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ORIGINAL CONTRIBUTION

Is vitamin D deficiency a public health concern for low middle income countries? A systematic literature review

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Abstract

Purpose Vitamin D deficiency has been receiving increasing attention as a potential public health concern in low and lower-middle income countries (LMICs), of which there are currently 83. We aimed to conduct a comprehensive systematic literature review (SLR) of available data on vitamin D status and prevalence of vitamin D deficiency in all 83 LMICs.

Methods We followed the general methodology for SLRs in the area of serum 25-hydroxyvitamin D. Highest priority was placed on identifying relevant population-based studies, followed by cross-sectional studies, and to a lesser extent case-control studies. We adopted the public health convention that a prevalence of vitamin D deficiency (serum 25-hydroxyvitamin D < 25/30 nmol/L) at > 20% in the entire population and/or at-risk population subgroups (infants, children, women of child-bearing age, pregnancy) constitutes a public health issue that may warrant intervention.

Results Our SLR revealed that of the 83 LMICs, 65% ($n = 54$ countries) had no published studies with vitamin D data suitable for inclusion. Using data from the remaining third, a number of LMICs had evidence of excess burden of vitamin D deficiency in one or more population subgroup(s) using the above convention (Afghanistan, Pakistan, India, Tunisia and Mongolia) as well as possibly other LMICs, albeit with much more limited data. Several LMICs had no evidence of excess burden.

Conclusion Vitamin D deficiency is a public health issue in some, but certainly not all, LMICs. There is a clear need for targeting public health strategies for prevention of vitamin D deficiency in those LMICs with excess burden.

Keywords Vitamin D deficiency · Serum 25(OH)D · Low and lower-middle income countries · Systematic review · Food fortification · FAO food balance sheets

Introduction

Countries have been classified by their level of development as measured by the World Bank Group's per capita gross national income [1, 2]. Those countries grouped as low- and lower-middle income economies are sometimes collectively referred to as 'Low middle income countries' (LMICs) and represent 83 countries as of March, 2017 (see Table 1). Importantly, nutritional concerns for LMICs have been highlighted [3] and while a clear priority is placed on improving the health and nutritional well-being of mothers, infants and children [3, 4], other segments of their populations, such as the elderly, may also be at nutritional disadvantage [5]. Amongst the nutritional concerns, vitamin D deficiency has been receiving increasing attention as a potential public health concern in LMICs [6, 7], above and beyond that evident in some upper-middle and high income countries in the Western world [8].

In terms of devising strategies for the prevention of vitamin D deficiency for any particular country, nationally representative data on vitamin D status (as reflected by serum 25-hydroxyvitamin D [25(OH)D]) are key underpinning data [9]. In the context of availability of such data for LMICs, in addition to some comprehensive narrative reviews [10–12], there have been two relatively recent systematic reviews [13,

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Table 1 Listing of World Bank designated 'Low-income countries' and 'Lower-middle-income countries'

Low-income countries[a]		
Afghanistan	Gambia, The	Nepal
Benin[b]	Guinea[b]	Niger[b]
Burkina Faso[b]	Guinea-Bissau	Rwanda[b]
Burundi[b]	Haiti[b]	Senegal[b]
Central African Republic[b]	Korea, Dem. People's Republic[b]	Sierra Leone[b]
Chad[b]	Liberia[b]	Somalia[b]
Comoros[b]	Madagascar[b]	South Sudan[b]
Congo Democratic Republic[b]	Malawi	Tanzania
Eritrea[b]	Mali[b]	Togo[b]
Ethiopia	Mozambique[b]	Uganda
		Zimbabwe
Lower-middle income countries[a]		
Armenia[b]	Kenya[b]	Samoa[b]
Bangladesh	Kiribati[b]	São Tomé and Principe[b]
Bhutan[b]	Kosovo[b]	Solomon Islands[b]
Bolivia[b]	Kyrgyz Republic[b]	Sri Lanka
Cabo Verde[b]	Lao PDR[b]	Sudan[b]
Cambodia	Lesotho[b]	Swaziland[b]
Cameroon	Mauritania[b]	Syrian Arab Republic
Congo, Republic[b]	Micronesia, Fed. Sts.[b]	Tajikistan[b]
Côte d'Ivoire[b]	Moldova	Timor-Leste[b]
Djibouti[b]	Mongolia	Tonga[b]
Egypt, Arab Republic	Morocco	Tunisia
El Salvador	Myanmar[b]	Ukraine[b]
Ghana	Nicaragua	Uzbekistan[b]
Guatemala	Nigeria	Vanuatu[b]
Honduras	Pakistan	Vietnam
India	Papua New Guinea[b]	West Bank and Gaza
Indonesia	Philippines	Yemen, Republic
		Zambia[b]

[a]Based on a gross national income per capital of $1025 or less for Low-income countries, and of $1026 to $4035 for Lower-middle income countries

[b]No published studies or no included studies for this country identified during systematic literature searches or additional records through other sources

14] and one meta-regression analysis [15] of vitamin D status globally, all of which show how limited the information for LMICs appears to be. For example, the two systematic reviews of global vitamin D status only identified as few as 10 studies from 6 to 8 LMICs out of the very large numbers of studies included (*n* 103–195) [13, 14], suggesting no available data on vitamin D status for around 90% of LMICs. However, it should be noted that in these systematic reviews [13, 14], country of interest was not part of the a priori search strategy. It has recently been shown in a systematic review of vitamin D status in Southern European countries that searching within an a priori listing of countries yields a much higher number of studies than that captured by the more global/region-wide approach [16].

Data on vitamin D intakes in LMICs are also very limited [7] and moreover, representative data from national nutrition surveys in these countries are, for the most part, largely absent. In the absence of vitamin D intake data, one possibility is to generate information on per capita supply of vitamin D by taking information from the Food and Agriculture Organization (FAO) food balance sheets and coding their food commodities using dietary analysis software, as demonstrated for the Republic of Ireland [17].

Therefore, the aim of the present work was to conduct a comprehensive systematic literature review of available data on mean/median serum 25(OH)D concentrations as well as estimates of the prevalence of low vitamin D status (as defined by a number of internationally used thresholds of serum 25(OH)D) in all 83 currently listed LMICs using a priori defined countries in the electronic searches. In addition, we analysed available food balance sheets for those LMICs highlighted in our systematic review as having

published vitamin D status data to generate estimates of their per capita supply of vitamin D over the most recent decade.

Materials and methods

There were three component steps to our overall approach: firstly, we performed a series of LMIC-specific structured electronic searches of the available literature, and then secondly, for those LMICs with included studies reporting vitamin D status data, we derived per capita vitamin D supply data using food commodity data from the respective FAO balance sheets over a 10 year period (2003–2013) in combination with dietary analysis software. We also used the Global Alliance for Improved Nutrition (GAIN) online fortification database to ascertain whether these LMICs have vitamin D (in addition to vitamin A) added to vegetable oils and/or margarine as per their national standards. Finally, we used data from the World Health Organisation (WHO) in relation to global UV Index measures as a crude estimate of UVB availability in LMICs.

Systematic review of vitamin D status in LMICs

The methodology in the present work follows the general methodology for systematic reviews in the area of serum 25(OH)D as applied by us previously [18–20] and again very recently [16], with brief specific details as follows:

Studies included in the present systematic review were population-based studies, cross-sectional studies, or case-control studies (for which the control groups only were used) with well-defined/characterized samples of apparently healthy subjects resident in the LMICs. While we placed highest priority on population-based studies within our systematic review, followed by cross-sectional studies, it was clear from the two existing systematic reviews of global vitamin D status [13, 14] that the data were going to be very limited for the majority of LMICs. Therefore, we decided to allow inclusion of the control groups of case-control studies, and particularly where data from population-based or cross-sectional studies were lacking. Additional inclusion and exclusion criteria for study selection and the hierarchy applied for selection of available studies within a country and for a specific age-group(s) are outlined in the Online Supplemental Information.

