REVIEW

Vitamin D in Breastfed Infants: Systematic Review of Alternatives to Daily Supplementation

Karen M O'Callaghan,[1] Mahgol Taghivand,[1,2] Anna Zuchniak,[1,2] Akpevwe Onoyovwi,[1] Jill Korsiak,[1] Michael Leung,[1] and Daniel E Roth[1,2,3]

[1]Centre for Global Child Health and SickKids Research Institute, Hospital for Sick Children, Toronto, Canada; [2]Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Canada; and [3]Department of Pediatrics, Hospital for Sick Children and University of Toronto, Toronto, Canada

ABSTRACT

Daily oral vitamin D supplementation (400 IU) is recommended for breastfeeding infants (≤1 y). Recent studies have examined alternative approaches to preventing vitamin D deficiency in this population. This systematic review and meta-analysis aimed to estimate the effects of maternal postpartum (M-PP) or infant intermittent (I-INT) vitamin D supplementation on infant 25-hydroxyvitamin D [25(OH)D] concentrations in comparison to routine direct infant daily (I-D) oral supplementation (400 IU). MEDLINE, MEDLINE In-Process, Embase, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials were searched up to December 2018. Inclusion criteria consisted of published, peer-reviewed, vitamin D intervention trials involving lactating women and/or exclusively or partially breastfed term infants. Two reviewers independently extracted study characteristics (e.g., sample size, intervention dose, and duration and mode of administration) and related biochemical and clinical outcomes. Of 28 included trials, 5 randomized controlled trials were incorporated in meta-analyses examining infant 25(OH)D. Overall, M-PP supplementation resulted in modestly lower infant 25(OH)D compared with I-D supplementation (weighted mean difference = −8.1 nmol/L; 95% CI: −15.4, −0.9; $I^2 = 45\%$; $P = 0.14$; 3 trials), but the 2 most recent trials found M-PP to achieve similar infant 25(OH)D as I-D. Comparison of I-INT with I-D was confined to 2 trials with contradictory findings, and it was considered inappropriate for pooled analysis. Meta-analysis was therefore limited by a small number of eligible trials with variable quality of analytically derived 25(OH)D data and inconsistent reporting of safety outcomes, including effects on calcium homeostasis. Considering all 28 included trials, this systematic review highlights M-PP and I-INT regimens as plausible substitutes for routine daily infant vitamin D supplementation, but evidence remains too weak to support a policy update. Dose-ranging, adequately powered trials are required to establish the efficacy, safety, and feasibility of alternative strategies to prevent vitamin D deficiency in breastfeeding infants. This review was registered with PROSPERO as CRD42017069905. *Adv Nutr* 2020;11:144–159.

Keywords: 25-hydroxyvitamin D, micronutrient supplementation, rickets, vitamin D, vitamin D supplementation

Introduction

Routine vitamin D supplementation of breastfeeding infants is a core public health strategy for prevention of nutritional rickets in the United States (1), United Kingdom (2, 3) and Canada (4). This policy has been increasingly adopted in other regions (5) and has been proposed as a global recommendation, applicable even in tropical countries where rickets has emerged as a public health concern (6). It is well established that maternal prenatal 25-hydroxyvitamin D [25(OH)D] concentrations are a determinant of newborn vitamin D status, but beyond ∼2 mo of age, infants become dependent on other sources of vitamin D (6). Early infancy is therefore recognized as a life stage with a relatively high risk of deficiency (7, 8). The dose–response relation of 25(OH)D to epidermal UVB exposure in infants is unknown, but it would be expected to be dependent on individual and environmental factors such as skin pigmentation, clothing practices, latitude, and season (1, 9). Moreover, standard caution against direct exposure of infants to sunlight to avoid sunburn limits the potential for cutaneous vitamin D

KMO was supported by the SickKids Centre for Global Child Health Growth and Development Fellowship. AZ received support from the Canadian Institute of Health Research Canada Graduate Scholarships Master's Competition. The funding bodies had no role in the design, implementation, analysis, or interpretation of this work.
Author disclosures: KMO, MT, AZ, AO, JK, ML, and DER, no conflicts of interest.
Supplemental Tables 1–19 and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
Address correspondence to DER (e-mail: daniel.roth@sickkids.ca).
Abbreviations used: ALP, alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; Ca:Cr, calcium:creatinine ratio; I-D, infant daily; I-INT, infant intermittent; IOM, Institute of Medicine; M-PP, maternal postpartum; PTH, parathyroid hormone; RCT, randomized controlled trial; UL, upper limit; WMD, weighted mean difference; 3-epi-25(OH)D, 3-epi-25-hydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

production (1, 10), such that dietary or supplemental vitamin D is generally required in this age group.

Whereas commercial infant formulas are vitamin D fortified, human milk has historically been considered a poor source of vitamin D (~40 IU/L) (11–13). It is now known, however, that the vitamin D content of breast milk depends on maternal vitamin D intake (6) and can be modified by supplementation during lactation. Maternal vitamin D supplementation hence presents a pragmatic opportunity to provide infants with a natural source of vitamin D while simultaneously improving maternal vitamin D status (14). This approach has been suggested as an appealing strategy to mothers (15), and it could also be a feasible means of avoiding concerns that micronutrient supplementation in the first 6 mo of life may undermine public messaging regarding the optimality of exclusive breastfeeding during this period (16). In both pregnant women and nonpregnant adults, weekly or monthly supplementation can yield steady-state 25(OH)D concentrations similar to that attained by equivalent daily dosing regimens (17), yet only a limited number of trials have examined such regimens in lactating women. Intermittent infant dosing (e.g., weekly, monthly, or administered concurrently with routine immunizations) has also been proposed as an alternative to daily infant vitamin D supplementation (18), particularly in light of variations in adherence to existing recommendations (19). In Europe, single high doses or intermittent regimens in infancy were formerly used to both prevent and treat rickets (6), but their safety and efficacy with respect to maintenance of 25(OH)D at concentrations comparable to the standard daily regimen are not well established.

In this systematic review and meta-analysis of published trials, we primarily aimed to estimate the effect of maternal postpartum (M-PP) or infant intermittent (I-INT) vitamin D supplementation on circulating 25(OH)D in infancy (≤12 mo of age) in comparison to routine direct infant daily (I-D) oral supplementation (400 IU). Drawing upon a broader selection of studies including those that did not meet criteria for contribution to our primary aim, we synthesized the evidence pertaining to effects of alternative maternal and infant strategies on vitamin D status, safety parameters, and related health outcomes. Acknowledging potential forthcoming advances in this area, we also searched clinical trial registries to identify ongoing or unpublished trials that may be eligible for inclusion in future updates.

Methods

Search strategy

The search strategy was determined a priori (CRD42017069905) and conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (20). MEDLINE, MEDLINE In-Process, Embase, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials were searched from inception to December 4, 2018. A structured search strategy was devised using key terms selected from the Medical Subject Headings (MeSH) database (**Supplemental Table 1**). Bibliographies of selected papers were manually searched for additional references. No language or publication period restrictions were employed. In instances of missing data, efforts were made to contact corresponding authors, where necessary.

Eligibility

Inclusion criteria.

Prospective vitamin D (ergocalciferol or cholecalciferol) intervention trials were included for full-text article review if they met the following criteria: involved lactating women and/or exclusively or partially breastfed term infants; vitamin D supplementation was provided alone or in combination with a co-intervention that did not differ across intervention arms or was not considered to influence primary outcomes; and outcome data consisted of a maternal or infant circulating 25(OH)D concentration or related metabolite and/or serum or urinary calcium and/or calcium:creatinine ratio (Ca:Cr) and/or infant skeletal health outcomes including, but not limited to, rickets, fracture, bone mineral density (BMD), or bone mineral content (BMC) reported within the first 12 mo of life.

Exclusion criteria.

Trials were considered ineligible if the intervention was not assigned prospectively (e.g., medical record reviews); the intervention involved dose-ranging trial arms of I-D supplementation without an intermittent infant or a maternal supplementation arm; mode of infant feeding was not specified or infants received exclusive formula feeds only; or the sample population included participants presently diagnosed with rickets and/or any pre-existing metabolic disorder known to interfere with vitamin D metabolism.

Trials included in meta-analysis were limited to randomized controlled trials (RCTs) that permitted comparison of either M-PP (daily or intermittent) or I-INT vitamin D supplementation with routine vitamin D supplementation administered to a parallel control group (infants receiving 400 IU/d), and in which there was quantitative reporting of infant 25(OH)D outcomes (e.g., summary measures reported in tables or text, not just as figures). Studies not meeting the criteria for meta-analysis were summarized in the narrative review.

