Review

nutrition and health

Nutrition and Health
2019, Vol. 25(1) 61–70

DOI: 10.1177/0260106018805360
journals.sagepub.com/home/nah
SAGE

A systematic review and meta-analysis of prevalence of vitamin D deficiency among adolescent girls in selected Indian states

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Abstract

Background: Vitamin D deficiency among adolescents is an emerging public health priority as adolescence marks a period of rapid growth and the onset of the reproductive phase. However, lack of national prevalence data and intervention strategies is of public health concern. **Objective:** The objective of this study was to determine the pooled prevalence of vitamin D deficiency among adolescent girls in selected Indian states. **Methods:** A systematic literature review was performed using three different search engines. The searches yielded nine eligible articles. Study quality was assessed for 10 different criteria. Meta-analysis was performed to estimate pooled prevalence of vitamin D deficiency among adolescent girls and to assess the heterogeneity among selected studies. **Results:** A sample of $n=1352$ was used to study prevalence among adolescent girls. The random effects combined estimate for overall prevalence was 25.70% (95% CI 3.89–2137.9). High heterogeneity ($tau^2=1.71$, $I^2=100\%$) was observed and seven out of nine studies showed low to moderate risk and two showed high risk of bias. The test for overall effect was observed to be $Z=0.77$ ($p=0.44$). **Conclusions:** High prevalence of vitamin D deficiency among adolescent girls identifies the need to introduce screening of adolescents and introduce proven public-health interventions such as fortification of foods to address deficiency.

Keywords

Vitamin D deficiency, adolescent girls, India, systematic review, meta-analysis

Introduction

Globally the prevalence of low vitamin D status is widespread among all age groups (Holick and Chen, 2008; Palacios and Gonzalez, 2014, Mansbach et al., 2009). High prevalence has been reported across age groups even among countries with adequate sunshine. Developed nations through representative data report the following prevalence: Europe 42%, USA 33%, Iran 35%, Mexico 9%, Saudi Arabia, 81% and Korea 68% (Edwards et al., 2014). High prevalence >70% has been estimated in the Asian region (Nimitphong and Holick, 2013). As per 2014 reports, prevalence among adolescents in India from individual studies is estimated to be 91% (Edwards et al., 2014). Vitamin D deficiency among adolescents is an emerging public-health priority as adolescence marks a period of rapid growth and onset of the reproductive phase. Evidence suggests adolescent girls are prone to deficiency as compared to boys (Moore et al., 2004; Rockell et al., 2005; Saintonge et al., 2009). Vitamin D serves as a regulatory hormone for growth and development of bones and calcium homeostasis. Deficiency in this phase is likely to affect accrual of bone mass and cause diminished muscle strength (Pérez-López et al., 2010; Smith et al., 2016). The impact of this vitamin, other than bone on health, has been researched extensively in the recent years. Its role in gene expression in reproductive tissue, deficiency states associated with polycystic ovary syndrome (PCOS), endometriosis and impaired fertility emphasizes the importance of this vitamin to achieve reproductive maturity (Grundmann and von Versen-Höynck, 2011). It is also known to impact immune and cardiovascular systems, and protect against various malignancies, type I diabetes and systemic lupus erythematosus (Holick, 2007).

Commonly established factors associated with deficiency of vitamin D include exposure to sunshine, ultra

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violet (UV) B radiation, skin pigmentation and application of topical sunscreens; adiposity and vitamin D intake are some of the factors associated with deficiency (Tsiaris and Weinstock, 2011). In Asia being young in age, female, less physically active and residing in an urban area increase the risk of deficiency (Chailurkit et al., 2011; Choi et al., 2011; Lu et al., 2009). In India low dietary intake of calcium and a cereal-based diet contributing to high fibre, genetic factors and depleted body stores are known to contribute to the risk of deficiency (Kapil et al., 2017; Londhey, 2011). Scientists propose an adaptation mediated by parathyroid hormone (PTH) and insulin like growth factor-1(IGF-1) that alter the manifestation of vitamin D deficiency in adolescents. Although indicators in severe deficiencies and adaptive malfunctions are identified, subclinical manifestations go unnoticed (DeLuca, 2004; Holick, 1996; Thacher and Clarke, 2011). Despite literature evidence of adolescents facing high risk, national data on prevalence of deficiency of this vitamin are currently scarce. This review, therefore, aims to study the overall estimate of vitamin D deficiency among healthy adolescent girls in India through a systematic review and meta-analysis.