Search strategy, data collection and quality assessment of eligible studies

During March–May 2017, electronic searches were performed for each LMIC individually in PubMed/Medline databases from inception to May 18th 2017 (date of the final screen) by using a structured search strategy which accounted for the inclusion/exclusion criteria outlined above. An exemplar search strategy specifically adapted for PubMed/Medline is shown in Supplemental Table 1. In addition, information on the quality assessment of eligible studies is suppled in the Onlined Supplemental Information. The methods used in the present review follow the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [21].

Data synthesis, extraction and presentation

Information on the combined number of LMIC-specific records identified, abstracts and full-text articles screened, and articles excluded and included in the review is shown in Fig. 1.

As there is no agreed definition of vitamin D deficiency, data on the prevalence of serum 25(OH)D < 12.5, 25, 50, 75 nmol/L (or alternative cognate thresholds) are presented. However, most agencies internationally suggest that a serum 25(OH)D < 25/30 nmol/L represents an increased risk of vitamin D deficiency (i.e., rickets in children and osteomalacia in adults) [22–25]. Furthermore, it has been suggested that from a public health perspective, a prevalence of vitamin D deficiency (serum 25(OH)D < 30 nmol/L, or a lower threshold, if used) at > 20% in the entire population and/or in subsets of the population considered especially at risk (i.e., infants, children, pregnant women and women of child-bearing age) constitutes a public health issue that may warrant intervention [7]. Thus, this was prioritized within the present review as an index of public health concern to highlight LMICs where the burden of vitamin D deficiency is of particular note and we designated such LMICs as 'hot spots' of excess burden of vitamin D deficiency. A LMIC was not designated as a 'hot spot', if the prevalence estimates within reported studies for that country were not consistently > 20% for the particular population subset(s) of the population. In addition, if a LMIC had consistent prevalence data showing another lifestage group (e.g., other than infants, children, pregnant women and women of child-bearing age) with excess burden, it was designated as a 'hot spot' of excess burden of vitamin D deficiency. However, if a LMIC had only one study reporting an excess burden, it was designated as a 'possible hot spot'.

Finally, a circulating concentration of 50 nmol/L has been suggested as that defining nutritional adequacy of vitamin D at least in terms of bone health [22, 24, 25], while the Task Force for the Clinical Guidelines Subcommittee of The Endocrine Society has suggested that to maximize the effect of vitamin D on calcium, bone, and muscle metabolism, serum 25(OH)D concentration should exceed 75 nmol/L [26]. Thus, the prevalences below these cut-offs were also commented on, where appropriate.

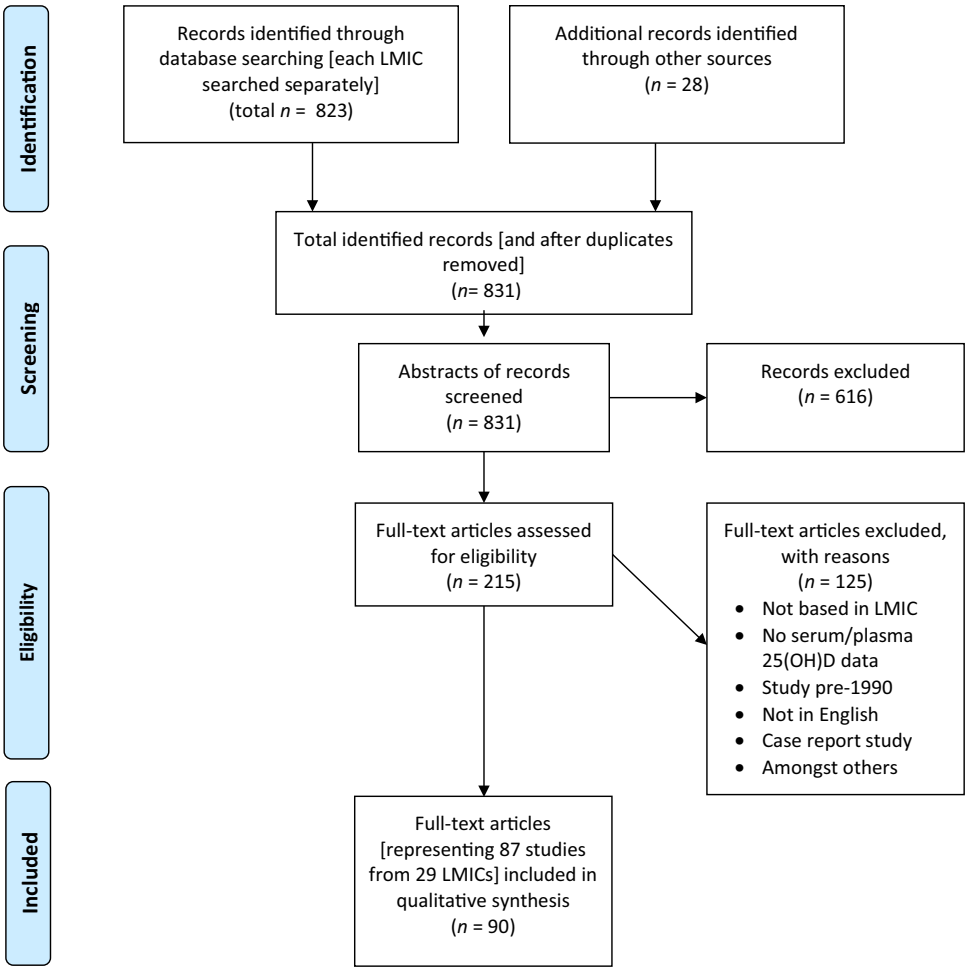

Fig. 1 Flow diagram of the screening procedure followed to identify eligible studies

Estimation of vitamin D supply in LMICs using FAO balance sheets from 2003 to 2013 and review of national standards for addition of vitamin D

The method of estimation of vitamin D supply using FAO food balance sheets has been outlined in detail elsewhere [17], but in brief. FAO food balance sheets for the period 2003–2013 were downloaded as csv files from the FAOSTAT database [27]. These food balance sheets provide overall per capita supply (as kg/year) for various food commodities. In order to determine the average vitamin D supply over this ten year period, these food commodities were coded and entered into WISP dietary analysis software (Tinuviel Software, Llanfechell, Anglesey, UK). The food composition databank supplied with this software is from McCance and Widdowson's The Composition of Foods, 5th and 6th editions plus supplements [28].

While the FAO balance sheet data will highlight low supply of vitamin D due to limited supply of naturally-rich food sources, we also cross-connected this data with the GAIN online fortification tracking database [29] to ascertain whether the LMICs have a policy of addition of vitamin D (in addition to vitamin A) to vegetable oils and margarine, on either a mandatory or voluntary basis, as part of their national standards.

Crude estimate of UVB availability in LMICs on the basis of global UV Index data from the World Health Organisation

The UV Index informs the public of the level of UV exposure expected in a given day and also as a general rule, UV Index scores ≥ 3 trigger raised awareness of adherence to sun protection advice [30]. However, beyond that it may provide some crude insight into the availability of UVB for pre-vitamin D_3 synthesis in exposed skin in individuals living in LMICs. It has been estimated that UVB (280–315 nm) in units of Wm^{-2} is 18.9 times the UV Index [31], thus the higher the UV Index, the higher the availability of UVB radiation. The monthly changes in UV Index over the course of a year in selected countries around the World at a variety of latitudes have been provided by the WHO [32], and we used this data as a crude proxy for UVB availability estimates in LMICs at similar latitudes.

Other databases accessed

Data on the proportion of a LMIC's population which are Muslim was accessed from the online World Factbook [33], while data in relation to ambient air pollution in LMICs was accessed from the WHO 2014 Air Pollution Ranking online database [34]. Data on the skin pigmentation/skin types were accessed from an online source [35] in addition to information specifically for Africa in the review by Prentice et al. [36].

Results

Systematic review of vitamin D status in LMICs

Our individual structured electronic searches of all 83 LMICs separately revealed that 65% of these countries (*n* 54), spread across 6 world regions, had no published studies with data on prevalence of low vitamin D status, or any distribution estimate of circulating 25(OH)D concentration, suitable for inclusion in the present systematic review (see Fig. 2; Table 1). Data on circulating 25(OH)D and/or the prevalence of vitamin D status in those remaining LMICs (*n* 29), which had published studies (87 in all reported in 90 articles [37–126]) that fit with the present review's inclusion criteria, are shown in Table 2 and Supplemental Table 2.