Data collection

Two reviewers independently screened titles and abstracts for inclusion using Covidence (21), a web-based systematic review platform. The full texts of relevant trials were assessed for eligibility, and any discrepancies were resolved following discussions with a third reviewer. REDCap (22) facilitated independent data extraction by 2 reviewers including country of origin, sample size, intervention dose, duration and mode of administration, and biochemical and clinical outcomes of interest. Risk of bias was assessed using the Cochrane Risk Assessment Tool (23), for which each trial was evaluated as having a high, low, or unclear risk of

bias based on the following 6 criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Criteria for "other" sources of bias was not defined a priori and was hence omitted from the current review. Bias assessment was based on the primary outcome of achieved maternal or infant 25(OH)D concentration or related metabolites following intervention. Any disagreements were resolved through consensus between reviewers.

For consistency, 25(OH)D concentrations were expressed in nanomoles per liter (1 ng/mL = 2.496 nmol/L), and all vitamin D doses were expressed in international units (1 μg = 40 IU). Where possible, distinctions were made between ergocalciferol (vitamin D-2) and cholecalciferol (vitamin D-3). Intermittent dosing regimens were defined as any dose provided less frequently than consistent daily supplementation.

Statistical analysis

The primary outcome was infant 25(OH)D concentration following intervention. Standard meta-analyses with random-effects models and inverse variance weights were performed to generate a weighted mean difference (WMD) and 95% CI using infant 25(OH)D as a continuous outcome. Statistical heterogeneity was quantified with the I^2 statistic (24). The effect of maternal supplementation (bolus or daily) compared with conventional I-D supplementation (400 IU) was assessed independently of the effect of I-INT supplementation. For trials with multiple intervention arms, study arms were disaggregated to create individual intervention–control comparison groups and included as separate entities in the meta-analysis. To avoid double-counting of participants, when multiple comparisons from the same trial were included in the same meta-analysis, the "shared" control group sample size was divided by the number of intervention arms (25). Meta-regressions for the primary outcome were planned for trial arms stratified by intervention dose (low compared with high), geographical region, and maternal or infant vitamin D status at randomization (<30 nmol/L compared with ≥30 nmol/L). Additional planned sensitivity analyses included restriction to trials with an overall low risk of bias. However, these secondary and sensitivity analyses were not performed due to the low number of eligible studies. All analyses were conducted using STATA, version 15.1 (Stata Corp.).

Identification of ongoing and planned trials

To determine the availability of newly anticipated data, 7 clinical trial registries (clinicaltrials.gov, WHO, ISRCTN, ANZCTR, DRKS, EU-CTR, and IRCT) were searched for current or planned trials of interest, as registered up to December 11, 2018. Trials were considered eligible if they met the primary inclusion criteria of vitamin D supplementation among apparently healthy breastfed infants or mother–infant pairs, if they had enrolled participants no earlier than January 2010, and if results were yet to be published in a peer-reviewed journal. Duplication of trials between registries was assessed by trial ID, title, intervention regimen, and trial investigators. All trials were screened independently for eligibility by a minimum of 2 reviewers, and any discrepancies were resolved by discussion with a third reviewer.

Results

Literature search and trial characteristics

From a total of 1652 texts screened for relevance, 35 articles fulfilled the inclusion criteria. Seven studies (26–32) were secondary or follow-up analyses of trials originally described in another article identified by the search strategy (**Supplemental Table 2**). Of the 28 distinct trials, 5 (33–37) were eligible for both narrative review and meta-analysis, and 23 (38–60) were summarized in narrative format only (**Figure 1**).

The 28 included trials contributed an overall sample size of 5908 participants or maternal–infant dyads, assigned to 72 individual trial arms. Year of publication ranged from 1978 to 2018 but was concentrated in the past decade (16/28 published in 2009 or after). All trials employed oral supplementation as the mode of administration, yet only a minority (11/28) quantified adherence (29, 33, 36, 37, 42–44, 47, 48, 52, 53). The majority of trials were conducted in the Americas (n = 9), followed by Europe (n = 5) and Southeast Asia (n = 5) (**Table 1**). Of the 26 trials that reported 25(OH)D analysis, 13 employed an immunoassay or combination of chromatography and immunoassay methods, for which Diasorin was the most commonly specified commercial manufacturer (n = 9). Proficiency testing was reported in 3 trials, all of which specified participation in the Vitamin D External Quality Assessment Scheme (DEQAS) (**Supplemental Table 3**). Six trials (21%) had low risk of bias across all criteria (23) (**Figure 2**).

The 5 RCTs (33–37) eligible for meta-analysis had small sample sizes (n range of 9–169 per trial arm at randomization), variations in study design and dosing frequency, and substantial between-trial differences in vitamin D status at randomization (Table 1 and **Table 2**).

Maternal postpartum supplementation

M-PP vitamin D supplementation was assessed in 19 trials, of which 14 (34, 35, 38–44, 46, 48, 50–52) used daily or weekly supplementation, 3 (33, 45, 53) included a bolus dosing regimen only, and 2 trials (47, 49) included both daily and bolus dosing regimens. Three of the trials (44, 48, 51) began supplementation prenatally, and 3 (40–42) included both maternal and infant supplementation in the same mother–infant pairs. Doses ranged from 400 to 6400 IU for daily regimens, whereas the cumulative doses provided by intermittent supplementation ranged from a single dose of 150,000 IU at delivery to >600,000 IU during the first 6 mo of lactation. Of the 17 trials that specified a calciferol form, most (n = 13; 76%) used vitamin D-3 (Table 1).

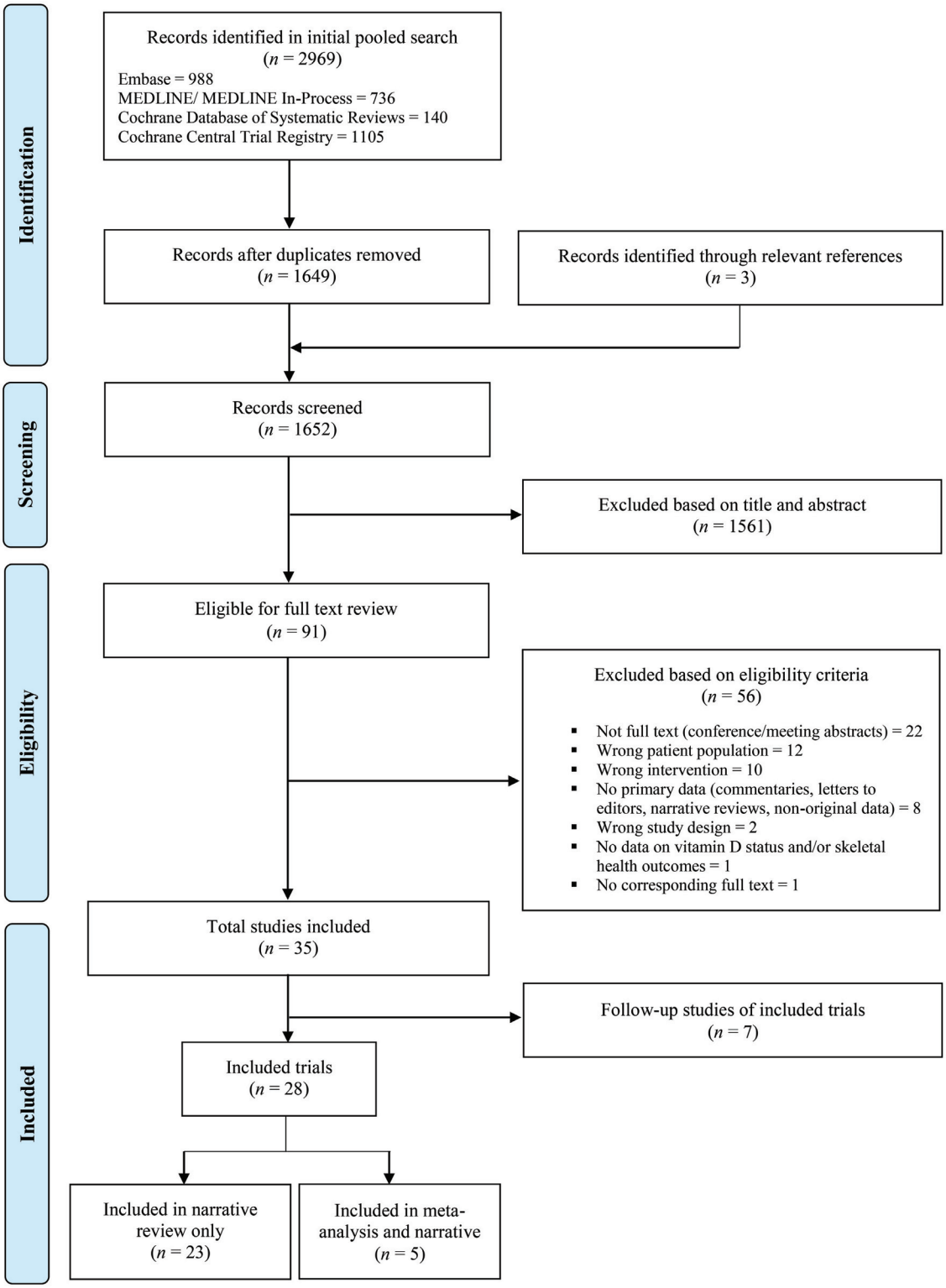

FIGURE 1 PRISMA flow diagram for screening and selection of studies for systematic review and meta-analysis of maternal postpartum or infant intermittent vitamin D supplementation. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Effects of maternal postpartum vitamin D supplementation on infant vitamin D status.

