. Serum 25-hydroxyvitamin D response to vitamin D supplementation in infants: a systematic review and meta-analysis of clinical intervention trials. *Eur J Nutr*. 2020;59(1):359–369
15. Pharande P, Pammi M, Collins CT, Zhou SJ, Abrams SA. Vitamin D supplementation for prevention of vitamin D deficiency in preterm and low birth weight infants. Available at: http://doi.wiley.com/10.1002/14651858.CD011529. Accessed November 13, 2021
16. Chowdhury R, Shaikh S, Sinha B, et al. Enteral vitamin D supplementation in preterm or low birth weight infants: protocol for a systematic review. Available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021238989. Accessed November 13, 2021
17. Higgins JPT, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions version 6.2. Available at: www.training.cochrane.org/handbook. Accessed November 13, 2021
18. Veritas Health Innovation. Covidence systematic review software. Available at: www.covidence.org. Accessed November 13, 2021
19. Cochrane Effective Practice and Organisation of Care (EPOC). EPOC Resources for review authors. Available at: epoc.cochrane.org/epoc-resources-review-authors. Accessed November 13, 2021
20. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898
21. Mavridis D, Salanti G. How to assess publication bias: funnel plot, trim-and-fill method and selection models. *Evid Based Ment Health*. 2014;17(1):30
22. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560
23. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Available at: https://gradepro.org/cite/guidelinedevelopment.org/handbook. Accessed November 13, 2021
24. McMaster University. GRADEpro GDT: GRADEpro guideline development tool. Available at: https://gradepro.org/cite/gradepro.org. Accessed November 13, 2021
25. Aly H, Mohsen L, Bhattacharjee I, et al. Vitamin D supplementation and T cell regulation in preterm infants: a randomized controlled trial. *J Pediatr Gastroenterol Nutr*. 2019;69(5):607–610
26. Backström MC, Mäki R, Kuusela A-L, et al. Randomised controlled trial of vitamin D supplementation on bone density and biochemical indices in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 1999;80(3):F161–F166
27. Backström MC, Mäki R, Kuusela AL, et al. The long-term effect of early mineral,

vitamin D, and breast milk intake on bone mineral status in 9- to 11-year-old children born prematurely. *J Pediatr Gastroenterol Nutr*. 1999;29(5):575–582

28. Anderson-Berry A, Thoene M, Wagner J, et al. Randomized trial of two doses of vitamin D3 in preterm infants <32 weeks: dose impact on achieving desired serum 25(OH)D3 in a NICU population. *PLoS One*. 2017;12(10):e0185950
29. Bozkurt O, Uras N, Sari FN, et al. Multidose vitamin d supplementation in stable very preterm infants: prospective randomized trial response to three different vitamin D supplementation doses. *Early Hum Dev*. 2017;112:54–59
30. Evans JR, Allen AC, Stinson DA, et al. Effect of high-dose vitamin D supplementation on radiographically detectable bone disease of very low birth weight infants. *J Pediatr*. 1989;115(5 Pt 1):779–786
31. Kislal FM, Dilmen U. Effect of different doses of vitamin D on osteocalcin and deoxypyridinoline in preterm infants. *Pediatr Int*. 2008;50(2):204–207
32. Fort P, Salas AA, Nicola T, Craig CM, Carlo WA, Ambalavanan N. A comparison of 3 vitamin D dosing regimens in extremely preterm infants: a randomized controlled trial. *J Pediatr*. 2016;174:132–138.e1
33. Kumar GT, Sachdev HS, Chellani H, Rehman AM, Singh V, Arora H, et al. 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*. 2011;342:d2975–d2975
34. Trilok-Kumar G, Kaur M, Rehman AM, et al. 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*. 2015;44(3):894–905
35. Hanson C, Lyden E, Nelson A, et al. Response of vitamin D binding protein and free vitamin D concentrations to vitamin D supplementation in hospitalized premature infants. *J Pediatr Endocrinol Metab*. 2015;28(9–10):1107–1114
36. Hanson C, Armas L, Lyden E, Anderson-Berry A. Vitamin D status and associations in newborn formula-fed infants during initial hospitalization. *J Am Diet Assoc*. 2011;111(12):1836–1843
37. Hanson C, Jones G, Lyden E, Kaufmann M, Armas L, Anderson-Berry A. Vitamin D metabolism in the premature newborn: A randomized trial. *Clin Nutr*. 2016;35(4):835–841
38. Hibbs AM, Ross K, Kerns LA, et al. Effect of vitamin D supplementation on recurrent wheezing in Black infants who were born preterm: the D-wheeze randomized dlinical trial. *JAMA*. 2018;319(20):2086–2094
39. Tergestina M, Rebekah G, Job V, Simon A, Thomas N. A randomized double-blind controlled trial comparing two regimens of vitamin D supplementation in preterm neonates. *J Perinatol*. 2016;36(9):763–767
40. Mathur NB, Saini A, Mishra TK. Assessment of adequacy of supplementation of vitamin D in very low birth weight preterm neonates: a randomized controlled trial. *J Trop Pediatr*. 2016;62(6):429–435
41. Natarajan CK, Sankar MJ, Agarwal R, et al. Trial of daily vitamin D supplementation in preterm infants. *Pediatrics*. 2014;133(3):e628–e634
42. Salas AA, Woodfin T, Phillips V, Peralta-Carcelen M, Carlo WA, Ambalavanan N. Dose-response effects of early vitamin D supplementation on neurodevelopmental and respiratory outcomes of extremely preterm infants at 2 years of age: a randomized trial. *Neonatology*. 2018;113(3):256–262
43. Alizadeh Taheri P, Sajjadian N, Beyrami B, Shariat M. Prophylactic effect of low dose vitamin D in osteopenia of prematurity: a clinical trial study. *Acta Med Iran*. 2014;52(9):671–674
44. Golan-Tripto I, Bistritzer J, Loewenthal N, Staretz-Chacham O, Dizitzer Y, Goldbart A. The effect of vitamin D administration on vitamin D status and respiratory morbidity in late premature infants. *Pediatr Pulmonol*. 2020;55(11):3080–3087
45. Huey SL, Acharya N, Silver A, et al. Effects of oral vitamin D supplementation on linear growth and other health outcomes among children under five years of age. *Cochrane Database Syst Rev*. 2020;12:CD012875
46. Tan ML, Abrams SA, Osborn DA. Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health. *Cochrane Database Syst Rev*. 2020;12(12):CD013046