

Review

## Vitamin D Insufficiency and Deficiency in the Eastern Mediterranean Region (EMR)—Misconceptions in Public Health Practice: A Scoping Review 2019–2020

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**Summary** Vitamin D insufficiency and deficiency are a growing concern in the reasonably sunny Eastern Mediterranean Region (EMR). Variances in the metabolism of vitamin D across populations were observed and several biological and environmental factors are reported to affect its pathways and regulatory mechanisms. Methodologies for the assessment of vitamin D indicator metabolite and threshold levels for inadequacy remain evidently controversial. This review was conducted to appraise how vitamin D status is evaluated in populations of EMR. Online databases including PubMed and Google Scholar, and websites of UN agencies and ministries of health were searched thoroughly. Surveys and cross-sectional studies conducted between 2009 and 2019 which are reporting vitamin D levels in countries of EMR were retrieved and included in this review. Surveys from Afghanistan, Iran, Iraq, Jordan, Kuwait, Oman, Pakistan, and Saudi Arabia, were included in this review. The indicator mostly reported for vitamin D status assessment was 25-hydroxyvitamin D in serum samples. Differences between countries in the cut-off levels used for assessment of vitamin D status were observed. Mostly the surveys adopted either the Institute of Medicine (IOM) or the Endocrine Society (ES) guidance, but even those showed overlap in defining insufficiency and deficiency. This discordance in cut-offs jeopardizes the credibility of results and regional and global comparability. We concluded that there is a lack of consensus on the methodologies used to assess vitamin D levels across EMR. There is an urgent need for guidance on clinical and public health practices on the assessment of vitamin D status.

**Key Words** 25-hydroxyvitamin D, vitamin D inadequacy, vitamin D assessment, supplementation, malpractice

Vitamin D is a fat-soluble vitamin exhibiting hormonal functions (1). It is mostly produced in the skin with sun exposure and can be obtained from a small number of foods (e.g. fatty fish and egg yolks) (1). Vitamin D complex metabolism is regulated by parathyroid hormone (PTH), calcium, and phosphate (1). Cross-populations and inter-individual variations in these regulatory mechanisms have been reported (2). Gender, age, genetics, nutritional status, adiposity, and other factors including environmental factors influence this regulation (1–3). The most commonly used vitamin D metabolite by researchers and clinicians to indicate vitamin D status is 25-hydroxyvitamin D (25(OH) D) (2, 4). However, taking a single indicator to evaluate these complex interactions has its shortcomings (2). Besides, at present, there are no globally accepted cut-offs for defining

vitamin D deficiency and insufficiency (1, 2, 4).

There has been mounting concern in the Eastern Mediterranean Region (EMR) about vitamin D inadequacy turning into a public health problem (5). This was related to the occurrence of osteoporosis and other chronic diseases (6). Although evidence on the association between vitamin D inadequacy and adverse health outcomes remains controversial, the apprehensions of the public are strongly present (7). Noticeably, a high prevalence of vitamin D insufficiency and deficiency was reported across countries, from all economic levels, in this reasonably sunny region (5, 8, 9). At present, there is no global guidance on the assessment of vitamin D status by the World Health Organization (WHO), which is the leading body to provide evidence-based guidance for most of EMR countries. This review was conducted to appraise how vitamin D status is assessed in populations in EMR, in the light of the ongoing controversy on the methodologies and rationales applied

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Table 1. Vitamin D status and assessment methodology in selected EMR countries.