Among the 3 trials included in the meta-analysis, 1 used a bolus regimen (33), 2 had a low attrition rate (34, 35), and 2 lacked data on intervention adherence (34, 35). Weighted pooled analysis demonstrated a modestly lower infant vitamin D status after M-PP compared with I-D supplementation (WMD = −8.1 nmol/L; 95% CI: −15.4,

TABLE 1 Characteristics of all trials eligible for inclusion in the review[1]

Reference	Country	Design	Total *n* randomized	Maternal or infant supplementation	Form of vitamin D	Dose (IU)	Supplementation timing	Additional vitamin D and/or micronutrient supplementation[2]
				Maternal vs. infant supplementation				
Ala-Houhala (38)	Finland	RCT	32	Maternal	D-2[3]	1000/d	From delivery to 20 wk	
			29	Infant	N/S	1000/d		
			31	Infant	N/S	400/d		
			8	Maternal and infant	No intervention		From delivery to 8 wk	
Ala-Houhala et al. (39)	Finland	Nonrandomized prospective intervention	17	Maternal	D-3	2000/d	From delivery to 15 wk	
			16	Maternal	D-3	1000/d		
			16	Infant	D-2	400/d		
Buğrul et al. (40)	Turkey	Nonrandomized prospective intervention	50	Maternal	D-3	400/d	Within 1 mo of delivery to 6 mo	All infants received 400 IU/d vitamin D-3.
			50	Maternal	No intervention			
Chan et al. (41)	United States	Nonrandomized prospective intervention	29	Infant	N/S	400/d	From 2 wk to 12 mo	All lactating mothers consumed a daily multivitamin supplement containing 400 IU vitamin D and 250 mg calcium.
			22	Infant	No supplementation			
			40	Infant	N/S	400/L of formula (Similac)		
Chandy et al.[4] (33)	India	RCT	74	Maternal	D-3	120,000/mo	Within 7 d of delivery to 9 mo	Mothers received 500 mg/d calcium.
			78	Infant	D-3	400/d		
			78	Maternal and infant	Placebo			
Czech-Kowalska et al. (42)	Poland	Double-blind RCT	86	Maternal	D-3	800/d + 400/d from multivitamin	From delivery to 6 mo	Maternal multivitamin contained 200 mg/d calcium and all infants received 400 IU/d vitamin D-3.
			88	Maternal	D-3	0 + 400/d from multivitamin		
Hollis and Wagner (43)	United States	RCT	9	Maternal	D-2	3600/d	From 1 mo of delivery to 4 mo	All mothers received a multivitamin containing 400 IU/d vitamin D-3.
			9	Maternal	D-2	1600/d		

(*Continued*)

TABLE 1 (*Continued*)

Reference	Country	Design	Total *n* randomized	Maternal or infant supplementation	Form of vitamin D	Dose (IU)	Supplementation timing	Additional vitamin D and/or micronutrient supplementation[2]
Hollis et al.[4] (34)	United States	Double-blind RCT	165	Maternal	D-3	6000/d + 400/d from prenatal vitamin	Within 4–6 wk of delivery to 7 mo	Infants received a liquid drop containing placebo.
			55	Maternal	D-3	2000/d + 400/d from prenatal vitamin		
			169	Maternal	D-3	0 + 400/d from prenatal vitamin	Within 4–6 wk of delivery to 7 mo	Infants received a liquid supplement containing 400 IU/d vitamin D-3.
March et al. (44)	Canada	Double-blind RCT	74	Maternal	D-3	2000/d	From 13–24 weeks of gestation to 8 wk postpartum	Intervention dose provided in the form of a multivitamin.
			76	Maternal	D-3	1000/d		
			76	Maternal	D-3	400/d		
Naik et al. (45)	India	Double-blind RCT	65	Maternal	D-3	600,000	Provided as 60,000 IU/d from delivery to 10 d	All mothers received 500 mg/d calcium and 125 IU/d vitamin D-3 postnatally.
			65	Maternal		Placebo	From delivery to 10 d	
Niramitmahapanya et al. (46)	Thailand	Double-blind RCT	35	Maternal	D-3	1800/d	From delivery to 6 wk	
			33	Maternal		Placebo		
Oberhelman et al. (47)	United States	RCT	20	Maternal	D-3	150,000	Single dose at delivery	
			20	Maternal	D-3	5000/d	From delivery to day 28	
Roth et al. (48)	Bangladesh	Double-blind RCT	260	Maternal	D-3	28,000/wk prenatal and postpartum	From 17–24 weeks of gestation to 6 mo postpartum	All mothers received daily 500 mg calcium, 66 mg iron, and 350 μg folic acid throughout gestation.
			260	Maternal	D-3	28,000/wk prenatal, 0/wk postpartum		
			260	Maternal	D-3	16,800/wk prenatal, 0/wk postpartum		
			260	Maternal	D-3	4200/wk prenatal, 0/wk postpartum		
			260	Maternal	D-3	Placebo prenatal and postpartum		
Rothberg et al.[4] (35)	South Africa	Double-blind RCT	20	Maternal	N/S	1000/d	From delivery to 6 wk	
			20	Maternal	N/S	500/d		
			20	Maternal		Placebo		
			17	Infant	N/S	400/d		

(*Continued*)

TABLE 1 (*Continued*)

Reference	Country	Design	Total *n* randomized	Maternal or infant supplementation	Form of vitamin D	Dose (IU)	Supplementation timing	Additional vitamin D and/or micronutrient supplementation[2]
Saadi et al. (49)	United Arab Emirates	Open-label randomized intervention trial	45	Maternal	D-2	60,000/mo	From delivery to 3 mo	All mothers received 600 mg/d calcium. All infants received 400 IU/d vitamin D-2.[5]
			45	Maternal	D-2	2000/d		
Takeuchi et al. (50)	Japan	Nonrandomized prospective intervention	50[6]	Maternal	D-2	1200/d	From 1 wk after delivery to 5 wk	
				Maternal	No intervention			
Thiele et al. (51)	United States	Double-blind RCT	8	Maternal	D-3	3400/d + 400/d from prenatal vitamin	From 24–28 weeks of gestation to 4–6 wk postpartum	All mothers were encouraged to supplement their infants with 400 IU/d vitamin D.[7]
			8	Maternal	D-3	400/d from prenatal vitamin		
Wagner et al. (52)	United States	Pilot RCT	9	Maternal	D-3	6000/d + 400/d from prenatal vitamin	From 1 mo after delivery for 6 mo	
			10	Maternal	D-3	0 + 400/d from prenatal vitamin		All infants received a multivitamin containing 300 IU/d vitamin D-3.
Wheeler et al. (53)	New Zealand	RCT	30	Maternal	D-3	100,000/mo	From 4 to 20 wk postpartum	
			30	Maternal	D-3	50,000/mo		
			30	Maternal		Placebo		
					Infant bolus vs. daily supplementation			
Holst-Gemeiner et al. (54)	Germany	Nonrandomized prospective intervention	11	Infant	D-3	200,000	Single bolus dose at birth	
			10	Infant	D-3	1200/d	From day 2 to day 10 of life	
Huynh et al.[4] (36)	Australia	Open-label RCT	34	Infant	D-3	50,000	Single bolus dose within 48 h of birth	
			36	Infant	D-3	400/d	From birth to 4 mo	Intervention dose provided in the form of a multivitamin.
Kumar et al. (55)	India	Double-blind RCT	1039	Infant	D-3	1400/wk	From 7 d to 6 mo	
			1040	Infant		Placebo		

(*Continued*)

TABLE 1 (*Continued*)

Reference	Country	Design	Total *n* randomized	Maternal or infant supplementation	Form of vitamin D	Dose (IU)	Supplementation timing	Additional vitamin D and/or micronutrient supplementation[2]
Lagomarsino et al. (56)	Chile	Nonrandomized prospective intervention	35	Infant	D-3	600,000	At 1st and 6th months[1] of age	
			43	Infant	D-3	400/d	From 15 d to 6 mo	
Moodley and Spector (57)	Mexico	Double-blind RCT	51[6]	Infant	D-3	50,000	Single dose at birth	
				Infant		Placebo		
Shajari et al. (58)	Iran	Randomized intervention trial	30	Infant	D-3	50,000	Day 15 and day 60 after birth	
			30	Infant	D-3	400/d	From 15 d to 3 mo	
			30	Infant	D-3	200/d		
Shakiba et al.[4] (37)	Iran	Randomized intervention trial	30	Infant	D-3	50,000 every 2 mo	At days 15–30, 2 mo, and 4 mo	
			45	Infant	D-3	400/d	From days 15–30 to 6 mo	
			45	Infant	D-3	200/d		
Shakiba et al. (59)	Iran	Nonrandomized controlled trial	34	Infant	D-3	30,000	Single bolus dose within the 1st wk of life	Bolus supplementation was repeated after 1 mo if a 25(OH)D concentration > 75 nmol/L was not obtained. If achieved, infants received 400 IU/d vitamin D-3.
			48	Infant	D-3	400/d	Within 15 d to 4 mo	
Zeghoud et al. (60)	Algeria	Randomized intervention trial	30	Infant	D-3	600,000	Single bolus dose at 15 d	
			15	Infant	D-3	200,000	Single bolus dose at birth	
			15	Infant	D-3	100,000 every 3 mo	From birth to 6 mo	

[1] N/S, not specified; RCT, randomized controlled trial; 25(OH)D, 25-hydroxyvitamin D.
[2] Unless otherwise stated, no additional vitamin D or micronutrient supplements were provided to either mothers or infants during the trial period.
[3] Vitamin D supplementation form obtained from authors' later paper (39).
[4] Denotes trials eligible for inclusion in meta-analysis.
[5] Specified in the authors' later paper (29).
[6] Sample size per intervention arm at randomization unclear; reported as total sample size at baseline.
[7] Specified in the authors' later paper (32).