Using the public health index of > 20% prevalence of serum 25(OH)D < 25/30 nmol/L in the entire population and/or in one or more subsets of the population considered especially at risk (e.g., infants, children, pregnant women and women of child-bearing age) highlights how only two of the 6 world regions have LMICs without evidence of this excess burden of vitamin D deficiency (Supplemental Table 2). For example, Moldova was the only one in the Europe and Central Asia world region and the prevalence of serum 25(OH)D < 30 nmol/L was 15% in Moldovan children/adolescents. Within the Latin America and Caribbean world region, the three included studies showed that 5–21% of children and adolescents from Guatemala had vitamin D inadequacy (serum 25(OH)D < 50 nmol/L), with a prevalence estimate of 46.3% for older adults.

The remaining four world regions contained LMICs which fit with our definition of either not being hot spots of such excess burden of vitamin D deficiency (see Supplemental Table 2) or being, or possibly being, such hot spots (see Table 2; Fig. 3).

The South Asia world region had the highest number of 'hot spot' countries, at 3 out of the 6 identified LMICs. Between 16.8 and 73% of Afghanistani children had serum 25(OH)D < 20 nmol/L, and likewise Pakistani neonates had a high prevalence of vitamin D deficiency (46.7–75.3%). Between 26.5 and 91.3% of pregnant women, and 25.3% of non-pregnant women in Pakistan had serum 25(OH)D < 20/25 nmol/L. The prevalence of serum 25(OH)D < 50 nmol/L in three large studies in Pakistan was 53.5% (*n* 4,830), 69.7/70.7% (males/females; *n* 4,788) and 66.1% (*n* 60,937), while the National Nutrition Survey in Pakistan reported 66.2 and 68.5% for non-pregnant (*n* 5,402) and pregnant women (*n* 699), respectively. Pregnant women in India had a high prevalence (31–59.5%) of serum 25(OH)D < 25/28 nmol/L. The prevalence of vitamin D deficiency in children and adolescents was 19.7%, and high, but variable, for adults and older adults at 19.4–87%.

The prevalence of serum 25(OH)D < 25/30 nmol/L in Nepalese pregnant/lactating women and young children was ~ 14%, and 12–38.9% deficiency in non-pregnant Bangladeshi women, depending on socio-economic status and veiled or unveiled. However, in both Nepal and Bangladesh, the prevalence of serum 25(OH)D < 30 nmol/L in infants was much lower (0.6 and 6%, respectively). There was a low prevalence of vitamin D deficiency in Sri Lankan children and adults (0–6.3%).

The Middle East and North Africa world region had one 'hot spot' and three 'possible hot spot' countries out of the six identified LMICs. In terms of the former, Tunisian pregnant women, infants and children/adolescents had high prevalence (40.9–90%) of serum 25(OH)D < 30 nmol/L, while the prevalence of vitamin D deficiency in adults was more variable (17.2–61.0%). Vitamin D status of women of child-bearing age in the West Bank and Gaza was low, with 56–70% having serum 25(OH)D < 27.5 nmol/L, while 61% of girls from Yemen had serum 25(OH)D < 30 nmol/L. Adults in Syria had low vitamin D status, with 58.2% with serum 25(OH)D < 25 nmol/L. All three LMICs were considered 'possible hot spot' countries, as based on only one study each. The prevalence of vitamin D deficiency in Tunisian adults (17.2 and 61%) and Moroccan older adults (7.1 and 51.6%) was variable, whereas there was a high prevalence (> 90%) of vitamin D inadequacy in infants and pregnant women in Morocco. Between 25.7 and 77.2% of Egyptian infants and women (pregnant and non-pregnant) had vitamin D inadequacy, while adolescents had variable estimates (11.5% versus 45%). Young children in the West Bank and Gaza had much better status at only 5–13% with vitamin D inadequacy.

There was one 'hot spot' country in the East Asia and Pacific world region which had 5 identified LMICs. There was a very high prevalence of vitamin D deficiency (serum 25(OH)D < 25 nmol/L) in Mongolian infants, children and adults (61–88.6%). The prevalence of vitamin D deficiency in Vietnam was variable, at 11.2–20.6% in children and 17.3% in women. The prevalence of vitamin D deficiency was low overall in Indonesian children and adults, and absent in Filipino postmenopausal women. Similarly, the prevalence of vitamin D deficiency in Cambodian women and

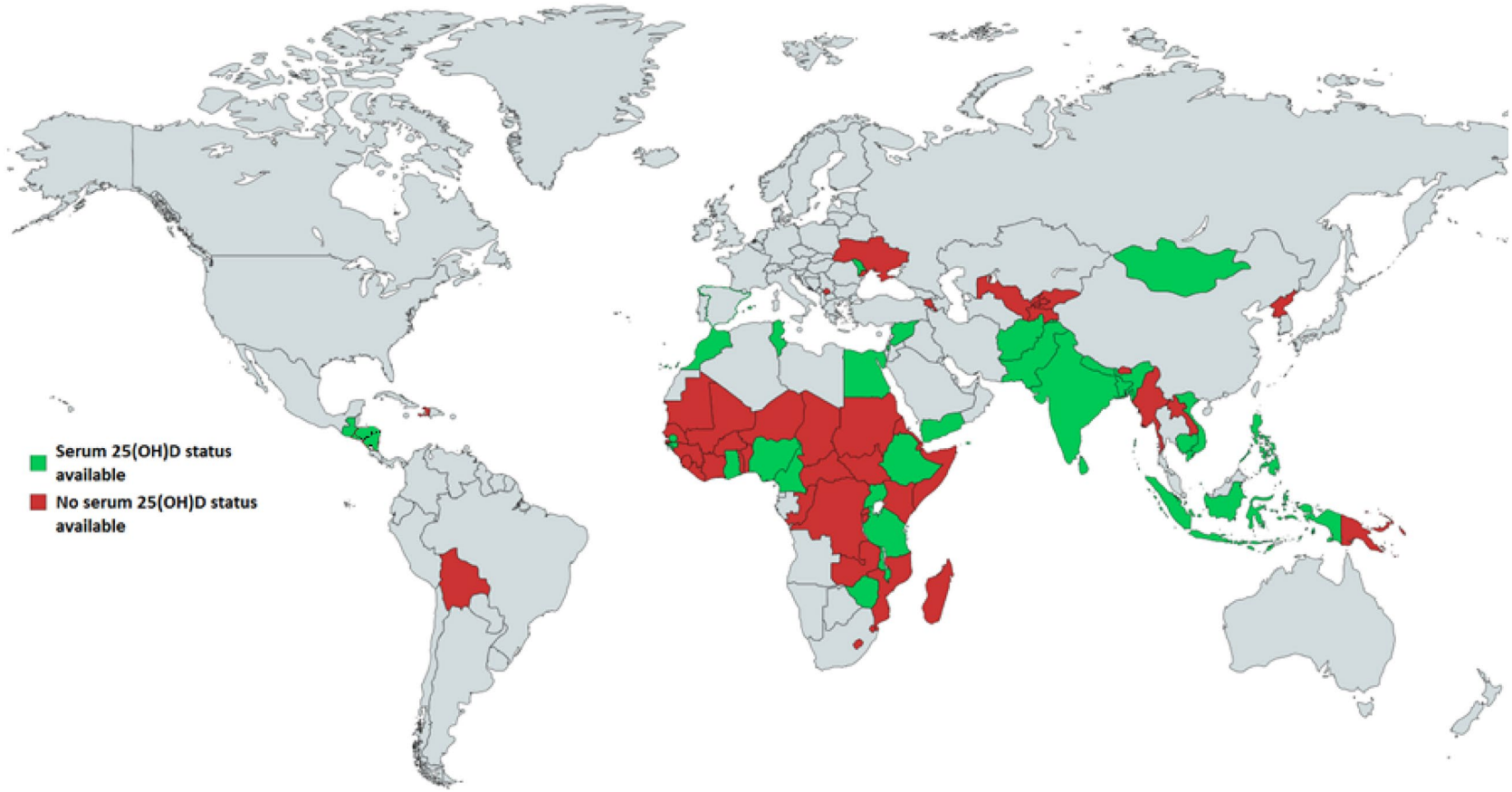

Fig. 2 Low middle income countries, spread across 6 world regions, which had [*n* 32; shown in green] and had not [*n* 51; shown in red*] published studies with circulating 25-hydroxyvitamin D [25(OH)D] concentration data suitable for inclusion in the present systematic review. *Note: 9 of the 51 countries too small to appear in the map