Methods

This review utilized the standard protocol for systematic review writing by Khan et al. (2003) and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (2009).

Literature search

Three search engines, PubMed, Google Scholar and Web of Science, were systematically explored for relevant literature by two researchers, independently in November 2017. The MeSH terms used for literature search on adolescent girls were ('epidemiology'[Subheading] OR 'epidemiology'[All Fields] OR 'prevalence'[All Fields] OR 'prevalence'[MeSH Terms]) AND ('vitamin D deficiency' [MeSH Terms] OR 'vitamin D deficiency'[All Fields]) AND ('adolescent'[MeSH Terms] OR 'adolescent'[All Fields] OR ('adolescent'[All Fields] AND 'girls'[All Fields]) OR 'adolescent girls'[All Fields]) AND ('India' [MeSH Terms] OR 'india'[All Fields])) AND ('2007/12/03'[PDat]: '2017/11/29'[PDat]).

To ensure selection of every eligible study, search was repeated with two additional terms 'vitamin D insuffiency' or 'vitamin D' status of adolescent girls.

The search syntax for the alternate terms was as follows: (('epidemiology'[Subheading] OR 'epidemiology'[All Fields] OR 'prevalence'[All Fields] OR 'prevalence' [MeSH Terms]) AND ('vitamin d'[MeSH Terms] OR 'vitamin d'[All Fields] OR 'ergocalciferols'[MeSH Terms] OR 'ergocalciferols'[All Fields]) AND insufficiency[All Fields]) OR (('vitamin d'[MeSH Terms] OR 'vitamin d'[All Fields] OR 'ergocalciferols'[MeSH Terms] OR 'ergocalciferols'[All Fields]) AND status[All Fields] AND ('adolescent'[MeSH Terms] OR 'adolescent'[All Fields] OR ('adolescent'[All Fields] AND 'girls'[All Fields]) OR 'adolescent girls'[All Fields]) AND ('india'[MeSH Terms] OR 'india'[All Fields])) AND ('loattrfree full text'[sb] AND 'loattrfull text'[sb]).

Study selection

The following selection criteria were applied: (a) studies that were original articles; (b) studies that estimated prevalence of vitamin D deficiency; (c) study designs that were observational, either population- or school-based baseline information on vitamin D levels from intervention studies; (d) India as study location; (e) studies on early (10–14 years) and late adolescence (15–19 years) (UNICEF, 2011); and (f) time frame for literature selection was restricted to those published between 2005–2016. Reference lists of the selected articles were used for manually identifying relevant literature. Full text articles that were unavailable and data required for participants in specific age groups were obtained from authors on request. All papers were screened and verified by two researchers independently.

Exclusion criteria

1. Earlier work has used >30 samples as a selection criterion (Zhang, 2015). In our search the least number of samples in the eligible studies was $n = 20$ and the next highest was $n = 50$. As smaller studies increase the risk of bias, studies with sample size less than 50 were excluded.
2. As the review aims to study prevalence of vitamin D deficiency among healthy adolescent girls those studies that documented prevalence related to disease conditions, were excluded.
3. Duplicate studies originating from different search engines.
4. Eligible studies from which data is unavailable from the authors after a request, were excluded.

States represented in the study

The studies selected for the review do not cover all the Indian states. The states represented in the review are therefore based on those studies that matched the selection criteria.

