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High prevalence of vitamin D insufficiency among South Asian pregnant women: a systematic review and meta-analysis

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Abstract

Insufficiency of vitamin D, during pregnancy, is a common cause of various pregnancy-related complications. Despite such insufficiency being frequently reported among South Asian pregnant women, the absence of systematic review and meta-analysis renders the true extent of this problem being poorly characterised. In this systematic review, three main databases (PubMed, Scopus and Google Scholar) were searched for original studies. We included original studies published between 1January 2001 to 31 December 2019, conducted on pregnant women who lived in South Asian countries and reported the prevalence of vitamin D insufficiency among the study participants. Twenty studies with a total of 7804 participants from four South Asian countries finally met our selection criteria. Overall pooled prevalence of insufficiency was 65 % (95 % CI: 51 %, 78 %) with a significant heterogeneity ($I^2 = 99{\cdot}37$ %; $P = 0{\cdot}00$). The average level of vitamin D ranged from 9 ng/ml to 24·86 ng/ml with a weighted mean of 16·37 ng/ml (weighted standard deviation 7·13 ng/ml). The highest prevalence of insufficiency was found in Pakistan (76 %) followed by India (67 %), Bangladesh (64 %) and Nepal (14 %). Results obtained in this study suggest that vitamin D insufficiency is highly prevalent among South Asian pregnant women. Being the first systematic review in this region, findings from this study will help the future studies and strengthen the evidence for policymakers to develop effective mitigation strategies.

Key words: Vitamin D insufficiency: Prevalence: Pregnant women: South Asia: Systematic review

Vitamin D has a wide range of physiological roles (e.g. anti-inflammatory and immune modulating effects) in our body[1,2]. During pregnancy, the mother needs more vitamin D than usual for the fetal development[3]. It has been reported previously that vitamin D supplementation during pregnancy can be positively associated to improved fetal growth and better nutritional status of the newborn[4]. On the contrary, vitamin D deficiency during pregnancy can result in several adverse outcomes including hyperparathyroidism and osteomalacia in mothers that may lead to neonatal hypocalcaemia[3,5]. Moreover, vitamin D deficiency is also associated to preeclampsia, gestational diabetes, bacterial vaginosis, HIV transmission from mother to child and respiratory infection, etc[3–7]. Furthermore, such a deficiency also plays a role in developing several kinds of polygenic and infectious diseases such as colon and breast cancer, CVD, type-1 diabetes, multiple sclerosis, rheumatoid arthritis and tuberculosis[1,2,8]. Consequently, a mother can be affected later in life with these diseases if she has vitamin D deficiency during or after pregnancy.

Vitamin D deficiency during pregnancy is prevalent worldwide[9]. Such deficiency can have a wide range; 15 to 90 % has been reported among pregnant women in countries like Australia, Kuwait, Iran, Germany, UK, USA, China, Turkey, India and Pakistan[9]. While such deficiency is common among pregnant women in both developed and developing countries, wide inter-country variation can be observed. For instance, a high prevalence of vitamin D deficiency has been reported for the pregnant women in the Middle Eastern countries like Iran and Kuwait (from 67 to 83 %). However, lower levels of deficiency are commonly reported in the Western countries like the USA and the UK prevalence usually ranges from 33 to 35 %[10–13].

To explain this large variance in the status of vitamin D, a variety of factors have been highlighted in the literature as the

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potential underlying variables[1,2,14]. Among such factors, geographical location is one of the most important as it has direct implications with the intensity and duration of direct sunlight exposure for the mass population[15]. Along with sunlight exposure, skin colour, attitude towards sunlight exposure, age, clothing practice, comorbidity, etc. are also commonly reported as the modulating factors to explain population-level variations of serum vitamin D[1,2,14]. Therefore, it is important from a public health perspective to understand the comparative variability among different countries in the context of the diversity of the prevailing factors that can potentially influence population-level vitamin D. At the same time, to understand the potential effects of such deficiency more precisely, the deficiency itself needs to be understood.