Table 2 Mean and/or median circulating 25(OH)D concentrations and prevalence of circulating 25(OH)D concentrations below selected thresholds reported for studies from Low Middle Income Countries (LMICs), identified as vitamin D deficiency 'hot spots' or 'possible hot spots', within the present systematic review

References	Country/region (latitude)	Sample size (*n*)	Population group/age[b]	Sampling months	Serum 25(OH)D (nmol/L)[c] Mean ± SD or median (IQR/range)	Prevalence below serum 25(OH)D threshold (%)[d]				Method (manufacturer)
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
World region: East Asia and Pacific										
Lander et al. [38]	Mongolia/ multiple sites (46.8°N)	98	*Infants/children* 20.0 ± 8.5 mo	Nov	–	–	61%	–	–	RIA (Diasorin)
Uush et al. [based on 4th National Nutrition Survey] [39]	Mongolia/21 provinces in 4 economic regions and Ulaanbaatar (46.8°N)	524 Children < 5 y [C] 867 Non-pregnant women [NPW]	*Children/adults* 6–59 mo [C] 39.0 ± 9.7 [NPW]	July–Sept	19.2 ± 7.7 (t) (winter) 56.2 ± 20.0 (t) (summer)	–	*30.0% [NPW]* *21.8% [C]* *(< 18 nmol/L)*	–	–	ELISA (NR)
Ganmaa et al. [40]	Mongolia/ Ulaanbaatar, (47.8°N)	420 (f)	*Adults (f)* 34.9 ± 4.8 y	March–April	19.0 ± 10.0	28.3%	88.6%	98.8%	99.8%	LC-MS/MS
Bromage et al. [41]	Mongolia/ multiple sites (46.8°N)	320 (160 indoor; 160 Outdoor)	*Adults* 39.0 ± 9.7 y	June–August and January–March	19.3 ± 7.8 (winter) 56.3 ± 20.0 (summer)	–	3.1% (summer) 80.1% (winter)	42.4% (summer) 99.6% (winter)	82.1% (summer) 0% (winter)	Liaison 25(OH)D total assay (Diasorin)
World region: South Asia										
Manaseki-Holland et al. [54]	Afghanistan/ Kabul (34.5°N)	107	*Children* 0.5–5 y	Jan	Median: 12.5 (range 5.0–60) (p)	–	*73%* *(< 20 nmol/L)*	–	–	HPLC
2013 National Nutrition Survey Report [55]	Afghanistan (34.5°N)	728[a] Children [C] 1190 Women of reproductive age [WRA]	*Children/adults* 6–59 mo [C] 15–49 y [WRA]	Jun/Jul and Sep/Oct	NR	–	*64.7% [WRA]* *16.8% [C]* *(< 20 nmol/L)*	95.5% [WRA] 81% [C]	98.6% [WRA] 97.5% [C]	NR

Table 2 (continued)

References	Country/region (latitude)	Sample size (*n*)	Population group/ age[b]	Sampling months	Serum 25(OH)D (nmol/L)[c] Mean ± SD or median (IQR/range)	Prevalence below serum 25(OH)D threshold (%)[d]				Method (manufacturer)
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Anwar et al. [56]	Pakistan/Karachi (urban) and Jhelum/Punjab (rural) (~25 and ~32°N, respectively)	269 pregnant [PW] 227 neonates [N]	*Pregnancy/neonates* 18–40 y [PW] [N]	N/A	Urban 13.4 ± 9.1 [W] 19.9 ± 13.6 [N] Rural 28.7 ± 18.0 [W] 29.6 ± 22.1 [N]	*29.0% [W]* *18.1% [IF]* Urban *35.7% [W]* *16.5%[IF]* Rural *6.5% [W]* *24.4% [IF]* *(< 10 nmol/l)*	Urban 91.3% [W] 75.3% [N] Rural 50.0% [W] 46.7% [N]	Urban 99.5% [W] 97.3% [N] Rural 89.0% [W] 82.2% [N]	Urban 100% [W] 98.4% [N] Rural 99.5% [W] 97.8% [N]	Liaison 25(OH)D total assay (Diasorin)
2011 National Nutrition Survey Report [57]	Pakistan multiple sites (~30°N)	699 pregnant women [PW] 5402 non-pregnant women [NPW]	*Pregnancy/adults* 6–59 mo [C] 15–49 y [WRA]	NR	NR	–	*25.3% [NPW]* *26.5% [PW]* *[NPW]* *46.3% Urban* *18.4% Rural* *[PW]* *50.7% Urban* *20.2% Rural* *(< 20 nmol/L)*	66.2% [NPW] 68.5% [PW]	85.1% [NPW] 86.1% [PW]	NR
Hassan et al. [58]	Pakistan (~30°N)	60,937 clinical specimens	*Various* 40.5 ± 19.7 y	All seasons	33.7 (18.5–62.7)	–	–	66.1% (t)	–	Various[e]
Riaz et al. [59]	Pakistan/5 cities: Lahore, Sialkot/ Gujranwala, Rawalpindi/ Islamabad, Abbotabad, Peshawar (~34.0°N)	4830	*Various* < 20 to > 70 y	All seasons	–	–	–	53.5%	84.7%	ECLIA (Roche diagnostics)
Iqbal et al. [60]	Pakistan/Karachi (24.9°N)	4,788	*Adults* 48.5 ± 18.6 y	All seasons	44.4 ± 38.7 (m) 45.9 ± 35.1 (f)			69.7% (m) 70.7% (f)	84.9% (m) 84.3% (f)	ECIA (Roche diagnostics)

Table 2 (continued)

References	Country/region (latitude)	Sample size (*n*)	Population group/ age[b]	Sampling months	Serum 25(OH)D (nmol/L)[c] Mean ± SD or median (IQR/range)	Prevalence below serum 25(OH)D threshold (%)[d]				Method (manufacturer)
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Mehboobali et al. [61]	Pakistan/Eastern Karachi (low income setting, 25.0°N)	858	*Adults* 32.5 ± 10.7 y	All seasons	–	–	–	58.4% (t) 33.0% (m) 76.0% (f)	89.8% (t) 47.0% (m) 21.0% (f)	ECLIA (Roche diagnostics)
Sachan et al. [68]	India/Lucknow, (26.8°N)	207 pregnant women [PW] 117 cord blood [Cb]	*Pregnancy/cord* 24.4 ± 4.5 y	Sep- Nov	34.9 ± 23.2 [PW] 21.2 ± 14.2 [Cb]		42.5% [PW]	*66.7% (< 37.4 nmol/L)* [PW]		RIA (Diasorin)
Marwaha et al. [69]	India/Delhi (28.7°N)	541 pregnant women	*Pregnancy* 24.6 ± 2.8 y	All seasons	23.2 ± 12.2	17.7%	59.5%	96.3%	–	RIA (Diasorin)
Farrant et al. [70]	India/Mysore (12.3°N)	559 pregnant women	*Pregnancy* 23.7 (30.0, 26.0) y	All seasons	37.8 (24.0, 58.5)		*31% (< 28 nmol/L)*	66.0%		RIA (IDS)
Krishnaveni et al. [71]	India/Mysore (12.3°N)	568 pregnant women	*Pregnancy* 24.0 ± 4.3 y	All seasons	39.0 (24.0, 58.0)	–	–	67%	–	RIA (IDS)
Filteau et al. [72]	India/Delhi (28.7°N)	902	*Children* 5.0 ± 1.0 y	All seasons	32.7 ± 23.0	–	43%	83%	–	RIA (Diasorin)
Kapil et al. [73]	India/Shimla (31.3°N)	626	*Children/adolescents* 13.1 ± 3.4 y (m) 13.2 ± 3.2 y (f)	All seasons	32.0 ± 16.3 (m, 6–11 y) 34.5 ± 13.0 (m, 12–18 y) 27.8 ± 13.3 (f, 6–11 y) 23.8 ± 12.3 (f, 12–18 y)	–	–	93.%	98.9%	CIA (Diasorin)
Basu et al. [74]	India/Kolkata (22.6°N)	310	*Children/adolescents* 1–5, 6–11, 12–16 y	All seasons	47.5 (27.5–70)	–	19.7%	72.6%	97.1%	CIA (Roche diagnostics)
Veena et al. [75]	India/Mysore (12.3°N)	468 Children [C] 472 adolescents [A]	*Children/adolescents* 9.7 ± 0.3 y [C] 13.5 ± 0.1 y [A]	All seasons	38.9 (23.5, 58.3) [C] 38.1 (23.5, 56.8) [A]	–	–	66.9% [C] 67.8% [A]	–	RIA (IDS)
Puri et al. [76]	India/Delhi (28.7°N)	3127 (f)	*Children/adolescents* 12.3 ± 3.1	July	31.9 ± 15.4			90.8%		RIA (Diasorin)

