Review Article

Global summary of maternal and newborn vitamin D status – a systematic review

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Abstract

Pregnant women and newborns are at increased risk of vitamin D deficiency. Our objective was to create a global summary of maternal and newborn vitamin D status. We completed a systematic review (1959–2014) and meta-analysis of studies reporting serum 25-hydroxyvitamin D [25(OH)D] concentration in maternal and newborn populations. The 95 identified studies were unevenly distributed by World Health Organization (WHO) region: Americas (24), European (33), Eastern Mediterranean (13), South-East Asian (7), Western Pacific (16) and African (2). Average maternal 25(OH)D concentrations (nmol L^{-1}) by region were 47–65 (Americas), 15–72 (European), 13–60 (Eastern Mediterranean), 20–52 (South-East Asian), 42–72 (Western Pacific) and 92 (African). Average newborn 25(OH)D concentrations (nmol L^{-1}) were 35–77 (Americas), 20–50 (European), 5–50 (Eastern Mediterranean), 20–22 (South-East Asian), 32–67 (Western Pacific) and 27–35 (African). The prevalences of 25(OH)D <50 and <25 nmol L^{-1} by WHO region in pregnant women were: Americas (64%, 9%), European (57%, 23%), Eastern Mediterranean (46%, 79%), South-East Asian (87%, not available) and Western Pacific (83%, 13%). Among newborns these values were: Americas (30%, 14%), European (73%, 39%), Eastern Mediterranean (60%, not available), South-East Asian (96%, 45%) and Western Pacific (54%, 14%). By global region, average 25(OH)D concentration varies threefold in pregnant women and newborns, and prevalence of 25(OH)D <25 nmol L^{-1} varies eightfold in pregnant women and threefold in newborns. Maternal and newborn 25(OH)D concentrations are highly correlated. Addressing vitamin D deficiency in pregnant women and newborns should be a global priority. To protect children from the adverse effects of vitamin D deficiency requires appropriate interventions during both pregnancy and childhood.

Keywords: prevalence, 25-hydroxyvitamin D, vitamin D deficiency, pregnancy, newborn, vitamin D.

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Introduction

Two recent meta-analyses have shown that lower serum 25-hydroxyvitamin D [25(OH)D] concentrations during pregnancy are associated with poor health outcomes for pregnant women and newborns (Aghajafari *et al*. 2013; Wei *et al*. 2013). The first meta-analysis examined 31 observational studies using a range of serum 25(OH)D concentration cut-off values (from 20 to 80 nmol L^{-1}) and showed that lower serum 25(OH)D concentration during pregnancy was associated with an increased risk of gestational diabetes, pre-eclampsia and small for gestational age (Aghajafari *et al*. 2013). The second meta-analysis examined 24 studies and showed that a serum 25(OH)D concentration <50 nmol L^{-1}

was associated with an increased risk of gestational diabetes, pre-eclampsia, preterm birth and small for gestational age (Wei *et al.* 2013).

Likewise, four global summaries of vitamin D status across the complete age range were published in the past 5 years (Hagenau *et al.* 2009; Mithal *et al.* 2009; Arabi *et al.* 2010; Hilger *et al.* 2014). The first meta-analysis examined 394 studies published from 1970 to 2004, including all studies globally that reported original data on serum 25(OH)D concentration (Hagenau *et al.* 2009). Mean serum 25(OH)D concentration was 54 nmol L^{-1}; serum 25(OH)D concentrations were higher in women compared with men, in Caucasians compared with non-Caucasians and in subjects >15 years old vs. those younger (Hagenau *et al.* 2009). The second meta-analysis examined 195 studies published from 1990 to 2011, including data from 44 countries, to describe patterns of 25(OH)D concentration worldwide by age, sex and region (Hilger *et al.* 2014). This review reported a mean 25(OH)D concentration range of 5–137 nmol L^{-1} with 37% of the included studies reporting mean 25(OH)D concentrations <50 nmol L^{-1} (Hilger *et al.* 2014). Age-related differences in 25(OH)D concentrations were observed in the Asia/Pacific and Middle East/African regions, with newborns and institutionalized elderly generally at higher risk of lower serum 25(OH)D concentrations (Hilger *et al.* 2014). The third meta-analysis examined 121 published studies from 1962 to 2009 to describe vitamin D status in six global regions: Asia, Europe, Middle East and Africa, Latin America, North America and Oceania (Mithal *et al.* 2009).

This review found that the prevalence of serum 25(OH)D <75 nmol L^{-1} varied widely (2–97%) in all six study regions. Serum 25(OH)D concentrations <25 nmol L^{-1} were more prevalent in the Asian (18–48%) and Middle Eastern (9–80%) regions (Mithal *et al.* 2009). The fourth meta-analysis focused on the prevalence of vitamin D deficiency in developing countries (Arabi *et al.* 2010). The review showed wide variability in serum 25(OH)D concentrations between and within different regions. In one-third to one-half of those living in sub-Saharan and Middle Eastern regions serum 25(OH)D concentrations were <25 nmol L^{-1} (Arabi *et al.* 2010). Vitamin D status was also described to be lower in China and Mongolia, especially in children, of whom up to 50% were reported to have serum 25(OH)D concentrations <12.5 nmol L^{-1} (Arabi *et al.* 2010).

Pregnant women and newborns are recognized as populations at increased risk of poor vitamin D status (Dawodu & Wagner 2007). All four meta-analyses on vitamin D status in the general population identified women and newborns as groups at increased risk of serum 25(OH)D concentrations <25 nmol L^{-1} (Hagenau *et al.* 2009; Mithal *et al.* 2009; Arabi *et al.* 2010; Hilger *et al.* 2014). To date, however, there has been no specific attempt to describe vitamin D status in maternal and newborn populations at a global level. Given the potential for poor vitamin D status during pregnancy to affect maternal and child outcomes that remain important determinants of global health, our objective was to provide a global summary of vitamin D status in pregnant women and newborns.

Key messages

- Globally, vitamin D deficiency, 25-hydroxyvitamin D [25(OH)D] concentration <50 nmol L^{-1}, is present in 54% of pregnant women and 75% of newborns, and severe vitamin D deficiency, 25(OH)D concentration <25 nmol L^{-1} in 18% of pregnant women and 29% of newborns.
- Currently, vitamin status is poorly defined in the African, South-East Asian and Eastern Mediterranean regions and in non-European populations in the Western Pacific region.
- Future studies of vitamin D status should report 25(OH)D results using standard cut-off values of <50 and <25 nmol L^{-1}.
- Future studies of vitamin D status should measure 25(OH)D concentrations using assays that have greater accuracy and precision and strong correlation with each other.

Methods

Search method

We identified published epidemiological studies that describe vitamin D status in women, either during pregnancy or at delivery (maternal studies), or in babies at birth (newborn studies). Publications were identified initially through searches of three databases: MEDLINE (Ovid), Embase and Cochrane Library. The search engines of MEDLINE (Ovid) and Embase are similar and, in both, the advanced search engine option was used. A Cochrane Library search was performed using title, abstract or keyword and could not be combined using Boolean operators.

The initial search was for publications reporting vitamin D status in pregnant women. The keywords used were 'pregnancy', 'mother', 'maternal', 'gestation', 'vitamin D' and 'cholecalciferol'. Searches using keywords with the same meaning such as pregnancy, mother, maternal and gestation were combined using the Boolean operator 'OR'. Vitamin D and cholecalciferol were also combined using 'OR'. Combining similar searches using 'OR' resulted in two major searches: maternal and vitamin D that were combined using 'AND'.

A similar search strategy was used to identify publications on newborn vitamin D status. The keywords used were 'neonatal', 'newborn', 'cord blood', 'fetal blood' and 'infant'. These keywords were combined with 'OR' and then combined using 'AND' with the keywords for vitamin D (vitamin D or cholecalciferol).

An initial review of titles and abstracts was undertaken followed by an in-depth review of full papers that could not be excluded by title and abstract alone. We excluded (1) non-human studies; (2) studies not in English; (3) case reports and commentaries that did not report data on vitamin D status; (4) studies that described vitamin D deficiency outcomes in pregnant women and/or newborns but without actual data on vitamin D status; and (5) other topics unrelated to the objectives of this review such as those papers reporting 25(OH)D data on general populations or on specific population age groups excluding maternal and newborn populations.