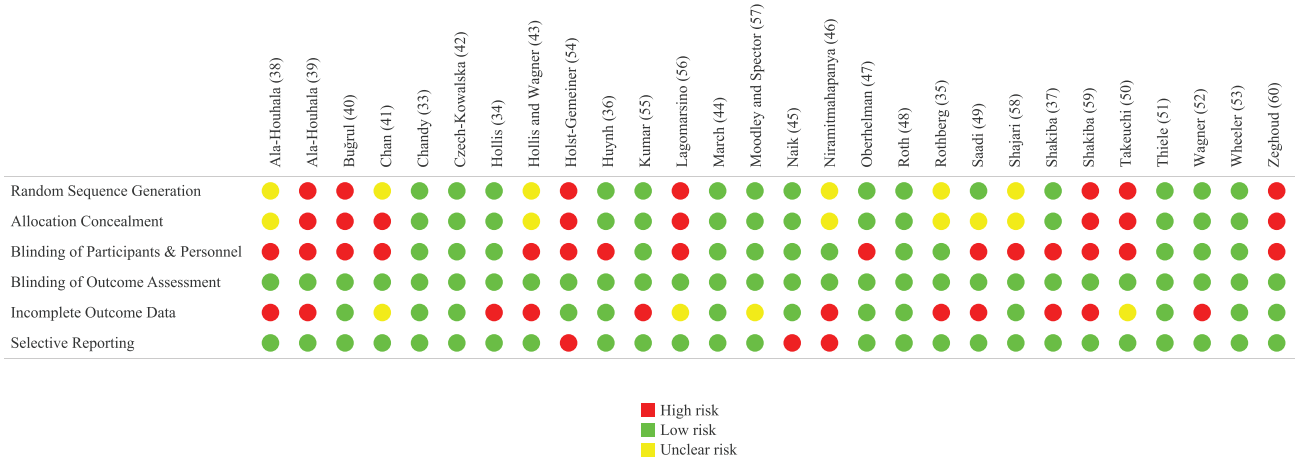

FIGURE 2 Risk of bias among trials included in the systematic review conducted using the Cochrane Risk Assessment Tool. Bias assessment was evaluated based on the primary outcome of maternal or infant achieved 25-hydroxyvitamin D concentrations or related metabolites following intervention.

−0.9; I^2 = 45%; P = 0.14) (**Figure 3**). Notably, the 2 most recent trials both concluded that M-PP achieved similar infant 25(OH)D concentrations to routine infant supplementation (400 IU/d) (Table 2).

Considering 16 additional trials included in the narrative review, trials of M-PP overall provided evidence of an effect of maternal vitamin D intake on infant 25(OH)D status, but the dose–response relation remained unclear (**Figure 4**, **Supplemental Table 4**). In 3 trials (29, 38, 43), supplementation of lactating women with vitamin D-2 was a pragmatic means of determining the unique contribution of the intervention to infantile vitamin D status, independent of UVB or other dietary contributions of vitamin D-3. However, only Hollis and Wagner (43) reported the separate quantification of circulating 25-hydroxyvitamin D-2 and 25-hydroxyvitamin D-3, demonstrating a dose-dependent effect of maternal vitamin D-2 supplementation on infant total 25(OH)D. Eight trials quantitatively reported the proportion of individuals meeting Institute of Medicine (IOM)-proposed thresholds for assessing vitamin D status

TABLE 2 Comparison of the response of infant 25(OH)D to intervention or control doses of vitamin D for trials considered eligible for inclusion in the meta-analysis[1]

			Baseline			Postsupplementation T1			Postsupplementation T2		
Reference	Total *n* randomized	Dose (IU)	*n*	25(OH)D (nmol/L)	Infant age	*n*	25(OH)D (nmol/L)	Infant age	*n*	25(OH)D (nmol/L)	Infant age
					Maternal vs. infant supplementation						
Chandy et al. (33)	74	120,000/m	NR			51	60.8 ± 29.0	3.5 mo		N/A	
	78	Control				47	61.3 ± 25.2			N/A	
Hollis et al. (34)	165	6400/d[2]	106	37.9 ± 23.3	4–6 wk	74	106.9 ± 35.1	4 mo	48	108.5 ± 38	7 mo
	169	Control	110	33.7 ± 23.5		74	109 ± 48		47	109.1 ± 31.8	
Rothberg et al. (35)	40[3]	1000/d	40[3]	22.2 ± 17.7[3]	Birth	9	23.5 ± 5.2	6 wk		N/A	
		500/d				9	25.5 ± 13.7			N/A	
		Placebo				10	2.7 ± 3.5			N/A	
		Control				12	37.9 ± 9.2			N/A	
					Infant bolus vs. daily supplementation						
Huynh et al. (36)	34	50,000	29	33 ± 19.3	Within 48 h of birth	31	154 ± 65.3	10 d	26	65 ± 15.6	4 mo
	36	Control	33	32 ± 13.6		31	48 ± 17.0		23	81 ± 9.8	
Shakiba et al. (37)	30	50,000 every 2 mo	NR			30	134.0 ± 48.7	4 mo		N/A	
	45	Control				26	95.8 ± 28.5			N/A	

[1] Values are means ± SDs unless otherwise noted. Control is defined as infants receiving 400 IU/d. N/A, not applicable. NR, not reported; T1, first follow-up time point; T2, second follow-up time point; 25(OH)D, 25-hydroxyvitamin D.
[2] 6400 IU/d provided as 6000 IU + 400 IU from prenatal supplement.
[3] Baseline data not reported separately by group.

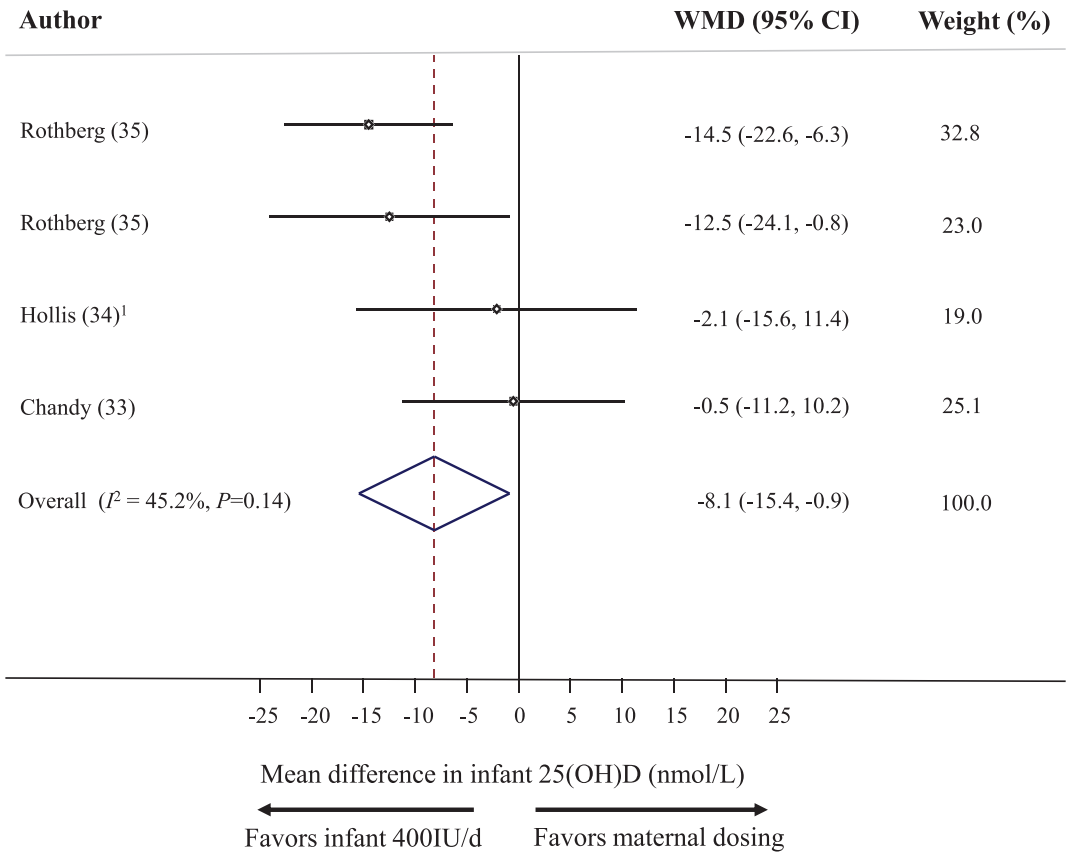

FIGURE 3 WMDs and 95% CIs for infant circulating 25-hydroxyvitamin D (25(OH)D) concentrations (nmol/L) in response to maternal postpartum vitamin D supplementation compared to direct infant supplementation with 400 IU/d, calculated from a random-effects model using inverse variance weights. Test for heterogeneity: $\chi^2 = 5.47$, df = 3 ($P = 0.14$), $I^2 = 45.2\%$. Test for overall effect: z = 2.19 ($P = 0.028$). [1]Mothers of the control group received 400 IU/d vitamin D-3.