Table 2 (continued)

References	Country/region (latitude)	Sample size (*n*)	Population group/ age[b]	Sampling months	Serum 25(OH)D (nmol/L)[c] Mean ± SD or median (IQR/range)	Prevalence below serum 25(OH)D threshold (%)[d]				Method (manufacturer)
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Harinarayan et al. [77]	India/Tirupati (13.6°N)	76 urban children (UC) 70 rural children (RC) 943 urban adults (UA), 205 rural adults (RA)	*Children/adults* 12.5 ± 0.6 y (UC) 12.6 ± 0.4 y (UA) 46.0 ± 0.4 y (UA) 43.0 ± 1.0 y (RA)	All seasons	42.5 nmol/L (UA)[f] 53.3 nmol/L (RA) 42.5 nmo/L (UC) 44.9 nmol/L (RC)			62.0/75.0% (UA; m/f) 44.0/70.0% (RA; m/f) 81.5/62.9% (UC; m/f) 76.5/72.2% (RC; m/f)	88.0/94.0% (UA; m/f) 83.5/99.0% (RA; m/f) 96.3/88.6% (UC; m/f) 91.2/86.1% (RC; m/f)	RIA (DiaSorin)
Beloyartseva et al. [78]	India/mutiple locations	2,119	*Adults*[g] 42. 7 ± 6.8 y	Dec–Mar	35.9 ± 26.6	-	–	79%	94%	RIA (DiaSorin)
Shivane et al. [79]	India/Mumbai (19.1°N)	1,137	*Adults* 30.4 ± 3.6 y	May–Jun	43.5 ± 22.8	2.9%	19.4%	70.0%	92.8%	RIA (DiaSorin)
Goswami et al. [80]	India/Delhi (28.7°N)	642	*Adults* 33.7 ± 13.5 y	Nov–Mar	17.5 ± 10.2	–	87.0%	–	–	RIA (DiaSorin)
Marwaha et al. [81]	India/Delhi (28.7°N)	1,600	*Adults/older adults (> 50 y)* 57.7 ± 9.5 y	N/A	24.5 ± 19.8 (50–60 y) 23.0 ± 22.0 (60–70 y) 27.5 ± 21.8 (> 70)	27.9% (t)	61.8% (t)	91.2% (t)	98.2% (t)	RIA (DiaSorin)
World region: Middle East and North Africa										
Fenina et al. [85]	Tunisia/Tunis city (36.8°N)	225 pregnant	*Pregnancy* 31 ± 5.8 y	All seasons	18.0 ± 13.6 (median, IQR)	*31.4% (< 15 nmol/L)*	*82.3% (< 30 nmol/L)*	96.8%		Liaison 25(OH)D total assay (Diasorin)
Ayadi et al. [86]	Tunisia/Tunis (35°N)	87 Mother [W] Infant [N] pairs	*Infant/adults* 31.2 ± 4.9 y [W] [N]	Oct–Nov	17.0 ± 12.9 [W] 14.8 ± 10.4 [N]	–	*87% [W]* *90% [N]* *(< 30 nmol/L)*	97% [W] 98% [N]	–	ECIA (Roche diagnostics)
Bezrati et al. [87]	Tunisia/Tunis (35°N)	225 (m) Football academy	*Children/adolescents* 7–16 y	Jan–March	Range 9.5–77.5	–	*40.9% (< 30 nmol/L)*	85%	–	Liaison 25(OH)D total assay (Diasorin)

Table 2 (continued)

References	Country/region (latitude)	Sample size (*n*)	Population group/ age[b]	Sampling months	Serum 25(OH)D (nmol/L)[c] Mean ± SD or median (IQR/range)	Prevalence below serum 25(OH)D threshold (%)[d]				Method (manufacturer)
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Meddeb et al. [88]	Tunisia/Ariana, Tunis (33.9°N)	389 (67% f)	*Adults* 20–60 y	Jan–March	–	0.3%	17.2%	*47.6%* *70.5% (Veiled f)* *48.9%* *(Unveiled f)* *(< 37.5 nmol/L)*	–	RIA (Incstar)
Nasri et al. [89]	Tunisia/Tunis (33.9°N)	64 Healthy controls	*Adults* 21–41 y	All seasons	28.3 ± 13.8	–	*61%* *(< 30 nmol/L)*	92%	–	Liaison 25(OH)D total assay (Diasorin)
Bahlous et al. [90]	Tunisia/Manouba (36.8°N)	134 (f) (pm and osteopor) (28.3% veiled)	*Adults/older adults* 66.2 ± 7.6 y	March–April	68.7 ± 37.8 [− Fx] 53.3 ± 32.0 [+ Fx]	–	–	45.2% (t) 25.0% [− Fx] 51.0% [+ Fx]	–	HPLC
Abdeen et al. [101]	West Bank and Gaza/Hebron and Gaza city (~ 31°N)	366 as Women [W]-Child [C] pairings	*Adults* 18–49 y [W] *Infants* 35–59 mo [C-1] *Children* 60–83 mo [C-2]	August	*Hebron* 24 (17–41) [W] 66 (61–91) [C-1] 80 (64–94) [C-2] *Gaza* 10 (10–26) [W] 71 (55–84) [C-1] 64 (55–80) [C-2]	–	*Hebron* [W] *56%* *(< 27.5 nmol/L)* *Gaza* [W] *70%* *(< 27.5 nmol/L)*	*Hebron* 84% [W] 5% [C-1] 9% [C-2] *Gaza* 97% [W] 13% [C-1] 12% [C-2]	–	RIA (Diasorin)
Sayed-Hassan et al. [102]	Syria/Damascus (33.3°N)	372	*Adults* 34.1 ± 10.0 y	All seasons	24.7 ± 16.9	30.4%	61.0%	90.1%	99.2%	ECIA (Roche diagnostics)
Elemraid et al. [103]	Yemen/Sana'a (~ 15° N)	74 (f) Healthy Controls	*Children* 8.2 ± 3.9 y	March–May	27.0 (95% CI 24.6–29.8)	*6.8%* *(< 15 nmol/L)*	*58.2%* *(< 30 nmol/L)*	96%	–	LC–MS/MS
World region: Sub-Saharan Africa										
Pfitzner et al. [110]	Nigeria/Jos (~ 9.9 °N)	218	*Children* 22 (6–35) mo	March–April	66.8 ± 24.2	–	0%	*1.4%* *(< 31 nmol/L)*	–	RIA (Incstar)

Table 2 (continued)