Data extraction

Each selected article was evaluated using a standardized data extraction sheet. The outcome of interest was the prevalence of vitamin D deficiency in India among adolescent girls. For this we extracted the prevalent estimate of vitamin D deficiency from the selected individual studies. In addition, associated variables that described the study characteristics such as study design, study setting, socio-demographic and economic status, and criteria used for categorizing deficiency and sufficiency and season of study were recorded. Data relating to factors that affect serum vitamin D levels such as skin pigmentation, sun exposure, diet and lifestyle were also extracted. Data extracted was verified in duplicate by VS and AJ.

Assessment of study quality

A checklist validated by Hoy et al. (2012) was adopted to assess the risk of bias in the selected articles. As per this model, 10 criteria are used for assessment of risk of bias. The selected articles were thus assessed for representation of population, sampling, random selection, non-response bias, data collected directly from subjects, case definition, reliability and validity of the method used, mode of data collection whether similar, length of shortest prevalence period, and numerator and denominator. Further, to summarize the overall study quality Cochrane standards (Higgins and Altman, 2008) that categorizes as *low* (all 10 criteria assessed presenting low risk) *moderate* (at least two criteria showing high risk) or *high risk* (more than two criteria showing high risk) were used.

Statistical analysis

Meta-analysis was performed by using random effects model due to the variation between the studies. Review Manager (RevMan) software version 5.3 (Cochrane Collaboration, 2014) was used to obtain a forest plot to demonstrate the degree of heterogeneity among the selected articles. The software uses Chi^2, I^2, Tau^2 to study heterogeneity. Estimating pooled prevalence is a testing strategy where prevalence from a number of studies are aggregated into a single sample (or pool) to determine the prevalence of interest (Sergeant, 2017). In this review, reported prevalence in individual papers was extracted, log transformed and standard error of proportion of prevalence was estimated. This model assists in controlling for unobserved and observed heterogeneity. The P value is the probability from Chi-square statistic calculated using estimates of individual study weight, effect size and overall effect size.

Results

Description of studies

PRISMA guidelines followed for the literature search to identify articles for eligibility and inclusion among adolescent girls for prevalence of vitamin D deficiency is provided in Figure1. Search for literature yielded 89 articles. Screening of title, abstract and outcome of interest and cited references yielded 13 articles of which nine fulfilled our inclusion criteria. The secondary search with two additional terms ‘vitamin D insufficiency’ or ‘vitamin D status’ of adolescent girls, identified three duplicate articles through Pubmed search and through the other two search engines (Google Scholar and Web of Science) the nine selected papers eligible as per selection criteria matched the earlier search results. No new eligible articles were identified.

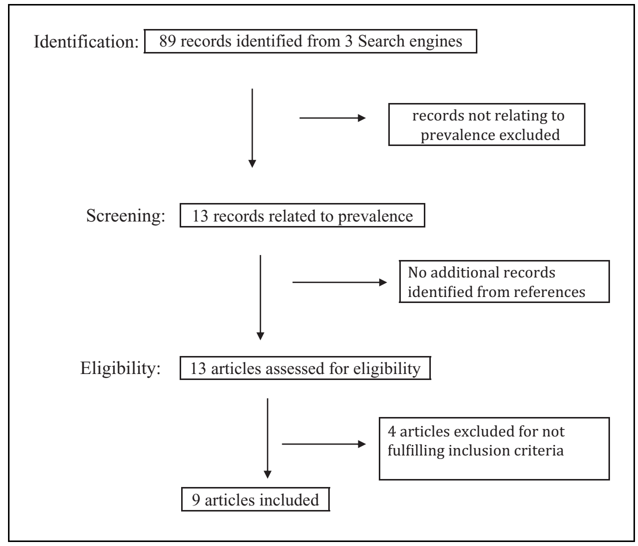

Figure 1. PRISMA guidelines for selection of studies among adolescent girls to estimate vitamin D deficiency.