(61). Most of the regimens attained concentrations >30 nmol/L in most or all infants, but the proportion surpassing the 50 nmol/L threshold was more variable (**Supplemental Tables 5** and **6**).

Effects of maternal postpartum vitamin D supplementation on maternal vitamin D status.

Wide between-study variation in the maternal 25(OH)D response to postpartum supplementation was apparent (**Supplemental Table 7**). Vitamin D metabolites were quantified in breast milk samples from 6 trials (26, 43, 47, 50, 52). Acknowledging potential analytical challenges in older studies (26, 50), the most recent evidence indicated elevations in breast milk antirachitic activity were predominantly attributable to an increase in the parent compound rather than circulating 25(OH)D (43, 47, 52).

Rickets and skeletal outcomes.

Prevalence of rickets was assessed in 8 trials, determined primarily by biochemical and/or clinical diagnosis. Only 2 trials reported on radiologically confirmed rickets. In contrast to our trial in Bangladesh, in which the presence of rickets was confined to the placebo and low-dose (4200 IU/wk prenatally and placebo postpartum) groups only (48), Naik et al. (45) reported an equal number ($n = 2$) of cases among infants of mothers receiving placebo and bolus dose (600,000 IU) supplementation. BMC was assessed in 2 trials, neither of which found intergroup differences following supplementation. In the only trial to assess infant BMD, similar between-group increases were shown throughout the intervention period when either 400 or 1200 IU/d vitamin D as maternal supplementation was combined with standard infant dosing (400 IU/d) (42) (**Supplemental Tables 8–10**).

Infant clinical outcomes and adverse effects.

The effect of maternal vitamin D supplementation on infant calcium homeostasis was described in 13 trials, 5 of which reported both circulating and urinary calcium measurements (Supplemental Table 5). Our combined prenatal and postpartum trial identified a small number of episodes of asymptomatic hypercalcemia following both high- and low-dose maternal supplementation (48). No trial found significant intergroup differences in infant urinary

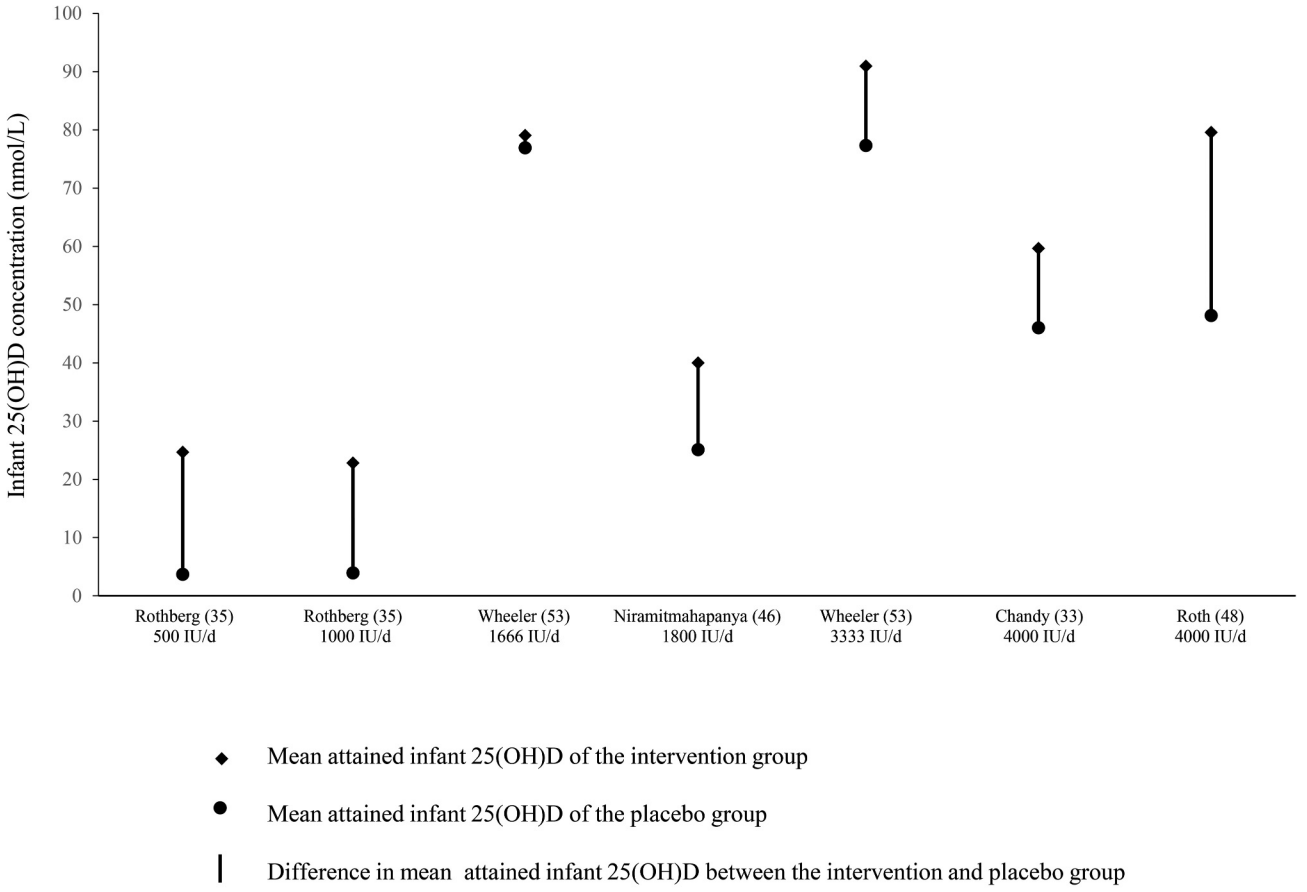

FIGURE 4 Mean attained infant 25(OH)D concentrations in response to maternal supplementation with vitamin D (diamonds) compared with placebo (circles) in order of vitamin D dose provided. Adjoining line represents the difference in mean attained 25(OH)D between the intervention and the placebo group following maternal vitamin D supplementation. Included trials were limited to those in which a placebo or null intervention group acted as a direct comparison to the trial arm involving maternal postpartum vitamin D supplementation. 25(OH)D, 25-hydroxyvitamin D.

Ca:Cr following maternal intervention. Although reported in only 5 trials, maternal supplementation was shown to have little or no impact on infant parathyroid hormone (PTH) concentrations. Among 4 trials that reported infant alkaline phosphatase (ALP), 2 showed significant decreases due to vitamin D supplementation (**Supplemental Tables 11–14**).

Maternal clinical outcomes and adverse effects.

All but 1 trial (40) described maternal calcium homeostasis as a safety measure (Supplemental Table 5), albeit with variable definitions of hypercalcemia and hypercalciuria. Overall, vitamin D supplementation produced a rise in serum calcium but without a clear dose–response relation; statistically significant increases from baseline were reported in only 2 trials, across a range of administered doses. Episodes of elevated maternal serum calcium concentrations were reported in 2 of 7 trials that assessed this outcome, but there was no evidence that specific maternal bolus regimens increased the risk of hypercalcemia. Hypercalciuria was documented in 8 of 12 trials that collected urinary measurements, for which the frequency did not differ among women receiving high- or low-dose supplementation (**Supplemental Tables 15** and **16**). Fewer than half ($n = 8$) of trials considered maternal PTH as an outcome measure, and only 4 trials reported maternal ALP (**Supplemental Tables 17** and **18**).

Intermittent infant supplementation

Nine trials examined infant bolus vitamin D supplementation, administered as single doses (36, 54, 57, 59, 60), at 2- or 3-mo intervals (37, 56, 58, 60), and as a weekly regimen (55). All trials specified vitamin D-3 as the calciferol form, for which the largest dose provided at any 1 time point was 600,000 IU (56, 60) (Table 1).

Effect of intermittent infant supplementation on infant vitamin D status.