References	Country/region (latitude)	Sample size (*n*)	Population group/ age[b]	Sampling months	Serum 25(OH)D (nmol/L)[c] Mean ± SD or median (IQR/range)	Prevalence below serum 25(OH)D threshold (%)[d]				Method (manufacturer)
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Durazo-Arvizu et al. [111]	Nigeria/South-west (6 °N)	100 (f)	*Adults* 30.5 ± 11.0 y	N/A	64.4 ± 17.4	–	0%	24%	–	RIA (Diasorin)
Olayiwola et al. [112]	Nigeria/Ibadan (7.4 °N)	120	*Older adults* 60–96 y	April–Oct	–	–	51.4%	–	–	HPLC

Hot spot LMICs are those countries in which the prevalence of serum 25(OH)D < 25/30 nmol/L exceeds 20% in the entire population or at risk populat subgroups; and possible hot spot LMICs are those where only one study was available to suggest such high prevalence

t total sample of both males and females, *f* females, *m* males, *RIA* radioimmunoassay, *EIA* enzyme immunoassay, *ECIA* electro chemiluminescence immunoassay, *HPLC* high-performance liquid chromatography method, *LC-MS/MS* liquid chromatographic with tandem mass spectrometry, *CIA* chemiluminescence immunoassay, *W* women, *IF* infant, *BIF* breast-feed infant, *y* years, *mo* months, *CI* confidence interval, *Fx* fracture, *N/A* not specified, *NR* method assay not reported, *s-e* socio-economic, *pm* postmenopausal, *osteopor* osteoporotic

[a]*n* based on analysis of serum zinc as estimate, as not reported separately for serum 25(OH)D

[b]Unless otherwise specified

[c]Serum 25(OH)D unless measured in plasma, which will be represented as (p)

[d]Some authors used alternate serum 25(OH)D thresholds, where this occurred they have been reported in italics and with the cut-off indicated

[e]From a three-tier system comprising a tertiary laboratory in the main hospital in Karachi, 12 smaller laboratories providing routine testing facilities in eight cities of the country and 206 phlebotomy centres all over the country

[f]A study of Indian health-care professionals

[g]Data based on average of mean 25(OH)D for males and mean 25(OH)D for females, thus no variance estimate

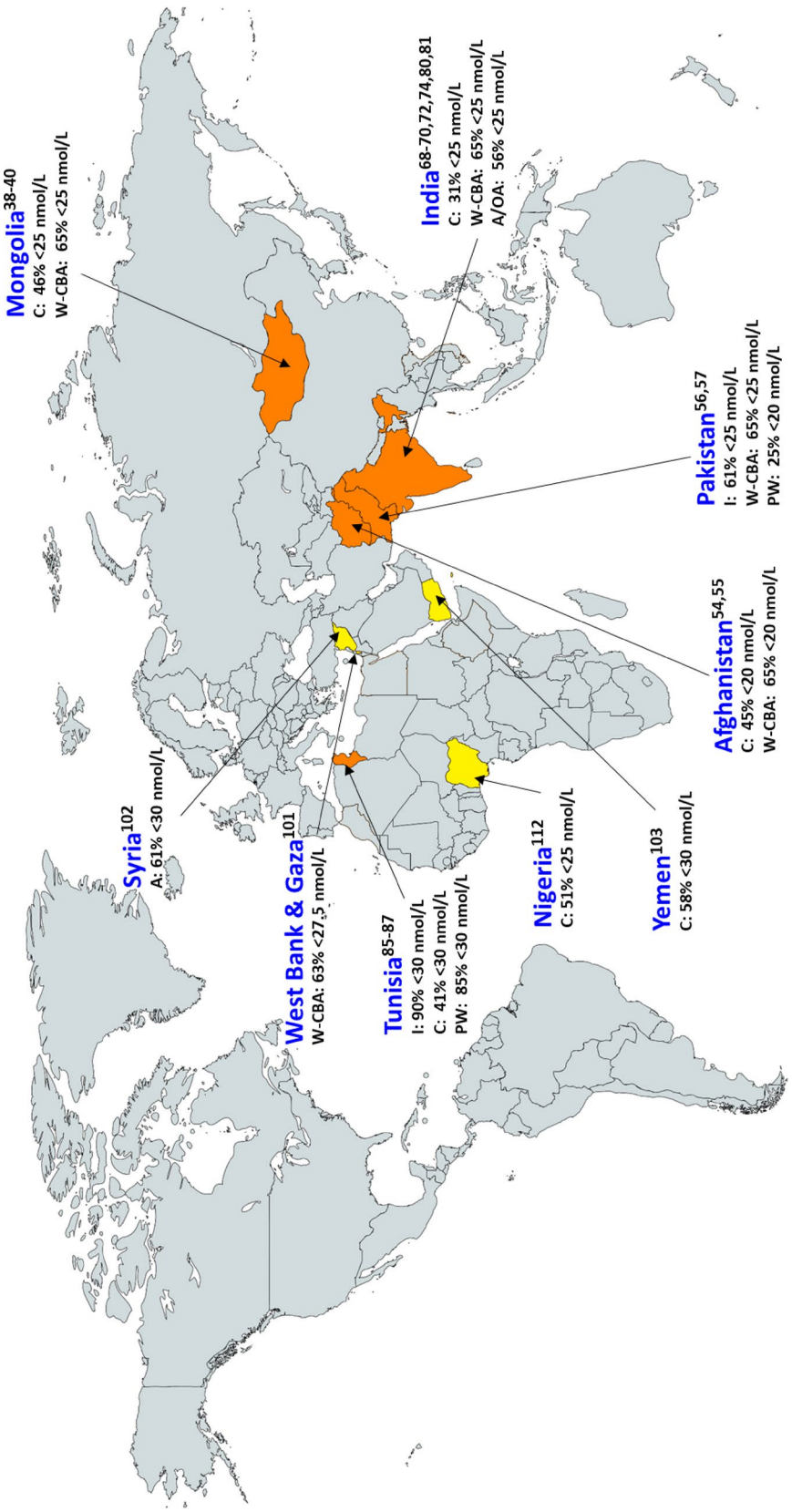

Fig. 3 Vitamin D deficiency 'hot-spot' (shown in orange) and 'possible hot-spot' (shown in yellow; data from only one study) low middle income countries, spread across 4 world regions, in which the percentage of a population subgroup(s) with serum 25(OH)D less than 20–30 nmol/L exceeds 20%, an index of excess burden of vitamin D deficiency and may warrant intervention [7]. *C* children, *W-CBA* women of child-bearing age, *I* infant, *A* adults, *OA* older adults

children was low, whether in rural or urban areas (2–4.4%). The prevalence of vitamin D inadequacy (serum 25(OH)D < 50 nmol/L) varied from 22.6 to 61.9% in Indonesia, and ranged from 1 to 57.7% in studies of Vietnamese adults and older adults.

Not unsurprisingly, the prevalence of serum 25(OH)D < 75 nmol/L in the 5 'hot spot' countries ranged from 85 to 100% (Table 2).

There was one 'possible hot spot' country in the Sub-Saharan Africa world region, which had 10 identified LMICs. The prevalence of serum 25(OH)D < 30 nmol/L was 51.4% in Nigerian older adults, but based on only one study. Nigerian adults had good vitamin D status with a 0% prevalence deficiency.

The mean serum 25(OH)D in children and adults in the Gambia was relatively high (mean range 61.8–113.3 nmol/L, depending on age group), and explains the only 0.5% prevalence of vitamin D deficiency in Gambian children. Similarly, adults from Guinea-Bissau, and children as well as adults from Nigeria, had a low prevalence of serum 25(OH)D < 25/30 nmol/L (0–4.9%). There was also a low prevalence of vitamin D deficiency in non-malnourished or malnourished children in Uganda (~ 2.5%), and only 25 and 36% of pregnant women and non-pregnant women, respectively, had serum 25(OH)D < 50 nmol/L. Likewise in Tanzania, adolescents, pregnant women and adults had low prevalence of vitamin D inadequacy (0–5.9%), while adults in both Zimbabwe and Malawi also had low prevalence (9 and 5.4% <50 nmol/L, respectively). Less than a quarter of older adults in the Cameroon had serum 25(OH)D < 37.5/40 nmol/L. A study of adults from Ghana reported a mean serum 25(OH)D of 75.7 nmol/L (serum 25(OH)D < 30 nmol/L of 0.2%). In Ethiopia, the prevalence of vitamin D deficiency in adults was variable (14.8–77%) and children had relatively high mean serum 25(OH)D concentrations (80.1 nmol/L).