Description of studies selected under adolescent girls is provided in Table 1. Of the selected nine studies, three represented North India; four West India and the other two represented South India. Figure 2 provides the geographic coordinates of the selected studies in India. Among the study designs Veena et al.’s work (2017) was a hospital-based cohort study. Of the remaining studies, except Sahu et al.’s work (2009) which was population based and had calculated sample size, all other studies were school-based cross-sectional studies. The sample size ranged between 50 and 435, with a total sample of 1352.

Adolescent girls 10–20 years of age formed the study sample. The articles represented samples from lower to upper socio-economic groups. More studies were from an urban sample. As six out of nine studies were from school-going children, they represented middle school to junior college. Three articles (Harinarayan et al., 2008; Sahu et al., 2009; Veena et al., 2017) provided details regarding the season in which the study was conducted, and two studies provided details about participant’s exposure to sunlight.

Risk of bias of selected studies

Table 2 gives the RoB for articles selected on adolescent girls. Of the nine selected studies among adolescent girls, two studies (Das et al., 2006; Harinarayan et al., 2008) showed high risk of bias as high risk was observed in three out of 10 domains pertaining to (a) representation of data, (b) randomness in selection and (c) as well as

Table 1. Description of selected studies among adolescent girls in India.

Study	Location (State)	School or Population based	Study design	Sample size	Age (years)	Socio economic status	Rural/ urban	Education	Season	Sun exposure
Marwaha et al., 2005	Delhi (North)	School	Cohort	435	10–18	Lower, upper	Urban	NM	NM	NM
Sahu et al., 2009	Lucknow (North)	Population	Cross sectional	121	10–20	Lower	Rural	NM	Winter/ summer	1000–1600hrs
Harinarayan et al., 2008	Tirupati (South)	Population	Cohort	75	11–13	NM	Rural and Urban	NM	Winter/ summer	NM
Kadam et al., 2011	Pune (West)	School	Cross sectional	80	10–12	Lower	Urban	Primary & middle level	NM	45 min/ day
Sanwalka et al., 2013	Pune (West)	School	Cross sectional	120	15–18	NM	Urban	School &junior college	NM	NM
Khadgawat et al., 2013	Delhi (North)	School	RCT	135	10–14	NM	Urban	Middle level	NM	NM
Veena et al., 2017	Mysore (South)	Population	Hospital based cohort	246	13–14	Lower	Urban	Middle level	Winter/ Summer/ Rainy season	NM
Patel et al., 2016	Gujarat (West)	School	Cross sectional	90	10–14	Lower, middle, upper	Nm	Primary and Middle level	NM	NM
Das et al., 2006	Pune (West)	School	Cross sectional	50	14.7(0.7)	NM	Urban	Middle level	NM	NM

RCT: Randomized controlled trial; NM: Not mentioned.

representation of numerator and denominator. Studies done by Veena et al. (2017), Sanwalka et al. (2013) and Kadam et al. (2011) were categorized as moderate risk, as at least one out of 10 domains indicated high risk. In these studies also, high risk pertaining to poor representation of population and numerator and denominator were observed. Work done by Sahu et al. (2009) and Marwaha et al. (2005) scored low risk in all domains. These studies were community based from a randomly drawn sample (low risk), with calculated sample size (low risk). Two studies (Das et al., 2006; Khadgawat et al., 2013) scored high risk pertaining to non-response bias, these studies did not mention the percent non-response and hence were categorized as high risk. Other domains pertaining to source from which data was collected, reliability and validity of the method, and mode of data collection scored low risk among all selected articles.

Heterogeneity among studies and estimated prevalence

Table 3 provides the techniques used in assessment of vitamin D status. Vitamin D status is measured through assay of 25(OH) D which is the major circulating form of vitamin D. Among the methods used for estimation of serum vitamin D levels, radio immunoassay was the commonly used technique in the studies selected. Other techniques included chemiluminescent assay (Khadgawat et al., 2013; Patel et al., 2016) and HPLC (Das et al., 2006).