Identification and selection of studies

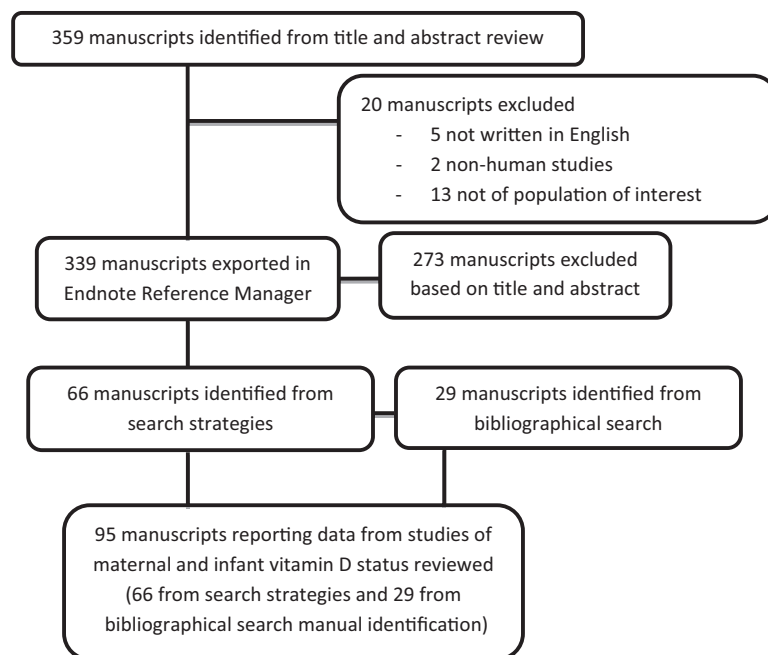We identified 359 publications through our database searches (Fig. 1). Twenty publications from the 359

Fig. 1. Screening and identification of studies on maternal and infant vitamin D status.

359 manuscripts identified from title and abstract review

20 manuscripts excluded
- 5 not written in English
- 2 non-human studies
- 13 not of population of interest

339 manuscripts exported in Endnote Reference Manager

273 manuscripts excluded based on title and abstract

66 manuscripts identified from search strategies

29 manuscripts identified from bibliographical search

95 manuscripts reporting data from studies of maternal and infant vitamin D status reviewed (66 from search strategies and 29 from bibliographical search manual identification)

retrieved articles were excluded during initial screening. The remaining 339 articles were exported into an EndNote reference manager database. The titles and/or abstracts of all identified studies were reviewed and full manuscripts obtained for all those that appeared potentially relevant. This title/abstract review identified 273 articles as being not relevant and 66 publications as being relevant to this review. Through bibliographic searches of these 66 studies, 29 additional studies were identified. A total of 95 papers were identified as relevant to the review (Supplementary Table S1).

Study characteristics

Study region and time interval

The 95 publications that reported circulating 25(OH)D concentrations in maternal and newborn populations were grouped by World Health Organization (WHO) global region of the study sample (Americas, European, Eastern Mediterranean, South-East Asian, Western Pacific and African). Once grouped by global region, the studies were further categorized according to decade during which the study was completed. Decade categories used were 1959–1979, 1980–1989, 1990–1999, 2000–2009 and 2010–2014 (Table 1). For publications where the date of sample enrolment was not provided, year of publication was used to define the study decade (Supplementary Table S1).

Reporting of maternal and newborn vitamin D status

The 95 publications were then categorized depending upon whether they reported vitamin D status in mothers only (34 publications), newborns only (9 publications) or both (52 publications) (Supplementary Table S1). The number of publications was unevenly distributed across the six WHO regions (Fig. 2): Americas (24 publications), European (33), Eastern Mediterranean (13), South-East Asian (7), Western Pacific (16) and African (2). In the Americas (14/24), European (19/33) and the Eastern Mediterranean (9/13) regions a larger proportion of the studies were on pregnant woman–newborn pairs then on either mothers or newborns separately (Fig. 2).

Meta-analysis

Without access to the raw data reported in each publication, we performed a meta-analysis to allow statistical comparison between WHO regions for the following outcomes: maternal and newborn 25(OH)D concentrations and prevalences of vitamin D deficiency and severe deficiency in these same two groups. In order to combine all the studies per region

Table 1. Number of publications reporting vitamin D status in pregnant women and newborns in each WHO region according to decade of sample enrolment or study publication

WHO region	Region population (in millions; United Nations 2013)	Women aged 15–64 years (in millions; United Nations 2013)	Study year					Total
			1959–1979	1980–1989	1990–1999	2000–2009	2010–2014	
Americas	1497	983	2 (1)	1	4 (1)	16	1	24
European	740	505	2	5 (4)	4 (1)	18	2 (1)	31
Eastern Mediterranean	4165	2821		2 (2)	4	9		15
South-East Asian				1	4	4 (1)		9
Western Pacific	37	24		1 (1)	1	7 (1)	5 (2)	14
African	1863	1016			1	1		2
Total	8302	5349	4	10	18	55	8	95

WHO, World Health Organization. Numbers in parentheses indicate studies categorized by date of publication rather than of study sample enrolment.

and to be able to generate a single mean 25(OH)D value for each region, the mean, standard deviation and sample size of each included study were used to calculate the standard error (SE), weight percentage (W%) and weight percentage average 25(OH)D (W% × mean) concentration (Cleophans & Zwinderman 2007). The W% × mean for each study per region was added to provide an overall average serum 25(OH)D concentration for each region. Similarly, for prevalence of deficiency (<50 nmol L^{-1}) and severe deficiency (<25 nmol L^{-1}), W% × prevalence was calculated for all studies with the required information.
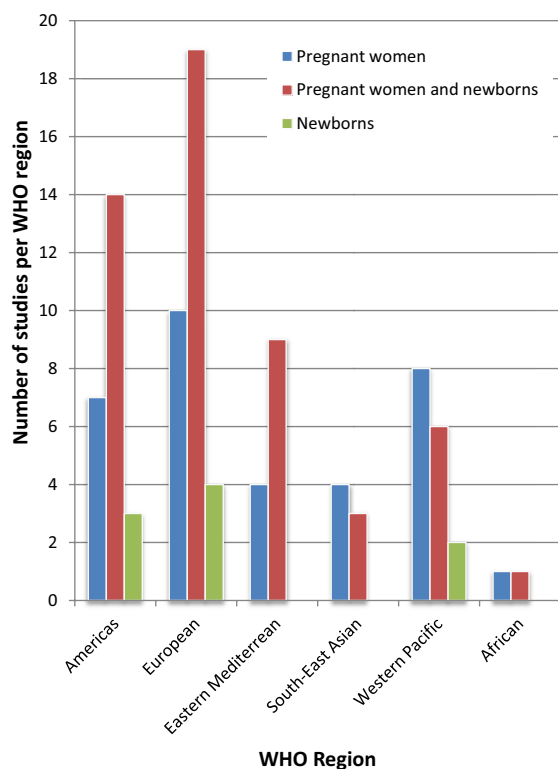

Fig. 2. Number of studies of vitamin D status of pregnant women and of newborn populations by World Health Organization (WHO) region.

Defining vitamin D status

Of the 95 papers identified, 27 reported mean serum 25(OH)D concentration, four reported median serum 25(OH)D concentration and nine reported prevalence of deficiency (Table 2 and Supplementary Table S2). Two measures: mean 25(OH)D concentration and prevalence of deficiency were reported in 42 studies, median 25(OH)D concentration and prevalence of deficiency in 12 studies, and mean and median 25(OH)D concentration in one study (Table 2 and Supplementary Table S2).

Serum 25(OH)D concentrations used to define vitamin D deficiency

In publications describing prevalence of maternal and newborn vitamin D deficiency, different 25(OH)D concentrations were used (Table 3). The serum 25(OH)D concentrations most frequently used to define abnormally low serum 25(OH)D concentrations were <25 and <50 nmol L^{-1}. Twenty-eight studies used <25 nmol L^{-1}, and 22 used <50 nmol L^{-1} (Supplementary Table S2).

Table 2. Measures used to report maternal and newborn vitamin D status by WHO region

WHO region	Vitamin D status measure					
	Mean 25(OH)D	Median 25(OH)D	Deficiency prevalence	Mean 25(OH)D and deficiency	Median 25(OH)D and deficiency	Mean and median 25(OH)D
Americas	7		2	12	2	
European	13	3	2	10	4	
Eastern Mediterranean	2	1	2	9	1	
South-East Asian	3		1	4	1	
Western Pacific	2		2	6	4	
African				1		1
Total	27	4	9	42	12	1

25(OH)D, 25-hydroxyvitamin D; WHO, World Health Organization.