Country	Study	Year	Type of study	Age group	Sample size	Biomarker	Cut-off values (nmol/L)	Sera assay method	Insufficiency, %	Deficiency, %
Afghanistan	National Nutrition Survey Afghanistan (NNS2013) (19)	2013	National cross-sectional, household-based survey	· Children 6–59 mo · Women 15–49 y	· WRA: 1,190 · Children: 728 <sup>1</sup>	Serum 25-OH-D <sup>3</sup>	Severe deficiency $\leq 20$ Deficiency $\leq 50$ Desirable $\geq 50$ –75 Sufficient $\geq 75$	Immune-chemiluminescence <sup>3</sup>	—	Deficiency: · Children: 81 · WRA: 95.5 Severe deficiency: · WRA: 64.7 · Children: 16.8
Iran	Second National Integrated Micronutrient Survey in Iran (NIMS-II) (20)	2011–15	National cross-sectional, household-based survey	· Children 15–23 mo · Children 6 y · Adolescent girls 14–20 y · Adolescent boys 15–20 y · Pregnant women · Men 50–60 y · Women: 45–60 y	· 15–23 mo: 4,393 · 6 y: 425 · Adolescents: 842 · Pregnant: 4,378 · Adults: 837	Serum 25-OH-D3	Insufficiency $\leq 50$	Immune-chemiluminescence (Elecys 2010)	· 15–23 mo: 23.3 · 6 y: 61.8 · Adolescent girls and boys: 76.0 · Pregnant: 85.3 · Adult men and women: 59.1	—
Iraq	Iraq National Micronutrient Deficiencies: Assessment and Response (MNAAR) 2011–2012 (21)	2011–12	National cross-sectional, household-based survey	· Non-pregnant women: 15–49 y	· Non-pregnant women: 776	Serum 25-OH-D3	Risk of deficiency $\leq 30$ Risk of inadequacy: 20–49.75 Sufficient: 50–125 Possibly harmful: >125	Liquid chromatography-tandem mass spectrometry	Risk for Inadequacy: 23.1	Risk of deficiency: 74.5
Jordan	National Micronutrient Survey 2010 (22)	2010	National survey	· Children: 12–59 mo · Non-pregnant women: 15–49 y	· Children: 916 · Women: 2,032	25-hydroxyvitamin D3	Deficiency: Children: $< 27.5$ Women: $< 30$	Liquid chromatography-tandem mass spectrometry	—	· Children: 19.8 · Women: 60.3
Kuwait	Evidence for nutritional transition in Kuwait: over-consumption of macronutrients and obesity (23)	2012	National cross-sectional survey	· Males and females: 1–86 y	· Children (1–8 y): 655 · Adults ( $\geq 19$ y): 1,049	Serum 25-hydroxyvitamin D	Low serum 25-hydroxyvitamin D (25[OH]D): 25	Not specified	—	· Males: 33 · Females: 17
Oman	Oman National Nutrition Survey (ONNS) (24)	2017	National cross-sectional, household-based survey	· Children 6–59 mo · Non-pregnant women 15–49 y	· Children: 1,083 <sup>2</sup> · Women: 1,508 <sup>2</sup>	25-OH-D (plasma in children, serum in women)	Deficiency: $< 30$ Insufficiency: $< 50$	Liquid chromatography-tandem mass spectrometry	· Children: 53.8 · Women: 41.5	· Children: 10.6 · Women: 16.2
Pakistan	Pakistan National Nutrition Survey (NNS 2018) (25)	2018	National cross-sectional, household-based survey	· Children: 0–59 mo · WRA: 15–45 y	· Children: 23,782 · WRA: 23,967	Serum 25-OH-D <sup>3</sup>	Severe Deficiency: $< 20$ Moderate deficiency: 20–50 Desirable: 50–75 Sufficient: $> 75$	Immune-chemiluminescence <sup>3</sup>	—	Moderate deficiency: · Children: 49.5 · WRA: 53.8 Severe deficiency: · Children: 13.2 · WRA: 25.7
Saudi Arabia	Deficiencies under plenty of sun: Vitamin D status among Adults in the Kingdom of Saudi Arabia, 2013, Saudi Health Interview Survey (SHIS) (26)	2013	Household-cross-sectional survey	· Males and females: 15 y and above	· Males: 2,336 · Females: 2,668	Vitamin D	Insufficient: 0–70 Sufficient: 70–267.5 Toxic level: $> 267.5$	Not specified	· Males: 40.6 · Females: 62.65	—

WRA: Women of reproductive age.

1 ng/mL = 2.5 nmol/L, all measurements were converted to ng/L.

<sup>1</sup> Taken from the zinc deficiency report conducted on the same sample.<sup>2</sup> Estimated from the response rate.<sup>3</sup> Confirmed by personal communication.

globally. This review identifies and highlights existing gaps in knowledge in both public health and clinical practices in the diagnosis of vitamin D deficiency and insufficiency in EMR.