The Institute of Medicine (IOM) (2011) categorizes serum vitamin D levels <50 nmol/l as deficient. However, others such as Lips classification follows <25 nmol/l as hypovitaminosis (Lips, 2004). Lancet (Reid, 2016) has proposed 25–30 nmol/l to consider as deficient state for pursuing supplementation trials. In this review four out of nine studies have used Lips classification while the remaining five used IOM classification. Among the individual studies selected, prevalence of vitamin D deficiency among adolescent girls ranged from 11.0 to 98.0%.

Figure 3 gives the forest plot of the selected studies. The extent of variation among studies is given by Tau^2 statistic. Tau^2 statistic was estimated to be 1.71 (df=8, p=<0.001, I^2=100%). The test for overall effect Z=0.77 (p=0.44). The above values indicate large variation among studies. The random effects combined estimate for overall prevalence, after log conversion of 1.41, is equal to 25.7% (Figure 3).

Discussion

To the best of our knowledge this is the first systematic review on adolescent girls in India to estimate the pooled prevalence of vitamin D deficiency. The pooled prevalence, as estimated

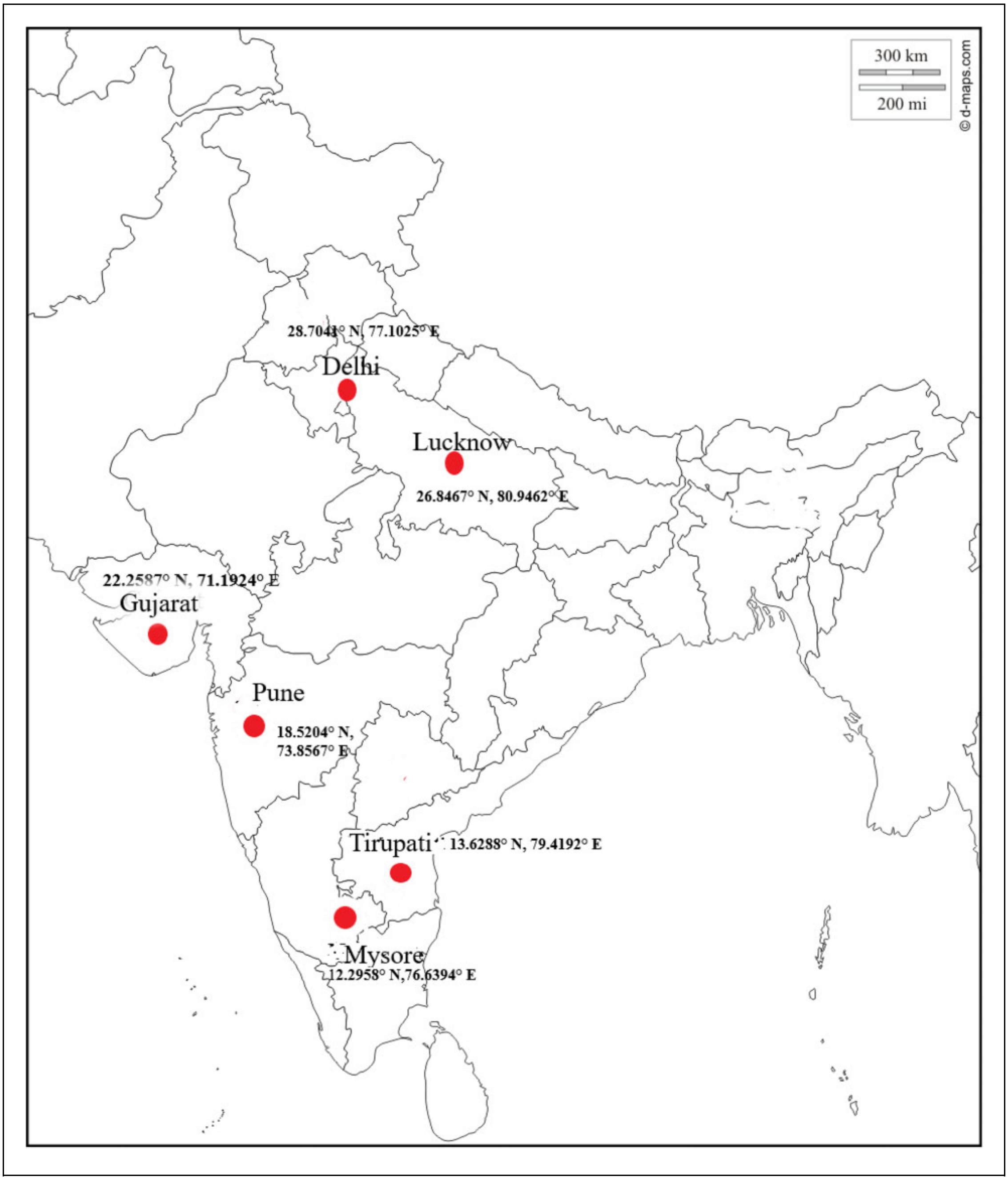

Figure 2. Geographic co-ordinates of the studies selected.

by this review, is 25.7%. As per the criteria for assessing public health significance >20% prevalence is of public health concern (Cashman et al., 2018). Although Asian studies have focused on different age groups (Akhtar, 2016), studies among adolescent girls are few (Malhotra and Mithal, 2009). Studies from other developing countries such as Sri Lanka, Pakistan and Bangladesh, despite cultural differences, may possibly be compared with India as they share the same geographical location and socio-economic characteristics. Studies in Sri Lanka and Pakistan that have focused on children indicating high prevalence of vitamin D deficiency (Hettiarachchi et al., 2011; Hettiarachchi and Liyanage, 2012). However, these were not epidemiological estimates (Bhattyet al., 2010; Qamar et al., 2012). In Bangladesh 46% deficiency and 52% insufficiency have been reported among adolescent girls (Zaman et al., 2017). Other studies among adolescents from