Comparison of I-INT dosing to daily supplementation was limited to 2 RCTs that met criteria for inclusion in meta-analysis. Due to differences in study design and a high degree of statistical heterogeneity ($I^2 = 96\%$), the

conflicting results were deemed inappropriate for pooled analysis (Table 2).

Similar to the maternal response, the average incremental change in infant vitamin D status attributed to bolus supplementation varied considerably across trials. Peak concentrations were dose dependent, but later 25(OH)D values were dependent on the time since dosing, as expected based on vitamin D pharmacokinetics (62). Overall, evidence from trials of single or intermittent supplementation indicate that bolus dosing (>50,000 IU) achieves a 25(OH)D concentration >50 nmol/L earlier than daily dosing, but it is likely to have similar efficacy in preventing a low vitamin D status in later infancy (Supplemental Tables 4 and 6).

Rickets and skeletal outcomes.

Clinical examination for rickets was reported in only 2 of 9 trials, neither of which specified radiologic confirmation. Evidence of widened fontanelles was observed in 1 trial following both I-INT and I-D supplementation (Supplemental Tables 5 and 8). Infant BMC and BMD were not reported in any I-INT supplementation trial.

Infant clinical outcomes and adverse effects.

Five trials reported biomarkers of calcium homeostasis, of which 4 indicated a relatively modest dose–response rise in circulating calcium, but with low risk of hypercalcemia. Shajari et al. (58) reported a high prevalence of hypercalciuria among infants who had received 2 doses of 50,000 IU vitamin D-3, but the risk was not significantly greater compared with that for infants who had received conventional or low-dose daily supplementation. As with maternal supplementation, PTH or ALP responses were seldom considered (Supplemental Tables 5 and 11–14). Notably, 1 trial showed significant increases in blood pressure following administration of high-dose vitamin D (600,000 IU) relative to the control group that received 400 IU/d (56).

Ongoing and planned trials

We identified 4 registered trials with a combined target enrolment of 562 participants (**Supplemental Figure 1**, **Supplemental Table 19**). Two trials are located in low-middle income countries, in cities of latitudes <35°N (New Delhi, India, and Hawassa, Ethiopia), and 2 trials are located in areas of high Northern (Qazvin Province, Iran) or Southern (Victoria, Australia) latitude. Rickets was specified as a clinical outcome in 2 of the trials (Supplemental Table 19).

Discussion

Vitamin D supplementation is effective for preventing vitamin D deficiency in breastfed infants, and its implementation as a public health policy has been shown to reduce the prevalence of rickets in early childhood (63, 64). The recommendation of infant supplementation at 400 IU/d has been adopted by several health authorities worldwide. Both M-PP and I-INT supplementation represent plausible alternative strategies with the potential to improve adherence and increase maternal and societal acceptability. However, because the evidence base to support the use of these regimens has been uncertain, they have not been widely advocated or incorporated into public health programs. Known variations in the compliance rates of current policies, coinciding with documented increases in rickets prevalence, have prompted re-examination of existing strategies using a multidimensional approach that considers not only the physiological response to supplementation but also the acceptability and uptake within a given population (5, 18, 65).

To assess the efficacy of substitute maternal and infant supplementation regimes relative to current recommendations, we considered infant 25(OH)D as the primary outcome measure because relevant clinical or functional outcomes (e.g., rickets) are rare in the general pediatric population, and we did not expect to find trials designed or powered for such endpoints. Overall, the available evidence supports the biological plausibility of both M-PP and I-INT regimens for preventing vitamin D deficiency in breastfeeding infants. In particular, trials of lactating women have clearly demonstrated that high-dose maternal supplementation increases the antirachitic activity of breast milk, in turn raising serum 25(OH)D of breastfed infants (34, 47, 52). We identified 2 trials (33, 34) that support the potential bio-equivalency of maternal high-dose regimens (120,000 IU/mo and 6400 IU/d) in comparison to I-D dosing, as well as 16 other trials that did not make direct comparisons to the I-D standard but nonetheless provided evidence supporting the potential efficacy of maternal regimens. Because most of the breast milk vitamin D activity is attributable to the parent compound, it is recent maternal oral vitamin D intake or cutaneous production, rather than vitamin D status [characterized by maternal circulating 25(OH)D], that primarily determines vitamin D delivery to the breastfed infant (66). This nuanced distinction has important implications for the expected biochemical response of infant 25(OH)D, particularly with regard to bolus supplementation. Given the relatively short half-life of the parent compound (~24 h) (67), an analogous dose of vitamin D is provided via breast milk within the immediate days following maternal dose ingestion. Because relatively low daily vitamin D intakes may not achieve sufficiently high breast milk concentrations of vitamin D, dual maternal–infant supplementation regimens may be required to prevent both maternal and infant vitamin D deficiency (68). Despite the accumulated pharmacological data supporting M-PP as a viable strategy, we did not find evidence that is yet sufficient to introduce a new policy recommendation. This is largely attributable to a lack of direct comparisons of different maternal doses [i.e., identification of the minimum effective maternal dose for maintaining 25(OH)D >30 nmol/L in 97.5% of infants] and insufficient data substantiating the safety of M-PP doses higher than the IOM-established upper limit (UL; 4000 IU/d) (61). The current meta-analysis included the high-dose (6400 IU/d) RCT by Hollis (34); however, the unpublished findings from the intermediate dosing arm (2400

IU/d) may provide additional valuable dose–response data. In the only trial to utilize a bolus maternal supplementation regimen (120,000 IU/mo), a placebo-controlled design and well-characterized population produced a robust finding that maternal supplementation at a dose equivalent to the UL (61) can yield similar infant 25(OH)D as achieved by the standard I-D recommendation (33).

In comparison to the data corroborating M-PP supplementation, we found weaker evidence to support administration of large intermittent doses of vitamin D to the infant. Two trials (36, 37) demonstrated the ability of bolus doses to raise serum 25(OH)D concentrations in early infancy. Although both trials were affected by poor compliance with daily supplementation, which is itself an argument in favor of bolus dosing regimens, the higher mean difference in 25(OH)D at endpoint following daily compared with a single dose administration (36) highlights the need for repeated prophylaxis to maintain 25(OH)D thresholds consistent with deficiency prevention. Assuming steady depletion of 25(OH)D following a bolus dose, smaller quantities at more frequent intervals may be more effective in maintaining a replete vitamin D status, due to reduced activation of the *CYP24A1* gene (31). Acknowledging the small sample size of both trials, we emphasize cautious interpretation of these findings and possible underestimation of the risks of vitamin D toxicity. For example, 1 older trial reported elevations in blood pressure following single bolus dosing (600,000 IU) (56). Although this finding has not been explored further in recent trials, it highlights the importance of considering potential harms of megadoses of vitamin D by measuring outcomes beyond the conventional pharmacokinetic indicators of the vitamin D–calcium system. Nonetheless, there may be practical opportunities to deliver safe quantities of vitamin D in conjunction with existing public health programs that involve intermittent contact with the health system (e.g., routine immunizations), particularly in low-resource settings.

Although this review has highlighted the potential of alternative regimens, it is important to acknowledge that routine I-D supplementation is a successful public health strategy in some settings (5, 63). Therefore, in the absence of strong policy-relevant data to support M-PP or I-INT regimens at present, policymakers may draw upon the strong historical experience and recent evidence base to support implementation of the standard I-D recommendation. Irrespective of the regimen, continuous monitoring of uptake and adherence is critical for examining nationwide acceptance, and these should be monitored alongside trends in rickets prevalence (5). Because routine postpartum and child health surveillance visits are mandated in only a few countries, the broad application of M-PP regimens requires careful consideration in a context in which serum 25(OH)D or calcium would not be monitored. Rather, we believe the published evidence to date provides a strong foundation for the design of a large-scale, multisite pragmatic trial of M-PP supplementation compared with the standard of care I-D regimen.

Several limitations of this review and the underlying evidence base must be acknowledged. Substantial heterogeneity in study design, population characteristics, and outcome ascertainment limited between-trial comparisons and pooling of effect estimates. The inconsistent approach to safety outcome reporting, including effects on calcium homeostasis, precluded quantitative evaluation, and there was inadequate information to enable sensitivity analyses of trials at low risk of bias. This review was particularly challenged by differences in laboratory techniques to quantify 25(OH)D, which have been well described in the literature (69). The limited number of trials reporting performance testing or external quality assessment was unsurprising because several of the trials were published prior to the introduction of recent programs such as the Vitamin D Standardization Program (70). As noted by Carter (71), reliability of 25(OH)D measurements can only be determined based on knowledge of the laboratory platform and performance testing employed. Full disclosure of analytical methods is now widely considered a prerequisite for publication of clinical studies involving 25(OH)D, accordingly enabling generation of dose–response curves from pooled trial data. Infants have been observed to have relatively high concentrations of 3-epi-25-hydroxyvitamin D [3-epi-25(OH)D], an epimer with unclear biological significance but that may be inadvertently included in reported total 25(OH)D by some methods (72). It is therefore especially important to report the separate quantification of 25(OH)D and 3-epi-25(OH)D in pediatric populations. Given the potential for wide intra- and intermanufacturer variations in labeled product content (73), reporting of the analytically derived supplement composition should also be mandatory, together with adherence data, to ensure that changes in 25(OH)D can be evaluated as responses to precisely quantified doses of vitamin D. Despite the widespread reliance on 25(OH)D as a vitamin D status biomarker, data supporting effects on clinical outcomes (e.g., rickets) are more policy relevant. Because conventional RCTs may be unfeasible or expensive methods of measuring such effects, consideration should be given to other study designs that may be embedded in health systems or combined with the rollout of prevention programs.