Table 3. Serum 25-hydroxyvitamin D concentrations used to categorize vitamin D status by WHO region

Units	25-hydroxyvitamin D concentration in nmol L^{-1}											
nmol L^{-1}	<12.5	<20	<25	<27.5	<28	<30	<31.2	<35	<37.5	<50	<75	<80
WHO region												
Americas			2			1			6	6	1	
European	1	2	8	1		1				5		
EM			8	1		1	1	1		1		
SE Asian			4	1						4		
WP			6		1					6	1	
African												1
Total	1	2	28	3	1	3	1	1	6	22	2	1

EM, Eastern Mediterranean; SE, South-East; WHO, World Health Organization; WP, Western Pacific.

It was not possible to use all 12 25(OH)D cut-off values (Table 3) reported by the 95 studies to define vitamin D deficiency. We chose to focus on two 25(OH)D cut-off values, <50 and <25 nmol L^{-1}, with 25(OH)D <50 nmol L^{-1} defining vitamin D deficiency and 25(OH)D <25 nmol L^{-1} defining severe vitamin D deficiency. For the purpose of this review, regional comparisons of vitamin D deficiency prevalence were made only using studies that reported serum 25(OH)D concentration cut-off values of <50 and <25 nmol L^{-1}.

Measurement of serum 25(OH)D concentration

Thirteen different assays were used to measure serum 25(OH)D concentration. The detection limit and reported inter- and intra-assay coefficients of variance of these assays vary widely (Table 4). The most commonly used assays were radioimmunoassays (RIA), competitive protein binding assays and liquid chromatography tandem mass spectrometry (LC-MS/MS). The LC-MS/MS assay, which is increasingly viewed as the gold standard technique for measuring 25(OH)D concentrations, has been used in only nine (Cockburn *et al.* 1980; Newhook *et al.* 2008; Sulaiman *et al.* 2010; Bendall *et al.* 2012; Amukele *et al.* 2013; Gernand *et al.* 2013; Haggarty *et al.* 2013; Streym *et al.* 2013; Grant *et al.* 2014) of the 95 studies included in the review. However, excellent correlations have been shown between LC-MS/MS assay and RIA (DiaSorin) ($r^2 = 0.95$) and LIAISON 25(OH)D assay

($r^2 = 0.94$) (Eyles *et al.* 2009; Hee-Won *et al.* 2012). Five studies did not report the assay techniques used to measure vitamin D status (Mallet *et al.* 1986; Ainy *et al.* 2006; Lee *et al.* 2007; Karim *et al.* 2011; Vercruyssen *et al.* 2012).

Results

Availability of data on maternal and newborn vitamin D status in each WHO region

Of the 95 studies, 63 (66%) have been performed since 2000. The number of studies varied widely by WHO region (from 2 to 31 studies per region). Fifty-five (58%) of the studies were conducted in the Americas and European regions, in which live 28% of the world's population of women 15–64 years of age (Table 1).

Maternal vitamin D status during pregnancy

Maternal serum 25(OH)D concentration during pregnancy

Large differences were evident between and within most regions in the distribution of mean serum 25(OH)D concentrations in pregnant women (Table 5). In the studies from the Americas region, mean and median 25(OH)D concentrations were within a relatively narrow range (mean 52–60, median 47–65 nmol L^{-1}) (Ginde *et al.* 2010; Shand *et al.* 2010; Hollis *et al.* 2011; Gernand *et al.* 2013). In contrast,

Table 4. Assays used to measure vitamin D concentration and their precision and the use of different assays by WHO region

Assay	Assay precision			WHO region						Total
	Detection limit	Inter-assay CV (%)	Intra-assay CV (%)	Americas	European	EM	SE Asian	WP	African	
Chemiluminescence immunoassay	–	5	2–6	2	2	2		2		8
Radioimmunoassay	–	3–5	5–8	7	7	6	7	3	1	31
High-performance liquid chromatography	1–4 nmol L^{-1}	6–8	–	3	3	2				8
Competitive protein binding assay	13 nmol L^{-1}	5–10	10–15	4	4	3	3			14
Liquid chromatography tandem mass spec.	0.2 nmol L^{-1}	6–8	8–10	2	4			2	1	9
ELISA	5–300 nmol L^{-1}	2–4	4–6	3	2	1	1			7
Roche modular analyser	–	10–19	–	1	1			1		3
Radioligand assay		5	6–10		1	1				2
Nichols advantage assay		5–6	–		1			1		2
LIAISON DiaSorin assay		<10	<10		1			1		2
Enzyme immunoassay		11	–		1			1		2
Radioprotein binding assay			–			1	1			1
IncStar kit	–	9	16							1
										90

CV, coefficient of variance; ELISA, enzyme-linked immunosorbent assay; EM, Eastern Mediterranean; SE South-East; WHO, World Health Organization; WP, Western Pacific.

Table 5. Serum 25(OH)D concentration (nmol L^{-1}) by WHO region and country within each region

Country	Year*	First author	Maternal and newborn serum 25-hydroxyvitamin D concentration			
			Maternal		Newborn	
			Mean (±SD)	Median (IQR)	Mean (±SD)	Median (IQR)
Americas						
USA	1959–1965	Gernand	52 ± 27			
USA	2001–2006	Ginde		65 (60–67)		
Canada	2004–2007	Shand		47 (35–67)		
USA	2004–2009	Hollis, 2011	60 ± 25			
USA	2006–2009	Belderbos			77 ± 3	
USA	2007	Basile			35 ± 20	
European						
UK	1978–1979	Heckmatt	15 ± 13			
Scotland	1980	Cockburn	17		28	
Belgium	1981	Bouillon	35 ± 15		20 ± 10	
France	1982	Delvin	45 ± 5		30 ± 25	
Sweden	1986	Axelson	50 ± 15		35 ± 13	
UK	1991–1992	Gale		50 (30–75)		
UK	1991–1992	Javaid	50 ± 15		35 ± 13	
UK	1998–2001	Harvey		60 (42–87)		
France	2003	Baiz, 2014			45 ± 37	
France	2003	Baiz, 2012			39 (40)[†]	
Netherlands	2003–2004	Leffelaar	55 (32–75)			
Greece	2003–2004	Nicolaidou		40 (28–52)		50 (35–75)
Germany	2006–2008	Weisse		55 (35–80)		28 (18–42)
Finland	2007	Viljakainen	40 ± 13		50 ± 15	
Turkey	2008	Halicioglu	30 ± 13		30 ± 18	
Denmark	2008–2010	Streym	72 ± 30		42 ± 20	
Belgium	2009–2010	Vercruyssen	55 ± 30			
Eastern Mediterranean						
Iran	1997	Bassir	13 ± 25		5 ± 10	
Iran	1999	Andiran	30 ± 10		20 ± 8	
Iran	2002	Maghbooli, 2007	28 ± 23		18 ± 13	
Iran	2005	Salek	130 ± 90		67 ± 28	
Iran	2005	Kazemi	20 ± 5		17 ± 3	
Pakistan	2008	Karim	60 ± 30		50 ± 28	
Iran	2008–2009	Asemi	18 ± 5			
South-East Asian						
India	1997	Farrant		37 (25–57)		
India	1997–1998	Krishnaveni		47 (32–67)		
Nepal	1998–2001	Jiang	52 ± 25			
India	2002	Sachan	35 ± 23		20 ± 15	
India	2005–2006	Sahu		40 (25–57)		
India	2006–2007	Marwaha	20 ± 8		22 ± 10	
Western Pacific						
Japan	1980	Seino	42 ± 13		32 ± 13	
NZ	1997–2001	Camargo				45 (30–77)
Australia	2008	Bowyer		52 (18–175)		60 (18–245)
Beijing	2010–2011	Song	72 ± 25			
Australia	2011	Thomas	47 ± 20		67 ± 40	
Australia	2011	Bendall	115 ± 28			
Australia	2012	Novakovic	55 ± 15		60 ± 18	
African						
Malawi	2000–2004	Amukele	92 ± 5	90 (75–110)	35 ± 8	27 (20–47)

25(OH)D, 25-hydroxyvitamin D; IQR, interquartile range; SD, standard deviation; WHO, World Health Organization. All mean and median with single values: no SD or IQR provided by the author. *Year of study or if not available year of publication. [†]Median and IQR: author provided the median as 39.2 nmol L^{-1} and IQR as 39.7 nmol L^{-1}.

mean 25(OH)D concentrations in pregnant populations in the European region varied more widely (range of means 15–72 nmol L^{-1}). One study from the European region reported a mean 25(OH)D concentration of <25 nmol L^{-1} (Heckmatt *et al.* 1979), six studies between 30 and 45 nmol L^{-1} (Cockburn *et al.* 1980; Bouillon *et al.* 1981; Delvin *et al.* 1982; Nicolaidou *et al.* 2006; Viljakainen *et al.* 2010; Halicioglu *et al.* 2012) and seven between 50 and 72 nmol L^{-1} (Axelson & Christensen 1988; Javaid *et al.* 2006; Gale *et al.* 2008; Vercruyssen *et al.* 2012; Streym *et al.* 2013; Weisse *et al.* 2013; Harvey *et al.* 2014).