Estimation of vitamin d supply in LMICs using FAO balance sheets from 2003 to 2013 and national standards for addition of vitamin D

The mean (± SD) estimated vitamin D supply using available FAO food balance sheet data for 26 of the 29 LMICs are shown in Table 3. Overall, 12, 19 and 23 of the LMICs had mean estimates of vitamin D supply < 1, < 3 and < 5 µg/day, respectively, and only three LMICs had estimates between 5 and 6 µg/day (Table 3). For those three LMICs (Ghana, Philippines, Sri Lanka), the vast majority of the vitamin D supply estimate came from Pelagic fish. This was also the case for the four LMICs (the Gambia, Indonesia, Tunisia, Morocco) which had mean vitamin D estimates between 3 and 5 µg/day.

While nine LMICs were not referenced in the GAIN global tracking of food fortification online database (as of October 2016), of the remaining 20, only one (Morocco) had mandatory fortification of vegetable oil with vitamin D, whereas five had voluntary fortification of vegetable oil or margarine under their national standards (see Table 3). We derived a mean per capita total plant-based oil intake for each of the 26 LMICs with FAO balance sheet data available, and these estimates showed a large range (5.6–51.2 g/day) (see Supplemental Fig. 1—panel A). As per Table 3, the range of levels of addition of vitamin D to vegetable oil in these countries, even under voluntary fortification, was 0.05–0.125 ppm. We used these two extremes to estimate the per capita supply of vitamin D from the oil supply estimates for each of the 26 LMICs (see Supplemental Fig. 1—panel B). Because of the variable use of the plant-based oil, the lower level of addition (assuming universal application of the standard) could provide as little as 0.3 µg/capita/day up to a maximum of 2.6 µg/capita/day, whereas the range was 0.7–6.4 µg/capita/day at the higher level of addition.

Crude estimate of UVB availability in LMICs on the basis of global UV Index data from the World Health Organisation

The WHO compiled [32] monthly changes in UV Index over the course of a year in selected countries around the World, stratified by latitude, are shown in Supplemental Table 3. The majority (93%) of the 29 LMICs with included studies in the present systematic review reside in a latitude band ranging from ~ 35°N to ~ 20°S (see Table 2 and Supplemental Table 2). Both the northern and southern hemisphere-based countries in this latitudinal band have much higher UV Index scores throughout the year compared to their equivalents at higher latitudes (> 35°). The 12-month average UV Index for countries in the band 35°N–20°S range from 6 to 12, while for countries > 35°N, it was 2–6. The minimum UV Index ranged from 2 to 10 in the 35°N–20°S band and from 0 to 2 in the > 35°N band (Supplemental Table 3).

Discussion

One of the most salient findings of the present systematic review is that almost two-thirds of LMICs had little or no studies reporting appropriate vitamin D status data that can inform our understanding of the prevalence of vitamin D deficiency in these countries. Use of the public health index of a > 20% prevalence of serum 25(OH)D < 25/30 nmol/L in the entire population and/or in subsets of the population considered especially at risk (e.g., infants, children, pregnant women and women of child-bearing age) [7] stratifies the

Table 3 Estimates of vitamin D supply using information from FAO balance sheets for the 29 low middle income countries (LMIC) for which vitamin D status was identified, and whether vitamin D is included in their national standards or not

LMIC[b]	FAO balance sheet vitamin D supply (μg/day)	GAIN database vitamin D in national standards[a]
Afghanistan	*0.39 ± 0.02*	*Y [vegetable oils; voluntary (0.06–0.09)]*
Bangladesh	0.30 ± 0.03	N (vitamin A only)
Cambodia	0.35 ± 0.03	N (vitamin A only)
Cameroon	2.30 ± 0.36	N (vitamin A only)
Egypt, Arab Republic	1.59 ± 0.25	Y [Vegetable oils; Voluntary (0.057–0.086)]
Ethiopia	0.22 ± 0.01	N (planning)
Gambia, The	4.57 ± 0.76	–
Ghana	5.71 ± 0.74	N (vitamin A only)
Guatemala	1.50 ± 0.17	N (vitamin A only)
Guinea-Bissau	0.38 ± 0.05	N (vitamin A only)
India	*0.59 ± 0.06*	*Y [vegetable oils; voluntary (0.05 min)]*
Indonesia	3.31 ± 0.34	Y [margarine; voluntary (0.0625–0.0875)]
Malawi	0.17 ± 0.03	N (vitamin A only)
Moldova	NA	–
Mongolia	*0.99 ± 0.08*	–
Morocco	3.22 ± 0.81[c]	Y [vegetable oils; mandatory (0.075 min)]
Nepal	0.36 ± 0.03	–
Nigeria	*1.97 ± 0.56*	*N (vitamin A only)*
Pakistan	*1.00 ± 0.06*	*N (vitamin A only)*
Philippines	5.68 ± 0.36	N (vitamin A only)
Sri Lanka	5.04 ± 0.50	–
Syrian Arab Republic	*NA*	–
Tanzania	0.37 ± 0.05	N (vitamin A only)
Tunisia	*3.31 ± 0.21*	–
Uganda	0.30 ± 0.01	N (vitamin A only)
Vietnam	0.37 ± 0.11	N (vitamin A only)
West Bank and Gaza	*NA*	–
Yemen, Republic	*1.35 ± 0.65*	–
Zimbabwe	0.64 ± 0.15	Y [vegetable oils; voluntary (0.125 min)]

NA, indicating that FAO balance sheet data was not available for this country

[a]*GAIN* Global Alliance for Improved Nutrition. If vitamin D (in addition to vitamin A) added to vegetable oils and/or margarine as per their national standards the min–max range (or minimum only) is indicated in brackets (in ppm). – refers to where the country was not included in the GAIN database

[b]LMICS in italics are those deemed as those where there is excess burden of vitamin D deficiency in one or more population subgroups

[c]Estimate does not capture oil fortification. Applying their stated minimum level of addition of 0.075 ppm to all plant-based oils in the balance sheet data and recalculated the vitamin D supply which yielded a updated mean (± SD) of 5.5 ± 0.9 μg/day

remaining one-third of LMICs (*n* 29 countries) into those where excess burden of vitamin D deficiency is evident or not. It should be stressed that the use of this public health index is not intended to belittle prevalences less than 20% in any LMIC but rather was used to highlight those hot spot countries in which more urgent consideration of an intervention may be warranted [7].

In terms of LMICs where there was little evidence of an excess burden of vitamin D deficiency, the Latin America and Caribbean world region reported low prevalence in four LMICs identified. For example, in addition to Guatemala being identified in the present review [103–105], a paper published in July, 2017, which was after the date of our final screen of electronic searches (May), included data on the prevalence of vitamin D inadequacy (serum 25(OH)D < 50 nmol/L) in adults ($n = 57–62$) and children ($n = 27–31$) in El Salvador, Honduras and Nicaragua (typically in the range 0–6.9%) as well as Guatemala [127]. In Moldova (47°N), within the Europe and Central Asia world region, 15% of children/adolescents had vitamin D deficiency in wintertime [37], a period when UVB availability would be expected to be lowest at that latitude [128].

Sub-Saharan Africa, the UVB-richest world region with the most available data on vitamin D status from included studies covering 10 different LMICs, in general, reported low prevalence of vitamin D deficiency [107–126]. However, over half of older adults in Nigeria had vitamin D deficiency [112], but this would need to be confirmed in additional studies as derived from only one study.

Some, but not all, LMICs in the other three World Bank Group's world regions had prevalence estimates for vitamin D deficiency which met with the definition of an excess burden (i.e., > 20%) amongst one or more of its population subgroups. For example, South Asia had three hot spot LMICs of excess burden of vitamin D deficiency. Infants in Pakistan (61%), children in Afghanistan and India (38%, on average), and pregnant women in Pakistan and India (53%, on average), all demonstrated high levels of vitamin D deficiency [54–57, 72, 74, 80, 81]. Mongolia was the only hot spot LMIC in the East Asia and Pacific world region which met with our definition, and exhibited very high prevalence of vitamin D deficiency amongst its infants, children and adults (in the range 61–88.6%) [38–40].