### Methods

Reports of recent national nutrition surveys that assess micronutrients status in several countries of EMR were retrieved. We looked specifically for reports of surveys and studies conducted on nationally representative samples. A study was included if vitamin D status was measured in all or selected age groups and genders. Online databases and websites including PubMed and Google Scholar were searched between October 2019 and January 2020 to retrieve surveys conducted in the last decade; between 2009 and 2019. The search also included the websites of agencies of the United Nations including; WHO, United Nations Children's Fund (UNICEF), Food and Agriculture Organization (FAO) and World Food Programme (WFP), as well as websites of the Ministries of Health of target countries. The authors contacted nutrition focal points at WHO Country Offices and Ministries of Health of some of the target countries for support and the possibility of sharing internal or inaccessible reports. Data were extracted on age groups covered, sample size, vitamin D status indicators, cut-off values used, assay methods used, prevalence levels reported in addition to other observations in the survey related to vitamin D deficiency. The extracted data is discussed in this narrative scoping review of literature in relation to the currently available guidelines and studies conducted in the region and to the global context as well.

### Results

Reports of national studies from eight countries in EMR are included in this review: Afghanistan, Iran, Iraq, Jordan, Kuwait, Oman, Pakistan, and Saudi Arabia. Extracted data are summarized in Table 1. The studies and reports were published between the years 2010 and 2018. The metabolite 25(OH)D in serum was reported as the indicator of vitamin D status in all reports except for those from Afghanistan, Pakistan, and Saudi Arabia, which did not report the specific metabolite measured but are assumed to have measured 25(OH)D. To unify and standardize the units of measurement for concentrations, all the cut-off levels used were converted to nmol/L. Reports from Iraq, Iran, Jordan, and Oman referenced the assay used for the assessment, Table 1. All the included reports cited very high levels of insufficiency and deficiency with overlap between those two concepts among the countries. The level of 50 nmol/L is a commonly reported cut-off in the studies included but it is used under different labels including; Deficiency, Moderate deficiency, Insufficiency, and Risk of inadequacy. Kuwait and Saudi Arabia used higher cut-offs of 62.5 nmol/L and 70 nmol/L respectively for deficiency and Jordan used a lower cut-off of 30 nmol/L.

We need to recognize the incomparability of the

reports included due to the differences in methodologies and settings. Except for the reports from Iraq and Saudi Arabia, all other reports included both children and adults especially women of reproductive age, Table 1. No report included specific reporting on postmenopausal women. Studies from Kuwait and Saudi Arabia included a wide range of age groups but lacked segregation of the results reported according to age. Generally, women (Pregnant or Non-pregnant) reported higher levels of deficiency compared to children and males except for Kuwait, Table 1. Almost all the women in reproductive age screened in Afghanistan were reported deficient in vitamin D, Table 1. Another remarkably high prevalence of 85.3% was reported among pregnant women in Iran. The lowest levels recorded among women in Oman and Kuwait of 16.2% and 17% respectively, Table 1.

### Discussion

As shown in Table 1, there is an evident lack of consensus on the methodologies used to assess vitamin D levels. The reports from the countries will be discussed in light of currently available guidance.

#### *Cut-off thresholds for vitamin D*

The most common internationally adopted cut-offs for vitamin D deficiency and insufficiency, are those highlighted in Table 2. Those were established by the Institute of Medicine (IOM) (10) and Endocrine Society (ES) (11). They primarily came out to guide the clinical practice for populations at risk and not for general populations. Dietary Reference Intake (DRI) guidance by the IOM was developed to determine the best practices to guide vitamin D intake within safe brackets to avoid toxicity with the assumption of minimal sun exposure in the United States and Canada (10). This is to avoid risks of melanoma with extensive sun exposure among Caucasians (10). The ongoing dispute on rationales and justifications for cut-off levels and safe thresholds is manifested on the differences between the IOM and ES definitions and thresholds, Table 2. Most of the national studies included in this review adopted either IOM or ES guidance, but even those showed overlap in the concepts of insufficiency and deficiency. Countries like Saudi Arabia chose to use their national guidelines in addition to Jordan and Kuwait, which adopted different thresholds from IOM and ES.

This discordance in the used cut-off to assess vitamin D status in populations subjects the results to questionable comparability between EMR countries and with global estimates and statistics. The current practical and clinically accepted cut-off levels for vitamin D adequacy and insufficiency are based on the regulatory mechanisms along the calcium, parathyroid hormone, vitamin D axis (1, 2, 4). The PTH is suppressed when 25(OH)D is at "normal" and adequate levels and it is stimulated when those levels drop. This is to maintain optimum calcium blood concentrations through targeting the gut, renal system, and bones (1, 4). This 25(OH)D and parathyroid hormone synergy is the most commonly applied rationale for determining thresholds

Table 2. The Institute of Medicine (IOM) and The Endocrine Society guidelines on vitamin D deficiency.