Mean serum 25(OH)D concentrations during pregnancy reported from the Eastern Mediterranean region ranged from 13 to 130 nmol L^{-1} (Bassir *et al.* 2001; Andiran *et al.* 2002; Maghbooli *et al.* 2007; Salek *et al.* 2008; Kazemi *et al.* 2009; Asemi *et al.* 2010; Karim *et al.* 2011). Three of the eight studies describing pregnant maternal 25(OH)D status reported a mean 25(OH)D concentration <25 nmol L^{-1} (Bassir *et al.* 2001; Kazemi *et al.* 2009; Asemi *et al.* 2010) and two a mean 25(OH)D concentrations of 28 and 30 nmol L^{-1} (Andiran *et al.* 2002; Maghbooli *et al.* 2007). Two studies reported 25(OH)D concentrations of 60 and 130 nmol L^{-1} (Salek *et al.* 2008; Karim *et al.* 2011). One of the eight studies, of Isfahani women living in central Iran, reported high 25(OH)D concentrations (130 nmol L^{-1}) (Salek *et al.* 2008). The authors of this study acknowledged that the values were high compared with other Middle Eastern studies particularly two from Tehran (Bassir *et al.* 2001; Ainy *et al.* 2006). They attributed the lower mean serum 25(OH)D concentration in Tehran to the air pollution in Tehran decreasing UVB exposure (Bassir *et al.* 2001; Ainy *et al.* 2006; Salek *et al.* 2008). In the South-East Asian region, mean serum 25(OH)D concentrations during pregnancy ranged from 20 to 52 nmol L^{-1}. Of the six studies, one reported a mean 25(OH)D concentration <25 nmol L^{-1} (Marwaha *et al.* 2011), four reported mean or median 25(OH)D concentrations between 35 and 47 nmol L^{-1} (Sachan *et al.* 2005; Farrant *et al.* 2009; Sahu *et al.* 2009; Krishnaveni *et al.* 2011) and one study reported a mean 25(OH)D concentration of 52 nmol L^{-1} (Jiang *et al.* 2005).

Data from the Western Pacific region were available from four studies conducted in Australia (Bowyer *et al.* 2009; Thomas *et al.* 2011; Bendall *et al.* 2012; Novakovic *et al.* 2012), one in Japan (Seino *et al.* 1982) and one in Beijing (Song *et al.* 2013). Mean maternal serum 25(OH)D concentration in three of the four Australian (Adelaide, Sydney and Melbourne) studies were 47, 52 and 55 nmol L^{-1}, respectively (Bowyer *et al.* 2009; Thomas *et al.* 2011; Novakovic *et al.* 2012). The fourth study reported a higher mean value of 115 nmol L^{-1} (Bendall *et al.* 2012). The possible explanation for this outlier value is that the study enrolled pregnant women living in Cairns (latitude 17°S) where an average of 7.5 h of sunshine per day is recorded from May to September, with enrolment into this study occurring in July and August (Bendall *et al.* 2012).

The one study from the African region reported a mean maternal 25(OH)D concentration of 92 nmol L^{-1} (Amukele *et al.* 2013), with this mean value being the third highest of all 33 global studies of maternal serum 25(OH)D concentration during pregnancy. The two highest values were 130 nmol L^{-1} reported in a study from Iran (Salek *et al.* 2008) and 115 nmol L^{-1} reported from Cairns, Australia (Bendall *et al.* 2012).

When the different studies from each region were combined using a meta-analysis mean maternal serum 25(OH)D in nmol L^{-1}, and then ranked by region, we observed large differences: Eastern Mediterranean 20, European 30, South-East Asian 30, Western Pacific 57, Americas 60 and African 92 (Fig. 3a).

Maternal vitamin D deficiency during pregnancy (Table 6)

Vitamin D deficiency [25(OH)D <50 nmol L^{-1}] during pregnancy was present in 42–72% of women from the Americas, 18–90% from the European, 46% from the Eastern Mediterranean, 66–96% from South-East Asian and 41–97% from the Western Pacific region. Regional ranking of the proportion of pregnant women with serum 25(OH)D <50 nmol L^{-1}
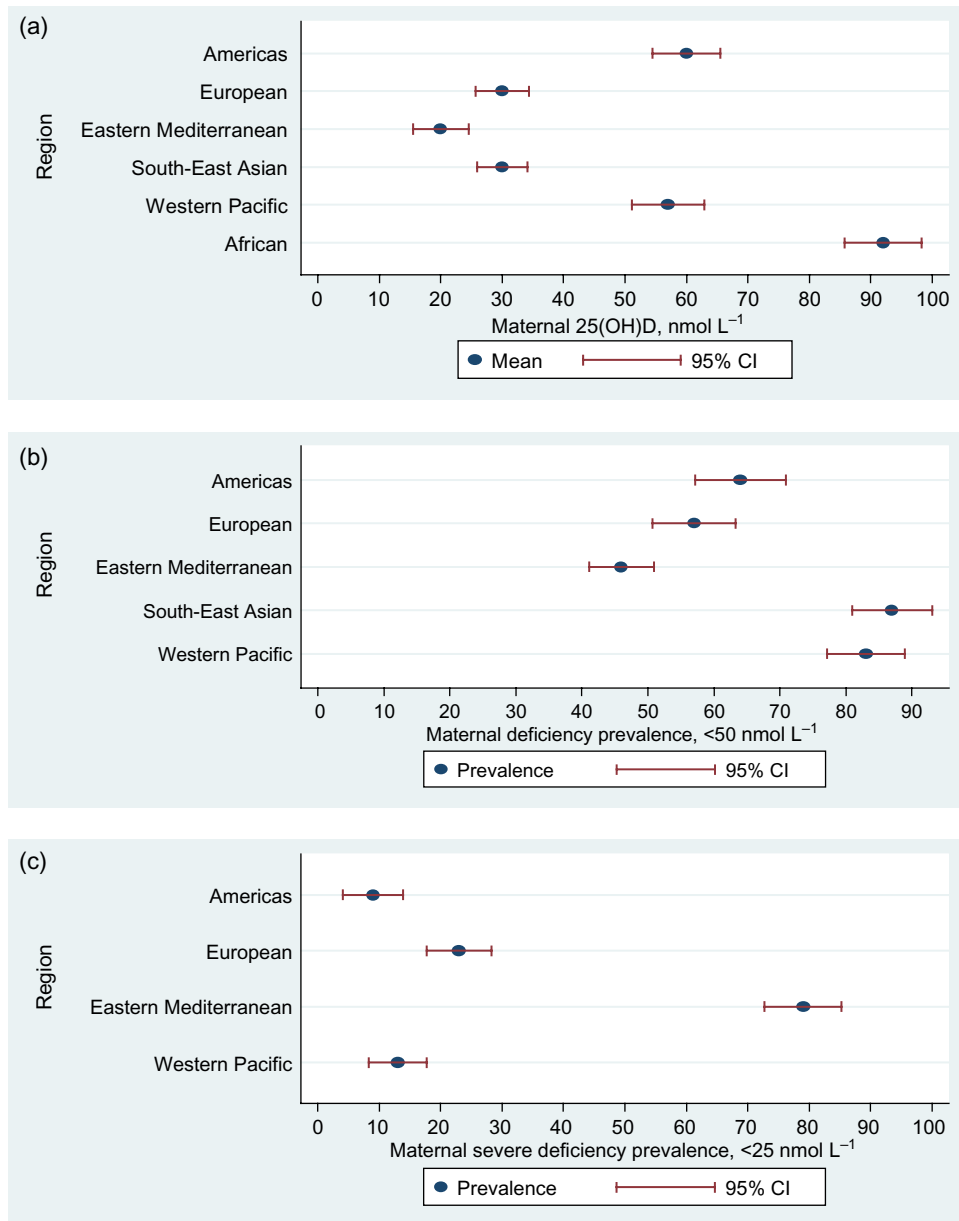
Fig. 3. (a) Global maternal mean 25-hydroxyvitamin D [25(OH)D] concentrations in different World Health Organization regions. (b) Global prevalence of maternal 25(OH)D deficiency (<50 nmol L^{-1}). (c) Global prevalence of maternal 25(OH)D severe deficiency (<25 nmol L^{-1}). CI, confidence interval.

was: South-East Asian 87%, Western Pacific 83%, Americas 64%, European 57% and Eastern Mediterranean 46% (Fig. 3b).