Mothers, infants and children in Tunisia, the only hot spot LMIC for the Middle East and North Africa region, appear to be at high risk of vitamin D deficiency (in the range 41–90%) [85–87]. In addition, while limited by the fact that there was only one study each, there was a high risk of vitamin D deficiency (i.e., > 50%) in women of childbearing age in the West Bank and Gaza [101] and girls in Yemen [103], as well as adults in Syria [102]. These possible hot spots would need confirmatory studies. Unfortunately, the prevalence estimate for pregnant women and their infants in Morocco were based on a serum 25(OH)D cut-off of < 50 nmol/L, but at such high levels (> 90%) they may also be indicative of high risk of vitamin D deficiency. Beyond these priority population groups, the prevalence of vitamin D deficiency/inadequacy in adolescents, adults and older adults were more variable in these LMICs.

There is no singular underlying reason for the high prevalence of vitamin D deficiency in some LMICs and not in others, despite the fact that these were within the same world regions and in some cases, were neighbouring countries. The combination of low UVB availability, as influenced by latitude, seasonality, air pollution, skin pigmentation, and cultural practises, and/or low dietary low dietary vitamin D supply are likely to be of major importance, as discussed in detail elsewhere [10–15]. Interestingly, Hagenau et al. in their meta-regression of global vitamin D status reported that while there was a significant decline in serum 25(OH)D concentration with increasing latitude for Caucasians, this was not the case for non-Caucasians [15]. It is likely that the vast majority of the participants in the studies included in the present analyses of LMICs where non-Caucasians and there seems to be no clear latitudinal trend amongst the prevalence of excess burden of vitamin D deficiency in the hot spot or possible hot spot LMICs, which spanned from ~ 6°N to ~ 48°N. Mithal et al. have suggested that skin pigmentation (increased skin pigmentation affects the synthesis of pre-vitamin D_3 [129]) and cultural practises may override the effect of other factors, including latitude [10]. This is likely to explain why prevalence estimates in some of the lower latitude LMICs had similar prevalences of vitamin D deficiency as those at higher latitudes (see Fig. 3). Cultural practises will vary also amongst some of the LMICs in the present work. For example, several of the hot spot LMICs with excess burden are Islamic, and as such, there may be an impact of traditional clothing, including the use of veils, on risk of vitamin D deficiency in the women [88, 91, 94]. There may also be other personal and environmental factors that limit UVB availability in some of these LMICs. For example, the study of Tunisian mothers [86] showed that, while the majority of women (84%) had at least 30 min of sun exposure two to three times per week, their exposed surface was < 15% in 78% of cases and all women reported using sunscreen protection [86]. There is a heightened avoidance of sun by females in parts of Asia [46]. Some countries (e.g., Mongolia and Afghanistan) are at relatively high altitude and thus a cold environment leading to high levels of clothing, particularly during winter months. Finally, a number of the hot spot LMICs countries (Afghanistan, Mongolia, Pakistan, India) have been highlighted as countries with a high degree of air pollution [34]. High levels of ambient air pollution may lead to atmospheric absorption of UVB radiation and thereby lowering its availability for induction of vitamin D synthesis in exposed skin.

While increasing latitude has been recently shown to have a major impact on modelled UVB availability for synthesis of previtamin D_3 in the skin within Europe, its impact on vitamin D status can be amerloriated by increased dietary vitamin D either naturally by high oily fish consumption and/or fortification of foods with vitamin D [128, 130]. Unfortunately, data on vitamin D intakes in LMICs, especially representative data, are very limited, if not largely absent [7]. While clearly a surrogate for vitamin D intake data as measured with a food consumption survey, the FAO food balance sheet approach in the present work nevertheless provides some insight into possible contributory reasons for a high prevalence of vitamin D deficiency in some of these countries. The mean vitamin D supply estimates for the nine hot spot and possible hot spot LMICs, within the range 0.4–3.3 µg/day (and only three with ≥ 1 µg/day), were relatively low. These data highlight the fact that the dietary supply of vitamin D in these LMICs was totally inadequate to prevent the decline in vitamin D status which occurs when UVB-induced dermal synthesis is limited or absent, irrespective of underlying reason. A recent individual participant data-level analysis of vitamin

D randomized controlled trials, performed in UVB limited conditions of winter, showed that a vitamin D intake of ~ 8 and ~ 10 µg/day would be needed to maintain 95 and 97.5% of individuals, respectively, over the serum 25(OH) D threshold of 25 nmol/L [131]. Data acquired from the GAIN online fortification database highlighted how only 2 of the 9 LMICs had addition of vitamin D added to vegetable oils as per their national standards, and even at that on a voluntary basis. Morocco was the only LMICs identified as requiring mandatory addition of vitamin D to vegetable oils since 2004, and its mean supply was as high as 5.5 µg/day, and the fortified oil clearly augments that from food commodities only (estimated as 3.2 µg/day). It should be noted however, the FAO balance sheet approach employed in the present work used the UK food compositional data, as regional vitamin D compositional data for these LMICs were not available. This will add a certain degree of uncertainty to the estimates. While in general we worked under an assumption that beyond vitamin D added to margarine and/or vegetable oils via national standards, fortification of other foods with vitamin D is unlikely to be widespread for most of the LMICs in this review. We acknowledge that this may not be fully accurate for all of the LMICs. It is also worth noting that the estimates for per capita vitamin D supply in the present review were based on total population and were not weighted. Weighted estimates for males and females separately may even provide further insight.

While conscious of these limitations and not to overintrepret the data, the analyses of plant-based oil fortified with vitamin D at levels allowable under national standards from the collection of LMICs showed that it is a food-based strategy worthy of serious consideration. In particular, the higher level of addition (0.125 ppm) to the oil may make a nutritionally relevant contribution (in the range of ~ 3–6 µg/day, on average) in those identified LMIC hot spots of vitamin D deficiency that have relatively high plant-based oil consumption patterns, such as India, Pakistan, Tunisia, and possibly Yemen and Morocco. Those LMIC hot spots with lower plant-based oil consumption patterns (e.g., Afghanistan and Mongolia) had less benefits (gaining ~ 1 to 2 µg/day). Yang et al. [132] in their review of vitamin D fortification in Southeast Asia, suggested that higher levels of fortification of oil should be considered as the level of consumption of vegetable oil was variable amongst countries. They also suggested that for some countries there may be a need to consider fortification of additional foods with vitamin D [132]. From a logistical perspective, addition of vitamin D to oil is likely to be much less complex than that for other foods where there may be local as well as large-scale producers.

There are a number of considerations around the data presented in the present systematic review which would need to be borne in mind in terms of its interpretations in relation to vitamin D status in LMICs. The types of study design, including sample size, season of blood sampling, as well as the methods used for measurement of 25(OH)D were quite variable within the collection of included studies. Method-related differences in the estimate of serum 25(OH) D have been well publicized [133, 134], but there are means to try and minimize these effects and allowing for more valid between country/world region comparisions of the prevalence of vitamin D deficiency [135, 136]. These points raise some caution in relation to the representativeness and accuracy of the prevalence estimates of vitamin D deficiency.

In conclusion, while it has been argued that any prevalence of serum 25(OH)D below 25 nmol/L within any population may be a matter for some concern and should even be eradicated in light of the increased risk of metabolic bone disease [8, 9], the use of the index of consistently reported serum 25(OH)D < 25/30 nmol/L in > 20% of the population or population subgroups highlight a number of LMICs in at least three world regions where intervention to address this high prevalence needs to be considered seriously. Of concern, the population subgroups which the WHO prioritize for nutritional adequacy, namely women of child-bearing age, pregnancy, infants and children, are those which overall were at highest risk within these LMICs.

Compliance with ethical standards

Conflict of interest The authors wish to confirm that there are no known conflicts of interest associated with this publication.

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