As per the current guidelines (proposed by the Clinical Practice Guideline of the Endocrine Society), vitamin D deficiency, insufficiency and sufficiency defined as serum level of vitamin D $<$ 12 ng/ml ($<$ 30 nmol/l), $<$ 20 ng/ml ($<$ 50 nmol/l) and $>$ 20 ng/ml ($>$ 50 nmol/l), respectively[16–18]. However, there is an ongoing discussion about the definition of vitamin D deficiency[16]. Based on some of the newly published studies, the cut-off values for insufficiency and deficiency of serum vitamin D are being reviewed. As such, understanding the true extent of vitamin D deficiency and/or insufficiency prevailing in different countries and regions has become an important aspect.

South Asia (SA) is composed of eight countries – Bangladesh, India, Pakistan, Nepal, Bhutan, Maldives, Sri Lanka and Afghanistan. SA countries together occupy an area of 5131·1 thousand square kilometres with a population of about 1·8 billion[19,20]. The people of this area, both ethnically and culturally, share some common features, while differences are also observed regarding geography, culture, customs, religion, etc[21,22].

Due to generally poor socio-economic conditions, maternal health and nutritional deficiencies are highly prevalent in this region[22]. This contributes to disease burdens (many of which are attributable to hypovitaminosis D) and pregnancy-related complications in SA countries[23–28].

Given the likelihood that vitamin D could be a possible risk factor for many of the health problems in the SA countries, we found only one systematic review on the pregnant women in this region (on the Pakistani pregnant women only yet conducted on a small population, and no meta-analysis was performed)[29]. Due to this lack of systematic reviews, understanding of the extent of hypovitaminosis D (vitamin D insufficiency) in the SA region (and in the individual countries) is incomplete.

In this study, we assessed the prevalence of vitamin D insufficiency by performing a systematic review and meta-analysis among pregnant women in SA.

Methodology

We used recommendations and guidelines provided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses to conduct this study[30].

Data source and search strategy

The three main databases (PubMed, Scopus and Google Scholar) were used in this study (a search was performed after signing out of all Google accounts, to avoid personalised outcomes). Two researchers (BB and MMR) explored these three databases independently from 19 October 2019 until 19 January 2020. The details of the search strategy, list of original MeSH terms and the alternative terms (to minimise the chance of exclusion) used in this study are provided in the supplementary file (online Supplementary Table S1).

The searches were conducted in English. For information on ongoing and unpublished work, regarding insufficiency of vitamin-D, the author's personal profiles (corresponding author) available online and their profiles on Google Scholar, ResearchGate and ORCID were further explored.

To ensure that grey literature is included in this study, we go through online archives of newspapers that have been published in English from SA countries such as The Telegraph, New Age, The Nation, Daily Bhutan, Maldives Times, Himalayan Times, Sunday Observer, etc. We also explored governments' reports and published abstracts (in electronic media) as relevant sources from the conference held in SA countries.

Study selection criteria

In this review, we define vitamin D insufficiency as per the current guidelines mentioned above. The inclusion criteria were if they reported vitamin D insufficiency (cut-off $<$ 20 ng/ml) in SA pregnant women; conducted in SA countries during 1st January 2001 to 31 December 2019 and published in peer reviewed journals; conducted on apparently healthy pregnant women in both community level and hospital level whose physical condition was not associated with any chronic illness (chronic kidney, liver and heart disease, cancer, diarrhoea, anaemia, diabetes, etc.) or disease related to any coexisting morbidity (body aches and pain, proximal muscle weakness, osteoporosis, etc.);. studies (cross-sectional, longitudinal, case–control, randomised clinical trial) were included in this review if baseline data were available. However, we took the placebo data for a randomised clinical trial when baseline data were not available.

Studies were excluded if they had a sample size of $<$50[31]; did not mention the prevalence of vitamin D insufficiency and mean level of serum vitamin D; reported vitamin D levels after some form of intervention or supplementation; reported prevalence of vitamin D insufficiency associated to any kind of chronic diseases or any co-morbidity; did not mention prevalence of vitamin D insufficiency and mean level of serum vitamin D; letter to the editor, review article, editorial article; studies that satisfied selection criteria but were not able to obtain full text from the authors after request were also excluded.

Mendeley Desktop program (version 1.19.4) was used to monitor the references and to prevent duplications. After the elimination of duplicates, two researchers (MHS and URS) independently reviewed all papers before selection for final meta-analysis. Disagreements between researchers were resolved by discussion with co-authors.