Severe vitamin D deficiency [25(OH)D < 25 nmol L^{-1}] during pregnancy was present in 2–20% of women from the Americas, 20–40% from the Euro-

pean, 40–96% from the Eastern Mediterranean and 5–61% from the Western Pacific region. Regional ranking of the proportion of pregnant women with serum 25(OH)D <25 nmol L^{-1} was: Eastern Mediterranean 79%, European 23%, Western Pacific 13% and Americas 9% (Fig. 3c).

Table 6. Prevalence of maternal and newborn vitamin D deficiency [25(OH)D <50 nmol L^{-1}] and severe vitamin D deficiency [25(OH)D <25 nmol L^{-1}] by WHO region

Country	Year*	First author	Maternal and newborn vitamin D status deficiency and insufficiency			
			Maternal 25(OH)D		Newborn 25(OH)D	
			Deficiency % <50 nmol L^{-1}	Severe def. % <25 nmol L^{-1}	Deficiency % <50 nmol L^{-1}	Severe def. % <25 nmol L^{-1}
Americas						
USA	1959–1965	Gernand	56			
Canada	2004–2007	Shand	53			
USA	2005–2006	Newhook	42	2	35	4
USA	2006–2009	Belderbos			27	
USA	2008–2009	Collins-Fulea	72			
USA	2010–2011	Burris		20		22
European						
UK	1991–1992	Javaid	18			
Scotland	2000–2006	Haggarty		22		50
France	2003	Baiz, 2012				28
Greece	2003–2004	Nicolaidou		20		8
Netherlands	2004–2006	Dijkstra				43
Turkey	2005	Karatekin	68		88	
UK	2007	Yu		40		
Turkey	2008	Halicioglu	90			50
Denmark	2008–2010	Streym	23		61	66
Eastern Mediterranean						
Iran	1997	Bassir		80		
Iran	1999	Andiran		46		
Iran	1999–2000	Molla		40	60	
Iran	2005	Kazemi		86		
Iran	2005	Maghbooli, 2008		71		
Pakistan	2008	Karim	46		88	
Iran	2008–2009	Asemi		96		
South-East Asian						
India	1997	Farrant	66			
India	1997–1998	Krishnaveni	67			
Nepal	1998–2001	Jiang				14
India	2002	Sachan	84		96	43
India	2005–2006	Sahu	74			
India	2006–2007	Marwaha	96			
Western Pacific						
NZ	1997–2001	Camargo			57	19
Australia	2002–2003	Morley		7		
NZ	2006	Judkins	87	61		
Australia	2007–2008	Lau	41			
Japan	2008	Shibata	90			
Australia	2008–2009	Perampalam		35		
Australia	2008–2009	Perampalam		26		
Australia	2008–2009	Teale		5		
NZ	2010–2011	Grant	54	54		
Beijing	2010–2011	Song	97			45
Australia	2011	Bowyer		15		11
Australia	2011	Thomas	56	12	33	4

25(OH)D, 25-hydroxyvitamin D; WHO, World Health Organization. *Year of study or if not available year of publication.

Newborn vitamin D status during pregnancy

Newborn serum 25(OH)D concentration

Mean newborn 25(OH)D concentrations varied widely in the two studies from the Americas region [35 nmol L^{-1} (Basile *et al.* 2007) and 77 nmol L^{-1} (Belderbos *et al.* 2011)]. The mean/median 25(OH)D concentrations in newborn studies from the European region were all ≤50 nmol L^{-1}, with one of these studies reporting mean newborn 25(OH)D concentrations of 20 nmol L^{-1} (Bouillon *et al.* 1981) and 11 reported mean values of 28–50 nmol L^{-1} (Cockburn *et al.* 1980; Delvin *et al.* 1982; Axelson & Christensen 1988; Javaid *et al.* 2006; Nicolaidou *et al.* 2006; Leffelaar *et al.* 2010; Viljakainen *et al.* 2010; Halicioglu *et al.* 2012; Streym *et al.* 2013; Weisse *et al.* 2013; Baiz *et al.*, 2014). Of the six studies of newborn vitamin D status from the Eastern Mediterranean region, four reported mean serum 25(OH)D of <25 nmol L^{-1} (Bassir *et al.* 2001; Andiran *et al.* 2002; Maghbooli *et al.* 2007; Kazemi *et al.* 2009) and two ≥50 nmol L^{-1} (Salek *et al.* 2008; Karim *et al.* 2011). Both studies from the South-East Asian region had mean 25(OH)D concentrations <50 nmol L^{-1} (Sachan *et al.* 2005; Marwaha *et al.* 2011). In the Western Pacific region, two studies reported a median newborn 25(OH)D concentrations of 32 nmol L^{-1} (Seino *et al.* 1982) and 45 nmol L^{-1} (Camargo *et al.* 2010), and three studies reported newborn vitamin D concentrations in the range of 60–67 nmol L^{-1} (Bowyer *et al.* 2009; Thomas *et al.* 2011; Novakovic *et al.* 2012). In the one study from the African region, mean 25(OH)D concentration was 35 nmol L^{-1} (median 27 nmol L^{-1}) (Amukele *et al.* 2013).

When different studies from each region were combined using a meta-analysis newborn mean serum 25(OH)D in nmol L^{-1}, and then ranked by region, we observed large differences: Eastern Mediterranean 17, South-East Asian 22, African 35, European 35, Western Pacific 55 and Americas 82 (Fig. 4a).

Newborn vitamin D deficiency

In the two studies from the Americas region, newborn vitamin D deficiency [25(OH)D <50 nmol L^{-1}] was present in 27% and 35% of newborns (Newhook *et al.*

2008; Belderbos *et al.* 2011). The prevalence of 25(OH)D <50 nmol L^{-1} was 61% and 88% in the two studies from the European (Karatekin *et al.* 2009; Streym *et al.* 2013), 60% and 88% in the two studies from the Eastern Mediterranean (Molla *et al.* 2005; Karim *et al.* 2011), 96% in one study from the South-East Asian (Sachan *et al.* 2005) and 33% and 57% in the two studies from the Western Pacific region (Camargo *et al.* 2010; Thomas *et al.* 2011). Regional ranking of the proportion of newborns with serum 25(OH)D <50 nmol L^{-1} was: South-East Asian 96%, European 73%, Eastern Mediterranean 60%, Western Pacific 54% and Americas 30% (Fig. 4b).

In the two studies from the Americas region severe vitamin D deficiency [25(OH)D <25 nmol L^{-1}] was present in 4% and 22% of newborns (Newhook *et al.* 2008; Belderbos *et al.* 2011). Prevalence of 25(OH)D <25 nmol L^{-1} in the European region was between 8% and 66% (Nicolaidou *et al.* 2006; Dijkstra *et al.* 2007; Baiz *et al.* 2012; Halicioglu *et al.* 2012; Haggarty *et al.* 2013; Streym *et al.* 2013), in the South-East Asian region 14% and 43% (Jiang *et al.* 2005; Sachan *et al.* 2005) and in the Western Pacific region 4–45% (Table 6) (Bowyer *et al.* 2009; Camargo *et al.* 2010; Thomas *et al.* 2011; Song *et al.* 2013). Regional ranking of the proportion of newborns with serum 25(OH)D <25 nmol L^{-1} was: South-East Asian 45%, European 39%, Americas 14% and Western Pacific 14% (Fig. 4c).