The Institute of Medicine (IOM) Dietary Reference Intakes— Calcium Vitamin D (2011) (10)		The Endocrine Society Clinical Practice Guideline (2011) (11)	
Biomarker: 25-hydroxyvitamin D		Biomarker: 25-hydroxyvitamin D	
Cut-offs		Cut-offs	
Risk of deficiency—Related to bone health	<30 nmol/L (12 ng/mL)	Deficiency	<50 nmol/L (20 ng/mL)
At risk of inadequacy—some people	30–50 nmol/L (12–20 ng/mL)	Insufficiency	52.5–72.5 nmol/L (21–29 ng/mL)
Sufficient for all persons	50–75 nmol/L (20–30 ng/mL)	Sufficiency	75–250 nmol/L (30–100 ng/mL)
Not associated with increased benefits	>75 nmol/L (30 ng/mL)	Safety margin for risk of hypercalcemia	>250 nmol/L (100 ng/mL)
Concerning	>125 nmol/L (50 ng/mL)		
<i>Remarks:</i>		<i>Remarks:</i>	
<ul style="list-style-type: none"> <li>· Dietary Reference Intake (DRI) are based on dietary intake (food and supplementation) assuming minimal sun exposure</li> <li>· Developed with a focus on the population of North America &amp; Canada</li> <li>· Lack of clarity concerning the validity of the serum 25OHD measure as a biomarker of effect</li> <li>· The paucity of data on the effect of chronic vitamin D intake is challenging the definition of Tolerable Upper Intake Level (UL)</li> <li>· In studies administering calcium and vitamin D, distinguishing the health outcomes for vitamin D was challenging</li> <li>· Concerns about skin cancer risk preclude incorporating the effects of sun exposure in the DRI process</li> <li>· No sufficient evidence to establish a relationship between vitamin D and health outcomes other than bone health</li> <li>· No values for cut-off have been agreed upon by the scientific community for the definition of deficiency and insufficiency</li> </ul>		<ul style="list-style-type: none"> <li>· Variability in assays confounds attempts to define cut-offs for deficiency</li> <li>· Assays are more adequate in measuring higher levels of vitamin D in clinical practice, which is sensible to avoid risks of toxicity</li> <li>· Concerns about melanomas necessitate avoidance of excessive sun exposure</li> </ul>	
<i>Factors adversely affecting vitamin D status:</i>		<i>Recommendations:</i>	
<ul style="list-style-type: none"> <li>· Adiposity</li> <li>· Dark skin</li> <li>· Use of sunscreen</li> <li>· Indoor environments and institutionalized older persons</li> <li>· Use of certain medications</li> </ul>		<ul style="list-style-type: none"> <li>· Screening for individuals at risk only and not general population</li> <li>· Using 25(OH)D by reliable assay instead of 1,25(OH)2D</li> <li>· Age-specific dosages for vitamin D for individuals at risk</li> <li>· Maintenance of tolerable vitamin D not exceeding UL without medical supervision</li> <li>· Prescribing vitamin D for fall prevention and not beyond RDA for preventing CVD, death or improving Quality of Life (QoL)</li> <li>· Studies on vitamin D supplementation and outcomes at certain levels of 25(OH)D</li> </ul>	
		<i>Factors adversely affecting vitamin D status:</i>	
		<ul style="list-style-type: none"> <li>· Inadequate exposure to sunlight</li> <li>· Dark skin tone</li> <li>· Fat malabsorption syndromes</li> <li>· Nephrotic syndrome</li> <li>· Granuloma-forming disorders, lymphomas and 1ry hyperparathyroidism</li> <li>· Change in seasons and latitude</li> <li>· Sunscreen use</li> <li>· BMI &gt; 30 kg/m<sup>2</sup></li> <li>· Bariatric patients</li> <li>· Some medications</li> </ul>	

for optimum vitamin D status. The cut-off for 25(OH)D is set at the level at which the suppression of the parathyroid hormone plateaus (2). Above this cut-off, no further stimulation for the parathyroid hormone takes place. This manifestation in particular varied significantly when tested in different populations (2). When white and black subjects were put to comparison, black people reported significantly lower levels of vitamin D compared to whites with less significant changes in PTH (2). The synergism between vitamin D and PTH is not fully understood (2), hence cut-offs for insufficiency and deficiency remain debatable (10).