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Data extraction

A standardised Excel sheet was used for data extraction of the selected articles that met eligibility criteria. The following information has been collected for each study: publication details (e.g. first author, publication date, journal name and publisher); research setting, participants' characteristics and assay method (e.g. country, study area, study design, socio-economic status, method of measurements and sample size) and major findings (e.g. mean level of vitamin D and prevalence). Through revisiting the included papers, all investigators checked the accuracy of the collected data.

In this review, where values of serum level of vitamin D (25-hydroxyvitamin D or 25(OH) D) were presented in nanomol per litre (nmol/l) unit[35,39,41,43,45,46,51,54], they were converted to nanogram per millilitre (ng/ml) by dividing with 2·5 (according to the international system of unit conversion).

Evaluation of study quality

A checklist of 10 criteria validated by Hoy et al in 2012 was used to determine (as low, moderate and high) the risk of bias for the selected studies[32]. Regarding this checklist, studies with scores 0–3 were considered low risk of bias, scores between 4 and 6 moderate risk and studies with scores 7–9 are considered as high risk of bias. The risk of bias was assessed on all original papers.

Statistical analysis

The mean value of the serum vitamin D levels and the prevalence of vitamin D insufficiency among pregnant women in SA are considered as summary measurements. The weighted mean level of vitamin D was calculated by using Microsoft Excel (version 2016). The weighted pooled prevalence was calculated with a CI of 95 % using a random-effect model. To assess heterogeneity, the Cochran Q test and the I^2 Statistics were used[33]. The impact of geography was also demonstrated in analyses according to participants with vitamin D insufficiency. Significant heterogeneity was indicated with an I^2, more than 75 %[34]. The analyses were performed using the Stata version 15 (Stata Corp) 'metaprop', 'metabias', 'metafunnel' commands.

Result

A total number of 997 articles were retrieved from different databases by using the search strategy which describes above. Among these, 977 were excluded because of not matching our inclusion criteria. Finally, twenty study articles were selected for our analysis. The study article's selection process is shown in Fig. 1.

More than half of the studies (11 out of 20) mention demographic areas for the study population, and socio-economic status for the study population was not mentioned in most of the studies (8 out of 20). The study design was cross-sectional for more than half of our studies (11 out of 20). Only three studies were case control and the rest of them were randomised control trials. Several kinds of measurement methods were used to determine serum vitamin D levels like ELISA, RIA, chemiluminescence immunoassay, chemiluminescent microparticle immunoassay, etc. Among these measurement methods, RIA and ELISA were mostly used (9 out of 20). A summary outlining the features of selected studies was available in Table 1.

The studies selected in this systematic review consisted of 7804 pregnant women. Participants were 18 years or above in all studies. In five studies they did not mention participant's age[39–41,43,49]. Prevalence of insufficiency and the average level of vitamin D were mentioned in all studies. Prevalence of insufficiency ranged from 9 to 97 % and the average vitamin D level were ranged from 9 to 24·86 ng/ml. The overall pooled prevalence of vitamin D insufficiency was 65 % (95 % CI: 51 %, 78 %) (Fig. 2). The weighted mean level of serum vitamin D was 16·36 ng/ml, and the weighted standard deviation (weighted SD) was 7·12 ng/ml.

A high degree of heterogeneity was observed in the prevalence of vitamin D insufficiency ($I^2 = 99·37$ %; $P = 0·00$).

Country-wise result

Studies from four out of eight SA countries (Bangladesh, India, Pakistan and Nepal) matched our selection criteria, and hence were included in this study. No studies were found from Bhutan, Sri Lanka, Afghanistan and Maldives regarding serum vitamin D levels and prevalence of vitamin D insufficiency among pregnant women. The Forest plot shows the country-wise prevalence of vitamin D insufficiency (Fig. 2). Weighted mean level of vitamin D among SA pregnant women can be found in the Supplementary file Fig. S1.

India

We found twelve studies from India which consisted of 3182 participants[35–46]. Study design was mostly cross sectional (nine out of twelve), with the others being either case controlled or randomised control trial studies. Out of twelve studies, half of these did not mention demographic areas for the study population, and the rest were either urban or rural or both. One-third of total studies did not mention socio-economic status for study participants, and rest of the studies include either both socio-economic groups (upper and lower) of populations or only lower economic groups of populations. The weighted mean level of vitamin D for study participants was 16·31 ng/ml (weighted SD 7·90 ng/ml), and random effect meta-analysis showed that the weighted pooled prevalence of vitamin D insufficiency was 67 % (95 % CI: 46 %, 85 %) with a significant heterogeneity ($I^2 = 99·30$ %; $P = 0·00$).