Relationship between maternal and newborn vitamin D status

Fifty-two studies described vitamin D status in both mothers and their newborns. Serum 25(OH)D concentration was measured in cord blood samples in all but one Australian study where dried blood spots obtained from newborn screening cards were used (Thomas *et al.* 2011). Two studies compared 25(OH)D concentrations on cord blood samples and venous blood samples taken from newborns (Heckmatt *et al.* 1979; Ergur *et al.* 2009).

In 40 of the 52 studies, the relationship between maternal and newborn vitamin D status was described using correlation coefficients (*r*) (Table 7). Thirty-seven of the 40 studies reported maternal
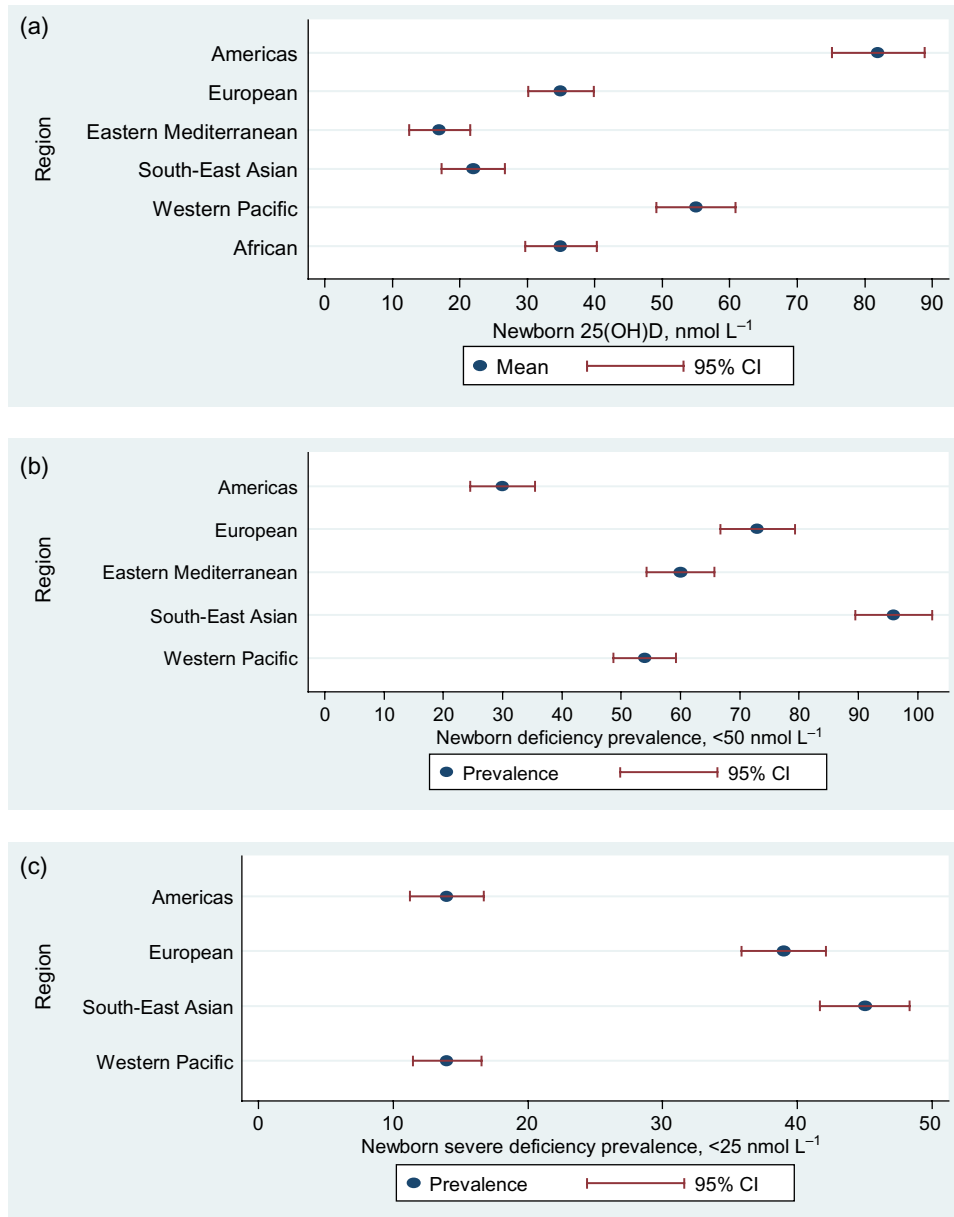
Fig. 4. (a) Global newborn mean 25-hydroxyvitamin D [25(OH)D] concentrations in different World Health Organization regions. (b) Global prevalence of newborn 25(OH)D deficiency (<50 nmol L^{-1}). (c) Global prevalence of newborn 25(OH)D severe deficiency (<25 nmol L^{-1}). CI, confidence interval.

25(OH)D concentrations to be higher than newborn concentrations (Table 7). Only one study reported the actual difference between maternal and newborn 25(OH)D concentration. In this study from New Zealand the mean maternal serum 25(OH)D concentration measured at 36 weeks gestation was 35 nmol L^{-1} higher than the cord blood 25(OH)D concentration (maternal 72 vs. cord blood 37 nmol L^{-1}) (Grant *et al*. 2014). Other studies that have quantified the relationship between maternal and cord blood 25(OH)D describe cord blood 25(OH)D concentration being 36% (Amukele *et al*.

Table 7. Correlation between maternal and newborn serum 25(OH)D concentrations by WHO region

Country (first author)	Year	Correlation coefficient	P-value	Maternal sample taken at	Relationship between maternal and newborn 25(OH)D	
					Newborn 25(OH)D lower	Newborn 25(OH)D higher
Americas						
USA (Hillman)	1974	0.76	<0.0005	Pre-delivery		✓
USA (Hollis, 1984)	1984	0.76	0.01	At delivery	✓	
USA (Bodnar c)	1997–2001	0.89	<0.001	At delivery	✓	
USA (Bodnar b)	1997–2001	0.97	<0.0001	Pre-delivery	✓	
USA (Lee)	2002–2003	0.68	<0.001	24–48 h after delivery	✓	
USA (Dror, 2012)	2006–2008	0.78	<0.0001	Pre-delivery	✓	
USA (Dror, 2011)	2008–2009	0.79	<0.0001	Pre-delivery	✓	
European						
London (Brooke)	1977–1979	0.93	<0.001	28–32 weeks	✓	
UK (Heckmatt)	1978–1979	0.93	<0.001	24 h after delivery		✓
Edinburg (Cockburn)	1980	0.71	<0.001	At delivery	✓	
France (Mallet)	1980–1989	0.95	<0.001	At delivery	✓	
Belgium (Bouillon)	1981	0.83	<0.001	At delivery	✓	
France (Delvin)	1982	0.90	<0.0005	At delivery	✓	
Israel (Shany)	1984	0.91	<0.001	At delivery	✓	
Sweden (Axelson)	1986	0.83	<0.0001	At delivery	✓	
Scotland (Haggarty)	2000–2006	0.50	<0.001	19 weeks	✓	
Norway (Godang)	2001–2008	0.42	<0.001	30–32 weeks	✓	
Cardiff (Nicolaidou)	2003–2004	0.63	<0.001	At delivery	✓	
Turkey (Karatekin)	2005	0.79	<0.05	At delivery	✓	
Germany (Weisse)	2006–2008	0.81	<0.001	34 weeks	✓	
UK (Yu)	2007	0.45	<0.0001	At delivery	✓	
Turkey (Halicioglu)	2008	0.65	<0.001	Pre-delivery	✓	
Denmark (Streym)	2008–2010	0.83	<0.001	1–2 weeks post delivery	✓	
Eastern Mediterranean						
Saudi Arab (Serenius)	1984	0.80	<0.001	At delivery	✓	
Iran (Bassir)	1997	0.88	<0.0001	At delivery	✓	
Iran (Andiran)	1999	0.63	0.01	During consent	✓	
Kuwait (Molla)	1999–2000	0.79	<0.001	At delivery	✓	
Iran (Maghbooli, 2007)	2002	0.71	0.0001	At delivery	✓	
Iran (Salek)	2005	0.79	<0.001	At delivery	✓	
Iran (Kazemi)	2005	0.55	<0.001	Pre-delivery	✓	
Pakistan (Karim)	2008	0.03	<0.003	No indication	✓	
Pakistan (Hossain)	2010	0.68	<0.001	At delivery	✓	
South-East Asian						
Korea (Namguang)	1993–1994	0.81	0.0001	At delivery	✓	
India (Sachan)	2002	0.79	<0.001	Pre-delivery	✓	
India (Marwaha)	2006–2007	0.78	0.0001	Third trimester	✓	
Western Pacific						
Japan (Seino)	1980	0.85	<0.0005	At delivery	✓	
Australia (Bowyer)	2008	0.74	<0.001	30–32 weeks	✓	
NZ (Grant)	2010	0.79	<0.001	36 weeks	✓	
Australia (Thomas)	2011	0.23	0.02	Third trimester	✓	
Australia (Novakovic)	2012	0.19	<0.001	28 weeks		✓

25(OH)D, 25-hydroxyvitamin D; WHO, World Health Organization.