A study was conducted in Syria to identify a cut-off

level for vitamin D at which the PTH starts to rise (12). The study recognized the need for population-specific cut-offs, since the current cut-offs were built on studies conducted mainly in Caucasians (12). The study identified a lower threshold of vitamin D level at which the PTH rises in response which was 32.5 nmol/L (12). The difference in the population percentage classified as deficient using the (ES) cut-off of 50 nmol/L and the cut-off identified in the Syrian study was 18% (90% using ES guidelines and 72% using the identified cut-off) (12). Although the prevalence is still significantly high but on population levels, such differences would have a major impact on health systems. On the other

Table 3. The World Health Organization (WHO) guidelines on vitamin D supplementation in pregnant women.

## World Health Organization Guidelines:

## Vitamin D supplementation in pregnant women (2012)

*Scope & purpose:*

· Global, evidence-informed recommendations on vitamin D supplementation during pregnancy as a public health intervention for the purpose of improving maternal and infant health outcomes. It is intended to help decision-makers to take evidence-informed decisions.

*Remarks:*

- In cases of documented deficiency, vitamin D supplements may be given at the current RNI (5  $\mu\text{g}$  (200 IU) per day as recommended by WHO/FAO or according to national guidelines). The benefit of this intervention for other maternal or birth outcomes remains unclear.
- Pregnant women should be encouraged to receive adequate nutrition, which is best achieved through consumption of a healthy balanced diet and to refer to guidelines on healthy eating during pregnancy.
- There is limited evidence on the safety of vitamin D supplementation during pregnancy.

*Recommendations:*

- Vitamin D supplementation is not recommended during pregnancy to prevent the development of pre-eclampsia and its complications (strong recommendation).
- The use of vitamin D supplementation during pregnancy as part of routine antenatal care is not recommended (conditional recommendation).

hand, due to the lack of consensus on cut-offs, the varying methodologies for assessing vitamin D status and the scarcity of studies conducted in populations other than white populations, the associations between low levels of vitamin D and adverse health outcomes remain considerably blur.

*Risk factors for vitamin D deficiency/insufficiency*

Despite the controversy around assessment methodologies, we need to reflect on the distinctive presence of risk factors for hypovitaminosis D in countries of EMR. Determinants of vitamin D deficiency were reviewed and reported from the different regions of the world by the International Osteoporosis Foundation's committee of scientific advisors (13). Several predictors were consistently reported from countries of the Middle East and North Africa. Those included being a multi-parous female and of older age as strong predictors as well as low socioeconomic status. Factors related to low sun exposure were cited including the widely spread covering clothing style, darker skin tone, winter season, and living in an urban setting (13). All the contextual factors mentioned are to be taken into consideration when assessing vitamin D status in a population.

The aforesaid determinants were also reported in an ecological study conducted by Grant et al. to link risk factors for vitamin D deficiency to the consumption of vitamin D rich foods in Europe and the Middle East (14). Data on food supply available for the populations of countries were obtained from FAO as an approximation to the levels of consumption. The foods under study included animal fat, eggs, ocean fish, meat, and milk (14). The levels of consumption were relatively lower in countries of the Middle East in most of the food groups (14). The authors stressed on the observation that, diets in Middle Eastern countries should be further studied as a possible contributing factor to vitamin D deficiency which might be concealed by the coexisting factors related to sun exposure (14). This is especially impor-

tant with the limited vitamin D food fortification programmes (14).