Conclusions

The current review highlights the promising role of M-PP and I-INT dosing regimens to promote vitamin D sufficiency in breastfed infants. However, there remains a lack of robust efficacy and comprehensive safety data necessary to support a policy change. High-dose maternal postpartum supplementation—referring to doses of ≥4000 IU/d—holds particular promise and may be especially well-suited to populations that have a high baseline prevalence of vitamin D deficiency in women of reproductive age but where prevention programs have yet to be introduced (e.g., South Asia). Intermittent infant dosing also offers an alternative to daily dosing, but there remains uncertainty regarding safety and the long-term maintenance of 25(OH)D concentrations. Adequately powered, dose-ranging trials with careful

attention to safety monitoring should be designed to test alternatives to standard I-D strategies. Future trials should target the minimum effective dose for prevention of both maternal and infant deficiency, as well as establish the safety of such regimens for application in the general population.

Acknowledgments

We thank Benjamin Wheeler (New Zealand Paediatric Surveillance Unit and Dunedin School of Medicine, Dunedin, New Zealand) and Alan Rothberg (University of the Witwatersrand, Johannesburg, South Africa) for kindly providing summary statistics and/or clarifications regarding their published findings. We also thank Lily Ren of the Hospital for Sick Children Learning Institute for her assistance in conducting the database search for this review, using the agreed upon search terms and phrases. The authors' responsibilities were as follows—DER: conceptualized and designed the study, provided methodological oversight, supervised study activities, and had responsibility for the final content; AO and JK: contributed to the design of the data extraction instruments and performed literature screening; ML: designed the data extraction instruments and contributed to statistical analyses; MT and AZ: performed literature screening, data extraction, and bias assessment and identified registered trials; KMO: performed literature screening, data extraction, and bias assessment, identified registered trials, conducted statistical analyses, and drafted the initial manuscript; and all authors: read and approved the final manuscript and agree to be accountable for all aspects of the work.

References

1. Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics 2008;122(5):1142–52.
2. Scientific Advisory Committee on Nutrition. Report on vitamin D and health. London: Public Health England; 2016.
3. Scientific Advisory Committee on Nutrition. Update on vitamin D: position statement by the Scientific Advisory Committee on Nutrition. London: Public Health England; 2007.
4. Infant Feeding Joint Working Group. Nutrition for healthy term infants: recommendations from birth to six months. [Internet][cited 2019 Mar 3]. Ottawa (Canada): Health Canada. Available from: https://www.canada.ca/en/health-canada/services/canada-food-guide/resources/infant-feeding/nutrition-healthy-term-infants-recommendations-birth-six-months.html.
5. Uday S, Kongjonaj A, Aguiar M, Tulchinsky T, Hogler W. Variations in infant and childhood vitamin D supplementation programmes across Europe and factors influencing adherence. Endocr Connect 2017;6(8):667–75.
6. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, Michigami T, Tiosano D, Mughal MZ, Makitie O, et al. Global consensus recommendations on prevention and management of nutritional rickets. Horm Res Paediatr 2016;85(2):83–106.
7. Saraf R, Morton SM, Camargo CA, Jr, Grant CC. Global summary of maternal and newborn vitamin D status—a systematic review. Matern Child Nutr 2016;12(4):647–68.
8. Manios Y, Moschonis G, Lambrinou CP, Tsoutsoulopoulou K, Binou P, Karachaliou A, Breidenassel C, Gonzalez-Gross M, Kiely M, Cashman KD. A systematic review of vitamin D status in southern European countries. Eur J Nutr 2018; 57(6):2001–36.
9. Webb AR. Who, what, where and when—influences on cutaneous vitamin D synthesis. Prog Biophys Mol Biol 2006;92(1):17–25.
10. Committee on Environmental Health. Ultraviolet light: a hazard to children. Pediatrics 1999;104(2):328–33.
11. 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):1134–7.
12. Reeve LE, Chesney RW, DeLuca HF. Vitamin D of human milk: identification of biologically active forms. Am J Clin Nutr 1982;36(1):122–6.
13. Hollis BW, Roos BA, Draper HH, Lambert PW. Vitamin D and its metabolites in human and bovine milk. J Nutr 1981;111(7):1240–8.
14. Hollis BW, Pittard WB, Reinhardt TA. Relationships among vitamin D, 25-hydroxyvitamin D, and vitamin D-binding protein concentrations in the plasma and milk of human subjects. J Clin Endocrinol Metab 1986;62(1):41–4.
15. Umaretiya PJ, Oberhelman SS, Cozine EW, Maxson JA, Quigg SM, Thacher TD. Maternal preferences for vitamin D supplementation in breastfed infants. Ann Fam Med 2017;15(1):68–70.
16. Centers for Disease Control and Prevention. Report of the Vitamin D Expert Panel meeting. Atlanta (GA): Centers for Disease Control and Prevention; 2001.
17. Ish-Shalom S, Segal E, Salganik T, Raz B, Bromberg IL, Vieth R. Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. J Clin Endocrinol Metab 2008;93(9):3430–5.
18. Roth DE, Abrams SA, Aloia J, Bergeron G, Bourassa MW, Brown KH, Calvo MS, Cashman KD, Combs G, De-Regil LM, et al. Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. Ann N Y Acad Sci 2018;1430(1):44–79.
19. Lehtonen E, Ormisson A, Nucci A, Cuthbertson D, Sorkio S, Hyytinen M, Alahuhta K, Berseth C, Salonen M, Taback S, et al. Use of vitamin D supplements during infancy in an international feeding trial. Public Health Nutr 2014;17(4):810–22.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
21. Veritas Health Innovation. Covidence systematic review software. [Internet][cited 2019 May 17]. Melbourne (Australia): Veritas Health Innovation. Available from: https://www.covidence.org.
22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377–81.
23. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
24. Higgins J, Thompson S. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539–58.
25. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0. [Internet]. [updated March 2011] [cited 2018 Dec 6]. Available from: https://www.handbook.cochrane.org.
26. Ala-Houhala M, Koskinen T, Parviainen MT, Visakorpi JK. 25-Hydroxyvitamin D and vitamin D in human milk: effects of supplementation and season. Am J Clin Nutr 1988;48(4):1057–60.
27. Basile LA, Taylor SN, Wagner CL, Horst RL, Hollis BW. The effect of high-dose vitamin D supplementation on serum vitamin D levels and milk calcium concentration in lactating women and their infants. Breastfeed Med 2006;1(1):27–35.
28. Sen S, Penfield-Cyr A, Hollis BW, Wagner CL. Maternal obesity, 25-hydroxyvitamin D concentration, and bone density in breastfeeding dyads. J Pediatr 2017;187:147–52.
29. Saadi HF, Dawodu A, Afandi B, Zayed R, Benedict S, Nagelkerke N, Hollis BW. Effect of combined maternal and infant vitamin D supplementation on vitamin D status of exclusively breastfed infants. Matern Child Nutr 2009;5(1):25–32.