2013), 67% (Waiters *et al*. 1998) and 80% (Hillman & Haddad 1974) of the matched maternal serum 25(OH)D concentration. The first two studies reported maternal 25(OH)D concentrations higher than cord blood 25(OH)D (Waiters *et al*. 1998; Amukele *et al*. 2013), and the third study reported cord blood 25(OH)D to be higher (Hillman & Haddad 1974).

Three studies reported cord blood 25(OH)D concentrations to be higher than maternal serum 25(OH)D concentration (Hillman & Haddad 1974; Heckmatt *et al*. 1979; Novakovic *et al*. 2012). Two of the three studies, one in the Americas region and the other from the Western Pacific region, observed this relationship to be present when maternal 25(OH)D concentrations were low (Hillman & Haddad 1974; Novakovic *et al*. 2012). In the US study, newborn 25(OH)D concentrations were higher than maternal concentrations only when maternal 25(OH)D concentrations were in the range of 7–12 nmol L^{-1} (Hillman & Haddad 1974). In the Australian study, newborn 25(OH)D concentrations were observed to be higher than maternal concentration only when maternal 25(OH)D was <45 nmol L^{-1} (Novakovic *et al*. 2012). In contrast, the third of these studies, from the United Kingdom, observed that newborn serum 25(OH)D concentration was higher than maternal 25(OH)D concentration across the whole range of 25(OH)D values (Heckmatt *et al*. 1979). Different assay techniques may have accounted for these differences. In the Australian study (Novakovic *et al*. 2012), serum 25(OH)D concentrations were measured using LIAISON vitamin D total kit (DiaSorin, Stillwater, MN, USA) whereas both American studies (Hillman & Haddad 1974; Heckmatt *et al*. 1979) have used modified versions of competitive protein binding assays (Haddad & Chyu 1971; Morris & Peacock 1976).

In all 40 studies where correlations were described, there was a significant positive correlation between maternal and newborn 25(OH)D concentrations. The range of correlation coefficients between maternal and newborn 25(OH)D concentrations, by region, was: Americas 0.68–0.97, European 0.42–0.95, Eastern Mediterranean 0.03–0.88, South-East Asian 0.78–0.81 and Western Pacific 0.19–0.85.

The correlation between maternal and newborn 25(OH)D concentration varied with timing of sample collection. In one study from the Americas region (Bodnar *et al*. 2007), serum 25(OH)D concentrations were measured in early pregnancy (4–21 weeks) and at delivery in 2211 study participants and newborn 25(OH)D concentrations were measured on cord blood samples collected at delivery. Cord blood 25(OH)D concentrations had moderate positive correlations with maternal serum 25(OH)D measured during early pregnancy ($r = 0.58$, $P < 0.001$) and a stronger relationship with maternal serum 25(OH)D concentrations measured at delivery ($r = 0.89$, $P < 0.001$).

The effect of gestation on the correlation between maternal and newborn 25(OH)D concentration was investigated in one study from the Americas region that sampled mothers at delivery (Hillman & Haddad 1974). The correlations of maternal and newborn 25(OH)D concentration were $r = 0.86$ ($P < 0.001$) for newborns born preterm and $r = 0.76$ ($P < 0.0005$) for newborns born at term.

Discussion

This systematic review of vitamin D status of pregnant women and newborns worldwide, from 1959 to 2014, showed mean maternal 25(OH)D concentrations ranging from 13 to 130 nmol L^{-1} and mean newborn 25(OH)D concentrations ranging from 5 to 77 nmol L^{-1}. Vitamin D deficiency, as defined by a serum 25(OH)D concentration <50 nmol L^{-1}, was present in 54% of pregnant women and 75% of newborns, and severe vitamin D deficiency as defined by a serum 25(OH)D concentration <25 nmol L^{-1} in 18% of pregnant women and 29% of newborns.

Wide variability in vitamin D status between WHO regions was evident. From the meta-analysis, average maternal 25(OH)D concentrations were <25 nmol L^{-1} in the Eastern Mediterranean region, between 25 and <50 nmol L^{-1} in the South-East Asian and European regions, 50 to <75 nmol L^{-1} in the Americas and Western Pacific regions, and 75 to <100 nmol L^{-1} in the African region. Average newborn 25(OH)D concentrations were <25 nmol L^{-1} in the Eastern Mediterranean and South-East Asia

regions, between 25 and <50 nmol L^{-1} in the European and African regions, 50 to <75 nmol L^{-1} in the Western Pacific region, and >75 nmol L^{-1} in the Americas region.

Consistent with the low mean 25(OH)D concentration, studies where the proportion of pregnant women with serum 25(OH)D <50 and <25 nmol L^{-1} was defined showed that the majority of pregnant women in the South-East Asian region had vitamin D deficiency (87%) and the majority in the Eastern Mediterranean region had severe vitamin D deficiency (79%). Similarly, a higher proportion of pregnant women in the Western Pacific, Americas and European regions were vitamin D deficient (Western Pacific 83%, Americas 64%, Europe 57%) but a smaller proportion of pregnant women in these three regions had severe vitamin D deficiency (Western Pacific 13%, Americas 9%, Europe 23%). Vitamin D deficiency was more frequent in pregnant women in the South-East Asian (87%) than any other WHO region, but no data are available to estimate whether severe vitamin D deficiency is prevalent in pregnant women in the South-East Asian region.

As was seen with the studies of pregnant women, vitamin D deficiency (96%) was prevalent in newborns from the South-East Asian region. A large proportion of newborns in the Eastern Mediterranean region were vitamin D deficient (60%), but no data were available to estimate the prevalence of severe vitamin D deficiency in newborns in the Eastern Mediterranean region. In the European region both vitamin D deficiency (73%) and severe vitamin D deficiency (39%) were observed more frequently in newborns than pregnant women. As with pregnant women, in the Americas and Western Pacific regions severe vitamin D deficiency was less prevalent (Americas 14%, Western Pacific 14%) than vitamin D deficiency (Americas 30%, Western Pacific 54%).

The amount of within-region variability in vitamin D status differed by global region. Variability in average maternal serum 25(OH)D concentration between studies within the same region was 23% in the Americas, twofold in the Western Pacific, threefold in the South-East Asian, fourfold in the European and 10-fold in the Eastern Mediterranean region. Among newborns, within-region study vari-

ance in mean serum 25(OH)D concentration was 9% in the South-East Asian; twofold in the Western Pacific, Americas and European regions; and 13-fold in the Eastern Mediterranean region.

As described in the Introduction section, four reviews have been conducted previously that describe vitamin D status across the age range worldwide (Hagenau *et al.* 2009; Mithal *et al.* 2009; Arabi *et al.* 2010; Hilger *et al.* 2014). In the systematic review by Hilger *et al.* (2014; 195 studies in 44 countries), the prevalence of serum 25(OH)D <50 nmol L^{-1} was 37%. In comparison, in our review, the prevalence of serum 25(OH)D <50 ng/mL was 54% in pregnant women and 75% in newborns. As was evident from our study of pregnant women and newborns, Hilger observed that mean 25(OH)D values in the general populations were higher in the Americas (North America) (75 nmol L^{-1}) than in Europe (52 nmol L^{-1}) or the Middle East (50 nmol L^{-1}). Consistent with the reviews by Mithal *et al.* (2009) and Arabi *et al.* (2010), our review showed that vitamin D deficiency [25(OH)D <50 nmol L^{-1}] and severe vitamin D deficiency [25(OH)D <25 nmol L^{-1}] were more common in the South-East Asian and Eastern Mediterranean regions for both maternal and newborn populations.