*Osteoporosis*

On a closely related note, the epidemiological picture of osteoporosis in EMR is not comprehensively understood and researchers have a long way to go (6, 15). A recent review was conducted by Gheita and Hammam in 2018, they focused on the epidemiology and awareness of osteoporosis in the Middle East and North Africa (MENA) (6). Diverse prevalence levels were reported within countries as well as across the region (6). The highest and lowest numbers reported in the review from EMR were in Egypt with 47.8% (2009, age mean: 58.2 y) and 2.8% (2012, age mean:  $35.9 \pm 7.4$  y) respectively. There is limited comparability between the included studies due to differences in study designs, samples, and settings (6). Despite this, Gheita and Hammam highlighted that levels of osteoporosis in postmenopausal women in the Middle East and North Africa are relatively comparable to those reported in North America ranging from 10.3% to 30% but higher than the rates in Europe with an average of 20% (6). Factors influencing the levels of osteoporosis in the MENA regions were discussed and reported to include; genetic polymorphism, age, gender, socioeconomic status, nutritional status, menopause, parity, BMI, and others (6). Considering all these factors, the authors of the review stressed on the need for population-specific studies on Bone Density Measurements (BDM) for populations in MENA (6). Besides, the need for population-based studies on osteoporotic fractures to build a better understanding of the factual burden of the disease in the region (6). It should be noted that most of the studies included in our review sampled women in reproductive age and not menopausal women who are evidently at higher risks of deficiencies.

*Vitamin D supplementation*

The evidence on vitamin D supplementation is still

inconsistent (16, 17). The World Health Organization (WHO) has developed guidelines only for vitamin D supplementation for pregnant women in 2012, Table 3 (18). These guidelines state: "Vitamin D supplementation is not recommended during pregnancy." In a systematic review and meta-analysis conducted by Minjia Mo et al. on dose-response analysis of vitamin D supplementation across different populations, significant differences in the increases of 25(OH)D levels after supplementation were reported (3). Differences in response to supplementation between populations from the Middle East and North Africa compared to populations from Europe were brought to attention in this review (3). Age, pregnancy, and baseline concentrations of 25(OH)D were reported as factors affecting responses to vitamin D supplementation (3). A recent review by Yao et al. was conducted on vitamin D and calcium supplementation for prevention of fractures (16). The authors emphasized that the current evidence does not support the supplementation of vitamin D alone and favours the combination with calcium supplementation for the prevention of fractures. The review highlights the need for further studies on higher doses of vitamin D before making any recommendations for the concerns of efficacy and safety.

Taking into consideration all these inconsistencies in responses to supplementations and measurement methodologies, vitamin D supplementation, and other population-wide interventions targeting vitamin D "deficiency" are to be undertaken with caution.

#### Recommendations

- To countries of EMR: It is highly recommended, that countries should promote reasonable sun exposure as a cheap and accessible source for vitamin D, to encourage healthy eating habits and diets diversification, and to enforce fortification with vitamin D within safe margins. We invite you withhold population-wide supplementation interventions until solid evidence-based guidance is provided for the region. In the meantime, according to the current available guidance, testing for vitamin D deficiency is only recommended for the symptomatic or persons at risk. No recommendations for population-wide screening for vitamin D insufficiency and deficiency using 25(OH)D are advised.

- To the World Health Organization: There is an urgent need for evidence-based guidance on both public health and clinical practices on vitamin D deficiency in EMR. WHO is to encourage population-specific research and evidence generation on vitamin D to inform guidelines and interventions in EMR.

- To researchers: There is a high need for population-specific studies in EMR to focus on the physiology, regulatory mechanisms and significant thresholds for vitamin D. These studies are to represent different ethnic groups and genetically versatile compositions of those populations. Such evidence will eventually help in population-sensitive guidelines and interventions with progressive implications on clinical and public health practices.

- To clinical practitioners: Vitamin D levels in patients

should be well thought-out and to be interpreted in the perspective of the overall clinical picture and the individual's risk of deficiency. In addition to, recognition and understanding of the complex metabolism of vitamin D and the limitations of taking one indicator for its complex metabolic pathway and functions.

#### Conclusion

The reported prevalence levels of vitamin D deficiency and insufficiency are arbitrarily high in the reasonably sunny EMR. The methodologies currently applied for screening populations in EMR should be re-evaluated and critiqued given the inconsistency in the scientific evidence they are currently based on. In addition to this, the laxity in vitamin D supplementation with no manifest justifications should be discouraged, especially population-wide supplementations but rather more sun exposure should be promoted. In conclusion, there is an urgent need for guidance for both clinical as well as public health practices on the assessment and management of vitamin D inadequacy in EMR.

#### Authorship

Review concept and design: AA and EE, interpretation: EE, LR, RD and AA, writing manuscript: EE, RD and LR.

#### Disclosure of state of COI

No conflicts of interest to be declared.

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