Bangladesh

We could retrieve four studies from Bangladesh with a total of 3055 participants[47–50]. The majority of the studies were randomised control trials, whereas there was only one case–control study. In case of demography, two studies were conducted among urban population, one in rural population and one study did not mention about demographic areas for study population. On the other hand, socio-economic status for study participants was not mentioned in two studies, and two studies include participants from both lower and upper socio-economic groups. The weighted mean vitamin D level for study participants was

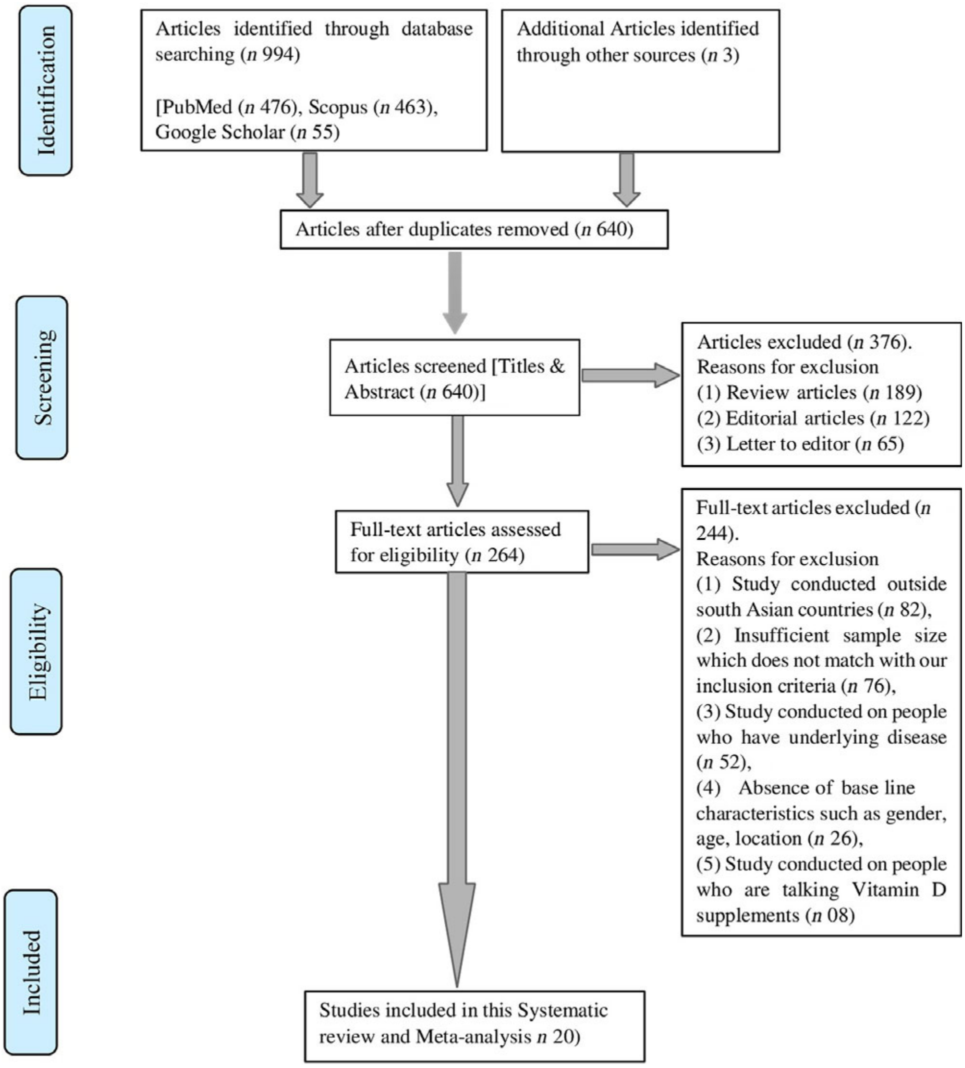

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the summary of search result and selection of studies for final analysis.

15·55 ng/ml (weighted SD 5·29 ng/ml), and random effect meta-analysis revealed that the weighted pooled prevalence of vitamin D insufficiency was 64 % (95 % CI: 62 %, 66 %).