these Asian regions were unavailable for comparison. This highlights the dearth of information on vitamin D status, lack of national statistics of prevalence among adolescent girls, and significant prevalence as per the current review. With current evidence on the role of vitamin D in reproductive health there is a need to assess the real burden, to define the outcome of clinical and subclinical deficiencies, especially among women in the reproductive-age group and address vitamin D deficiency through public-health interventions.

Table 2. Summary of risk of bias of selected studies.

	Sahu et al., 2009	Marwaha et al., 2005		Sanwalka et al., 2013	Veena et al., 2017	Khadgawat et al., 2013	Harinarayanet al., 2008		Patel et al., 2016	Das et al., 2006	Kadam et al., 2011
		LSES	USES				Urban	rural			
Representation of data	Low risk	Low risk	Low risk	High risk	Low risk	High risk	High risk	High risk	Low risk	High risk	High risk
Sampling	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Random Selection	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Non-response bias	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	High risk	Low risk
Data collected directly from subject	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Case definition	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Reliability and validity of method	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Same mode of data collected	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Length of the shortest period of the prevalence	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Numerator and denominator	Low risk	Low risk	Low risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk
Summary	Low risk of bias[a]	Low risk of bias	Low risk of bias	Moderate risk of bias[b]	Moderate risk of bias	High risk of bias[c]	High risk of bias	Moderate risk of bias	Moderate risk of bias	High risk of bias	Moderate riskof bias

[a]Low risk of bias: all criteria met (i.e. low for each domain).
[b]Moderate risk of bias: one to two criteria not met (i.e. high for each domain).
[c]High risk of bias: more than two criteria not met (i.e. high for each domain).
LSES: Lower socio-economic status; USES: Upper socio-economic status.