The increase in number of studies that have described maternal and newborn vitamin D status over time is apparent as is the uneven distribution of studies between global regions. Most studies (74%) were from three of the six WHO regions: Americas 25%, Europe 31% and Eastern Mediterranean 18%. Currently, the published data are insufficient to allow maternal and newborn vitamin status to be defined in the African region and in non-European pregnant women living in the Western Pacific region. Data from the South-East Asian and Eastern Mediterranean regions are also limited particularly in view of the large populations of those two regions. The limited data that are available from South-East Asia and the Eastern Mediterranean suggest vitamin D status that is poor relative to other global regions.

Our meta-analysis confirms the close relationship of maternal pregnancy with newborn serum 25(OH) concentrations. All 39 studies with paired maternal and cord concentrations of 25(OH)D showed a high correlation. In all but three studies, maternal

pregnancy 25(OH)D concentration was higher than newborn 25(OH)D concentration. These relationships are expected as the fetus cannot synthesize 25(OH)D, and thus this compound must be transferred from the mother via the placenta (Ron *et al.* 1984). Maternal vitamin D is the sole source of vitamin D to the fetus. The lower mean serum 25(OH)D concentrations seen in newborns compared with pregnant women in all regions, but the Americas, and higher prevalence of vitamin D deficiency and severe vitamin D deficiency in newborns compared with pregnant women observed in all regions is consistent with this relationship.

In the five global regions for which data are available, all but one (Eastern Mediterranean for pregnant women, Americas for newborns) show that vitamin D deficiency was present in more than half of pregnant women and newborns. In all but one region (Americas), vitamin D deficiency was present in at least one-third of newborns. With the recent evidence indicating that 25(OH)D <20 nmol L^{-1} is associated with an increased risk of poor pregnancy and early infant outcomes (Aghajafari *et al.* 2013; Wei *et al.* 2013), there is an urgent need to develop national and regional approaches aimed at improving vitamin D status in these populations.

The close relationship between maternal pregnancy and newborn vitamin D status implies that addressing vitamin D status during pregnancy is necessary if newborn vitamin D status is to be improved. Some regions, such as Europe and the Americas, have national policies that recommend supplementation of pregnant women to ensure the mother's requirements for vitamin D are met and to prevent vitamin D deficiency in young infants. However, recommended supplementary doses vary from country to country with current recommendations bearing little relationship with the national and regional data that describe vitamin D status. For example, in the European region, the recommended daily vitamin D supplementary doses are 10 μg day^{-1} (400 IU day^{-1}) in the Netherlands and Scandinavia, and 20 μg day^{-1} (800 IU day^{-1}) in Germany and Belgium (Nordic Council of Ministers 2004; Health Council of the Netherlands 2008; Gezondheidsraad 2009; Deutsche *et al.* 2013). Average serum 25(OH)D concentrations in nmol L^{-1} in preg-

nant women from these countries are: the Netherlands 55 (Leffelaar *et al.* 2010), Sweden 50 (Axelson & Christensen 1988), Denmark 72 (Streym *et al.* 2013), Germany 55 (Weisse *et al.* 2013) and Belgium 35 (Bouillon *et al.* 1981) and 55 (Vercruyssen *et al.* 2012).

Lower serum 25(OH)D concentrations during pregnancy are associated with poorer outcomes during pregnancy, at birth and during infancy and childhood (Hossain-nezhad & Holick 2013). Children born to mothers with lower 25(OH)D concentrations during pregnancy were at higher risk of being born preterm (Aghajafari *et al.* 2013; Wei *et al.* 2013) or small for gestation age (Wei *et al.* 2013), and are at higher risk of having reduced bone mineral content at birth (Viljakainen *et al.* 2010). In studies performed in the United States and Scotland higher maternal intakes of vitamin D during pregnancy were associated with a reduction in risk of recurrent wheezing in children during preschool years (Camargo *et al.* 2007; Devereux *et al.* 2007). In New Zealand cord blood 25(OH)D concentrations have been shown to be inversely related to the risk of parent-reported respiratory infections in the first 3 months of life (Camargo *et al.* 2011). Children born with low serum 25(OH)D concentrations had reduced bone mass at 9 years of age (Javaid *et al.* 2006).

Our review indicates that, even in countries where fortification of food with vitamin D is mandatory, and where the use of vitamin D supplements is recommended, substantial proportions of women will have poor vitamin D status during their pregnancy and, as a result, their offspring will very likely be born with vitamin D deficiency. Currently, recommended doses of vitamin D during pregnancy will not achieve serum 25(OH)D concentrations in the normal range in populations who because of skin pigmentation or lifestyle are less able to generate vitamin D from sunlight exposure (Hollis *et al.* 2011).

We believe that current policy for maintenance of adequate vitamin D status during pregnancy and at birth has not kept pace with the dramatic changes in lifestyle that have occurred in human populations over recent generations. Populations with traditional lifestyles and who have year-round exposure to sunlight have serum 25(OH)D concentrations that average 112 nmol L^{-1} (Luxwolda *et al.* 2012). In

studies of lactating women performed in Europe and the United States daily vitamin D intakes of at least 2000 IU, two to four times the currently recommended daily intakes, are required in order for breast milk vitamin D activity to be increased (Ala-Houhala *et al*. 1988; Hollis & Wagner 2004). Randomized controlled trials consistently show such doses to be safe (Hollis *et al*. 2011; Grant *et al*. 2014). These data imply that our current approach to vitamin D requirements, which is based upon a disease avoidance model (Heaney & Armas 2015), will inevitably result in substantial proportions of the pregnant women and newborns globally being vitamin D deficient.

Our study has several limitations. Design and methodological differences between the individual studies limited the precision of our global estimates of vitamin D status in pregnant women and newborns. Thirteen different assays were used in the 95 studies included in our review. Of the different assays that are available, the LC-MS/MS is increasingly considered the gold standard technique for measuring 25(OH)D concentration due to its high accuracy and precision (Farrell & Herrmann 2013). Within and between-run coefficients of variance are 2.4% and 2%, respectively (Farrell *et al*. 2012). Only 9/95 (9%) of the studies included in this review used this gold standard assay. Excellent correlations have been shown for the measurement of 25(OH)D concentration by LC-MS/MS and RIA and by the LIAISON assay (Eyles *et al*. 2009; Hee-Won *et al*. 2012). Of the studies included in our review 31/95 (33%) used RIA and only 2/95 (2%) used the LIAISON assay. The ability of our review to create precise estimates of the prevalence of vitamin D deficiency and severe vitamin D deficiency was also limited by the variability in 25(OH)D values used to report vitamin D status (Table 3). Data from 29% (21/72) of the studies could not be included because 25(OH)D cut-off values other than 25 and 50 nmol L^{-1} were used to define vitamin D status. An investigation of variance by global region in maternal and newborn vitamin D status with season or other demographic factors was considered beyond the scope of this meta-analysis.

In summary, this review shows that vitamin D deficiency [25(OH)D <50 nmol L^{-1}] is more prevalent in pregnant women and newborns than has been described in the general population globally. Wide variability is evident between WHO regions in serum 25(OH)D concentrations, within regions in the extent to which 25(OH)D varies between studies, and in the extent to which vitamin D status has been characterized. Vitamin D status during pregnancy is currently poorly defined in the South-East Asian, Eastern Mediterranean and African regions, and in non-European populations in the Western Pacific region. The high prevalence during pregnancy of vitamin D deficiency in the South-East Asian region implies a high likelihood of vitamin D deficiency and indicates that determining this should be a priority, as should be characterizing vitamin D status among non-European populations in the Western Pacific. To improve comparability of data between studies and hence between countries and WHO regions, standardization of the 25(OH)D cut-off values (e.g. <50 and <25 nmol L^{-1}), and development of a standard measurement of 25(OH)D or utilizing assays that have shown good correlation with each other is necessary.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions

RS conceived and designed the study, analysed and interpreted the data, and completed the first and final drafts of the manuscript. SMBM conceived and

designed the study, reviewed the manuscript and approved the final version as submitted. CAC helped with the interpretation of data, critically reviewed the manuscript and approved the manuscript as submitted. CCG conceived and designed the study, reviewed and revised the manuscript and approved the final manuscript as submitted.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Manuscripts included in the review by WHO region and by their reporting of maternal and/or newborn vitamin D status.

Table S2. Manuscripts included in review by the serum 25-hydroxyvitamin D [25(OH)D] concentration values used to describe vitamin D status.