30. Trilok-Kumar G, Arora H, Rajput M, Chellani H, Singh V, Raynes J, Arya S, Aggarwal S, Srivastava N, Sachdev HPS, et al. Effect of vitamin D supplementation of low birth weight term Indian infants from birth on cytokine production at 6 months. Eur J Clin Nutr 2012;66(6): 746–50.
31. Ketha H, Thacher TD, Oberhelman SS, Fischer PR, Singh RJ, Kumar R. Comparison of the effect of daily versus bolus dose maternal vitamin D3 supplementation on the 24,25-dihydroxyvitamin D3 to 25-hydroxyvitamin D3 ratio. Bone 2018;110:321–5.
32. Anderson CM, Gillespie SL, Thiele DK, Ralph JL, Ohm JE. Effects of maternal vitamin D supplementation on the maternal and infant epigenome. Breastfeed Med 2018;13(5):371–80.
33. Chandy DD, Kare J, Singh SN, Agarwal A, Das V, Singh U, Ramesh V, Bhatia V. 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 2016;116(1):52.
34. Hollis BW, Wagner CL, Howard CR, Ebeling M, Shary JR, Smith PG, Taylor SN, Morella K, Lawrence RA, Hulsey TC. Maternal versus infant vitamin D supplementation during lactation: a randomized controlled trial. Pediatrics 2015;136(4):625–34.
35. Rothberg AD, Pettifor JM, Cohen DF, Sonnendecker EWW, Ross FP. Maternal–infant vitamin D relationships during breast-feeding. J Pediatr 1982;101(4):500–3.
36. Huynh J, Lu T, Liew D, Doery JCG, Tudball R, Jona M, Bhamjee R, Rodda CP. Vitamin D in newborns: a randomised controlled trial comparing daily and single oral bolus vitamin D in infants. J Pediatr Child Health 2017;53(2):163.
37. Shakiba M, Sadr S, Nefei Z, Mozaffari-Khosravi H, Lotfi MH, Bemanian MH. Combination of bolus dose vitamin D with routine vaccination in infants: a randomised trial. Singapore Med J 2010;51(5):440–5.
38. Ala-Houhala M. 25-Hydroxyvitamin D levels during breast-feeding with or without maternal or infantile supplementation of vitamin D. J Pediatr Gastroenterol Nutr 1985;4(2):220–6.
39. Ala-Houhala M, Koskinen T, Terho A, Koivula T, Visakorpi J. Maternal compared with infant vitamin D supplementation. Arch Dis Child 1986;61(12):1159–63.
40. Buğrul F, Devecioğlu E, Özden T, Gökçay G, Ömer B. Effect of maternal and infant vitamin D supplementation on vitamin D levels of breastfed infants. Turk J Pediatr 2013;55(2):158.
41. Chan GM, Roberts CC, Folland D, Jackson R. Growth and bone mineralization of normal breast-fed infants and the effects of lactation on maternal bone mineral status. Am J Clin Nutr 1982;36(3): 438–43.
42. Czech-Kowalska J, Latka-Grot J, Bulsiewicz D, Jaworski M, Pludowski P, Wygledowska G, Chazan B, Pawlus B, Zochowska A, Borszewska-Kornacka M, et al. Impact of vitamin D supplementation during lactation on vitamin D status and body composition of mother–infant pairs: a MAVID randomized controlled trial. PLoS One 2014;9(9):e107708.
43. Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. Am J Clin Nutr 2004;80(6):1752S–8S.
44. March KM, Chen NN, Karakochuk CD, Shand AW, Innis SM, von Dadelszen P, Barr SI, Lyon MR, Whiting SJ, Weiler HA, et al. Maternal vitamin D(3) supplementation at 50 μg/d protects against low serum 25-hydroxyvitamin D in infants at 8 wk of age: a randomized controlled trial of 3 doses of vitamin D beginning in gestation and continued in lactation. Am J Clin Nutr 2015;102(2):402–10.
45. Naik P, Faridi MMA, Batra P, Madhu SV. Oral supplementation of parturient mothers with Vitamin D and its effect on 25OHD status of exclusively breastfed infants at 6 months of age: a double-blind randomized placebo controlled trial. Breastfeed Med 2017;12(10): 621–8.
46. Niramitmahapanya S, Kaoiean S, Sangtawesin V, Patpanaprapan A, Bordeerat NK, Deerochanawong C. Effect on vitamin D status of breastfeeding infants after vitamin D3 supplementation during breastfeeding lactation: a double-blind randomized controlled trial. Ann Clin Endocrinol Metabol 2017;1:006–14.
47. Oberhelman SS, Meekins ME, Fischer PR, Lee BR, Singh RJ, Cha SS, Gardner BM, Pettifor JM, Croghan IT, Thacher TD. Maternal vitamin D supplementation to improve the vitamin D status of breast-fed infants: a randomized controlled trial. Mayo Clin Proc 2013;88(12): 1378–87.
48. Roth DE, Morris SK, Zlotkin S, Gernand AD, Ahmed T, Shanta SS, Papp E, Korsiak J, Shi J, Islam MM, et al. Vitamin D supplementation in pregnancy and lactation and infant growth. N Engl J Med 2018;379(6):535–46.
49. Saadi HF, Dawodu A, Afandi BO, Zayed R, Benedict S, Nagelkerke N. Efficacy of daily and monthly high-dose calciferol in vitamin D-deficient nulliparous and lactating women. Am J Clin Nutr 2007;85(6): 1565–71.
50. Takeuchi A, Okano T, Tsugawa N, Tasaka Y, Kobayashi T, Kodama S, Matsuo T. Effects of ergocalciferol supplementation on the concentration of vitamin D and its metabolites in human milk. J Nutr 1989;119(11):1639–46.
51. Thiele DK, Ralph J, El-Masri M, Anderson CM. Vitamin D3 supplementation during pregnancy and lactation improves vitamin D status of the mother–infant dyad. J Obstet Gynecol Neonatal Nurs 2017;46(1):135–47.
52. Wagner CL, Hulsey TC, Fanning D, Ebeling M, Hollis BW. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. Breastfeed Med 2006;1(2):59–70.
53. Wheeler BJ, Taylor BJ, Herbison P, Haszard JJ, Mikhail A, Jones S, Harper MJ, Houghton LA. High-dose monthly maternal cholecalciferol supplementation during breastfeeding affects maternal and infant vitamin D status at 5 months postpartum: a randomized controlled trial. J Nutr 2016;146(10):1999.
54. Holst-Gemeiner D, Gemeiner M, Pilz I, Swoboda W. Plasma 25-hydroxycholecalciferol after daily vitamin D administration in comparison with massive single-dose prophylaxis (author's transl). Wien Klin Wochenschr 1978;90(14):509–12.
55. Kumar G, Sachdev H, Chellani H, Rehman A, Singh V, Arora H, Filteau S. 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.
56. Lagomarsino EF, Arnaiz PG, Vial PC, Heusser FR, Cantwell MA, Johnson MCP, Foradori AC. Efecto de dos formas de suplementación de vitamina D en el crecimiento y metabolismo óseo del lactante. Rev Chilena Pediatr 1996;67(5):219–23.
57. Moodley A, Spector SA. Single high-dose vitamin D at birth corrects vitamin D deficiency in infants in Mexico. Int J Food Sci Nutr 2015;66(3):336.
58. Shajari A, Shakiba M, Nourani F, Zaki M, Kheirandish M. Urinary calcium/creatinin ratio with different dosages of vitamin D3 prophylaxis in infants. Iran J Pediatr 2009;19(2):159–63.
59. Shakiba M, Pahloosye A, Mirouliaei M, Islami Z. Comparison of two regimens of vitamin D supplementation for vitamin D-deficient neonates. Singapore Med J 2014;55(5):266–70.
60. Zeghoud F, Ben-Mekhbi H, Djeghri N, Garabedian M. 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 1994;60(3):393–6.
61. Institute of Medicine. Dietary Reference Intakes for calcium and vitamin D. Washington (DC): National Academies Press; 2011.
62. Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr 2008;88(2):582S–6S.
63. Hatun S, Ozkan B, Bereket A. Vitamin D deficiency and prevention: Turkish experience. Acta Paediatr 2011;100(9):1195–9.
64. Lerch C, Meissner T. Interventions for the prevention of nutritional rickets in term born children. Cochrane Database Syst Rev 2007;(4):cd006164.
65. Oberhelman SS, Cozine EW, Umaretiya PJ, Maxson JA, Thacher TD. Vitamin D and the breastfeeding infant: family medicine

clinicians' knowledge, attitudes, and practices. J Hum Lact 2018;34(2):331–6.
66. Hollis BW, Wagner CL. Clinical review: the role of the parent compound vitamin D with respect to metabolism and function: why clinical dose intervals can affect clinical outcomes. J Clin Endocrinol Metab 2013;98(12):4619–28.
67. Clemens TL, Adams JS, Nolan JM, Holick MF. Measurement of circulating vitamin D in man. Clin Chim Acta 1982;121(3):301–8.
68. Aghajafari F, Field CJ, Weinberg AR, Letourneau N. Both mother and infant require a vitamin D supplement to ensure that infants' vitamin D status meets current guidelines. Nutrients 2018;10(4):E429.
69. Wise SA, Phinney KW, Tai SS, Camara JE, Myers GL, Durazo-Arvizu R, Tian L, Hoofnagle AN, Bachmann LM, Young IS, et al. Baseline assessment of 25-hydroxyvitamin D assay performance: a vitamin D standardization program (VDSP) interlaboratory comparison study. J AOAC Int 2017;100(5):1244–52.
70. Sempos CT, Vesper HW, Phinney KW, Thienpont LM, Coates PM. Vitamin D status as an international issue: national surveys and the problem of standardization. Scand J Clin Lab Invest Suppl 2012;243:32–40.
71. Carter GD. Accuracy of 25-hydroxyvitamin D assays: confronting the issues. Curr Drug Targets 2011;12(1):19–28.
72. Bailey D, Perumal N, Yazdanpanah M, Al Mahmud A, Baqui AH, Adeli K, Roth DE. Maternal–fetal–infant dynamics of the C3-epimer of 25-hydroxyvitamin D. Clin Biochem 2014;47(9):816–22.
73. USDA. Adult multivitamin/mineral (adult MVM-2017) dietary supplement national study: research summary. [Internet] [cited 2018 Jul 25]. 2017 Available from: https://dietarysupplementdatabase.usda.nih.gov/dsid_database/Res%20Summ%20DSID%204%20Adult%20MVM-8-2-17%20final.pdf .