Table 3. Description of the techniques and criteria used to assess vitamin D deficiency and the mean vitamin D levels in adolescent girls.

Study	Vitamin D estimation method	Mean 25(OH)D	Deficiency	Insufficiency	Sufficiency	Prevalence (%)
Marwaha et al., 2005	Radioimmunoassay	28.5 nmol/l (SD 5.8)	Mild hypovitaminosis: 25–50 nmol/L Moderate hypovitaminosis: 15–25 nmol/l Severe hypovitaminosis: <15 nmol/l	NM	NM	11.10
Sahu et al., 2009	Radioimmunoassay	29.5 nmol/l (SD 16)	<50 nmol/l	NM	NM	88.60
Sanwalka et al., 2013	Radioimmunoassay	21.92 nmol/l (SD 1.65)	Mild hypovitaminosis: 25–50 nmol/l Moderate hypovitaminosis: 12.5–25.25 nmol/l Severe hypovitaminosis: <12.5 nmol/l	NM	NM	64.0
Kadam et al., 2011	Radioimmunoassay	62.8 ± 26.6 nmol/L:	<50 nmol/l	NM	NM	34.20
Khadgawat et al., 2013	Chemi-iluminescent	29.22 ± 13.4 nmol/L	Mild: hypovitaminosis: 25–50nmol/L Moderate hypovitaminosis: 15–25 nmol nmol/l Severe hypo vitaminosis: <12.5nmol/l	NM	NM	98.0%
Patel et al., 2016	Chemi-iluminescent micropipette assay	44.25 ± 16.7 nmol/l	<50 nmol/l	50–75 nmol/l	>75 nmol/l	92.30
Veena et al., 2017	Radioimmunoassay	39.0(23.8,60.0)* nmol/l	<50 nmol/l	50–75 nmol/l	>75 nmol/l	67.5%
Harinarayan etal., 2008	Radioimmunoassay	46.87 ± 4.17 nmol/l	<50 nmol/l L	50–75 nmol/l	>75 nmol/l	32.0%
Das et al., 2006	HPLC	NM	<30nmol/l	NM	NM	70.0%

HPLC = high-performance liquid chromatography.
*Intraquartile range.

The Indian subcontinent has abundant sunshine, and being an agricultural country there is no lack of exposure to sunshine. However, risk transition as a consequence of urbanization minimizes sun exposure affecting the vitamin D status of the population (Mithal, 2009). Additionally, high levels of air pollution in urban settings increase the risk of deficiency. This phenomenon is observed in most developing countries (Akthar, 2016; Kruger et al., 2011; Misra et al., 2011). Urban area as a place of residence has been reported to increase the risk in developed countries as well (Conteras-Manzano et al., 2017). Between genders, adolescent girls and women are vulnerable due to increased demands for growth, metabolic and reproductive needs compared to men (Gaikhe et al., 2014). Deficiencies in a particular stage is likely to affect other life stages. Thus, deficiency during the reproductive phase affects the vitamin D status among children, persists through adolescence, which perpetuates to the reproductive phase and the following generation. This is common among poor and developing counties where intergenerational propagation of malnutrition is observed (Pettifor, 2014).

Climate and culture also affect sun exposure. As observed in hot countries women do not prefer sun exposure (Mithal, 2009). Compared to developed countries women in the South Asian region cover much of their body surface further restricting sun exposure. Substantial prevalence among adolescents living in Asian countries has been reported as darker skin prevents the synthesis of vitamin D (Goswami et al., 2012). Other than sun exposure, dietary sources majorly contribute to the plasma concentration of vitamins. In cereal consuming populations the dietary sources are poor and less bioavailable.

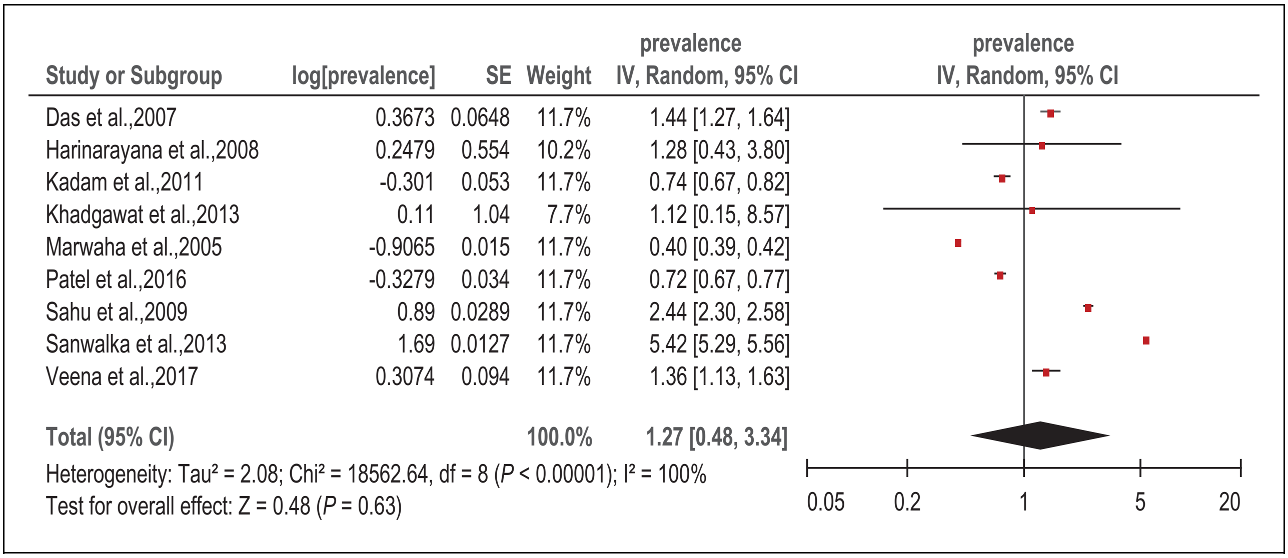

Figure 3. Forest plot to determine the pooled prevalence of vitamin D deficiency among adolescent girls in selected Indian sates.

A multidisciplinary approach is a requisite to prevent deficiency. Risk transition as an outcome of urbanization needs to be addressed in developing counties. Strategies to minimize exposure to environmental pollutants is essential. Creating awareness among those vulnerable, especially young girls to increase their intake of vitamin D during the reproductive phase would improve the nutritional status of themselves as well as their infants. Supplementation as a part of antenatal care needs to be considered in addressing this deficiency. In developing nations where cereals comprise the main staple, fortification could be considered as it has been tested to improve vitamin D status (Kadgawat et al., 2013).

The limitation of the present review focusing on vitamin D as the nutrient of interest was the high risk of bias due to low power of the selected studies. Variations in the methods used in the estimation of serum 25(OH)D status limits comparison. Studies carried out in developed countries have followed Liquid Chromatography–Mass Spectrometry (LC-MS/MS) as the standard technique for estimation of vitamin D (Eyles et al.,2009; Shah et al., 2011) and has been reported to be more sensitive compared to other techniques used in the reviewed studies. However, few studies in India or studies from developing countries have used this technique in estimating vitamin D. Because of the high cost of using LC-MS/MS, population-based studies in developing countries have not used this technique widely. Consensus on sensitive, standardized, cost-effective techniques for population screening, cut-offs for identifying clinical and subclinical manifest of deficiency are the need of the hour.

Conclusion

The findings of the present review suggest the need for epidemiological determination of vitamin D status among the vulnerable population. Uniformity in measurement and techniques would address the issues of heterogeneity that limits generalizability of results. It is essential to integrate screening for vitamin D deficiency in the maternal and child health programmes and initiate intervention in adolescence to ensure healthy pregnancy outcome.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

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