Pakistan

In Pakistan, we found three studies with a total of 404 participants[51–53]. Study designs were either cross sectional or randomised control trials. Only one study mentioned about demographic area for study population that represented both rural and urban populations. On the contrary, socio-economic status for study participants was mentioned in two out of three studies. One study was conducted on a lower socio-economic group of population and another one included participant from both lower and upper socio-economic classes. The random effect meta-analysis demonstrated that the weighted pooled prevalence of vitamin D insufficiency was 76 % (95 % CI: 39 %, 99 %) among the study participants with weighted mean of 11·27 ng/ml (weighted SD 6·28 ng/ml).

Nepal

We found only one study in Nepal that was a randomised control trial and that study was conducted among 1163 rural pregnant women[54]. The socio-economic status was not mentioned. Our study revealed that 14 % of the participants were vitamin D insufficient with an average of 20·44 ng/ml.

Study-Setting wise result

In case of study setting, more than half (11 out of 20) of the studies were hospital-based and the rest were community based.

Prevalence of vitamin D insufficiency was higher in the community-based studies (71 %; 95 % CI: 47 %, 90 %) compared with the hospital-based (60 %; 95 % CI: 40 %, 78 %) studies. High

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Table 1. Characteristics of selected study articles

Authors	Year	Country	Study area (Urban/Rural)	Study design	Timing of measurement (vitamin D levels) during pregnancy	Socio economic status	Vitamin D estimation method	Sample size (*n*)	Reported cut-offs used (ng/ml)	Average serum level of vitamin D (ng/ml)	Standard deviation (SD)	Overall objective of the selected studies
Sahu et al.[35]	2008	India	Rural	Community – CS	2nd trimester	Lower	RIA	139	< 20 ng/ml	15·12	7·92	To determine the population prevalence of vitamin Deficiency in rural pregnant women and adolescent girls, compare serum 25-hydroxyvitamin D (25OHD) status in adolescent boys from the same families and determine seasonal differences in serum 25OHD.
Sachan et al.[36]	2005	India	Both	Hospital – CS	NM	Both	RIA	178	< 22·5 ng/ml	14·3	9·5	To determine the prevalence of osteomalacia and hypovitaminosis D in pregnancy and in cord blood and to correlate maternal 25-hydroxyvitamin D (25(OH)D) status with sun exposure, daily Ca intake (dietary plus supplemental) and intake of parathyroid hormone (PTH) concentrations.
Ajmani et al.[37]	2015	India	NM	Hospital – CS	NM	Both	ELISA	200	< 20 ng/ml	23·25	18·49	To assess the prevalence of vitamin D deficiency in burka-clad pregnant women and to study feto-maternal outcome in these women.
Sheetal et al.[38]	2015	India	NM	Hospital – CS	NM	Both	ELISA	418	< 10 ng/ml	21·45	4·02	To determine the prevalence and risk factor for vitamin D deficiency in pregnant population
Sudhanshu et al.[39]	2016	India	Rural	Community – CS	2nd trimester	Lower	RIA	139	< 20 ng/ml	14	8	To document the effect of season and environmental pollution on UVB irradiance and to estimate cutaneous vitamin D synthesis in village women in different seasons.
Taru et al.[40]	2015	India	NM	Hospital – CC	NM	NM	NM	50	< 15 ng/ml	9	7·105	To evaluate maternal vitamin D levels in term normotensive and preeclamptic patients in labour and to assess additional factors such as maternal and cord blood levels of Ca, phosphorus, parathormone and alkaline phosphatase and associated factors such as BMI, birth weight and mode of delivery.
Krishnaveni et al.[41]	2011	India	NM	Hospital – CS	3rd trimester	Both	RIA	568	< 20 ng/ml	15·6	12·145	To examine the association between maternal serum vitamin D levels and anthropometric variables, body composition and cardiovascular risk markers in Indian children.
Singla et al.[42]	2014	India	Both	Hospital – CC	NM	NM	ELISA	100	< 20 ng/ml	14·8	6·68	Studying relation between vitamin D deficiency and preeclampsia and its complications.
Sahu et al.[43]	2009	India	Rural	Community – CS	2nd trimester	Lower	RIA	139	NM	12·92	10·78	To evaluate the effect of cholecalciferol supplementation during routine antenatal visits on maternal 25 hydroxyvitamin D (25OHD) at delivery.
Sharma et al.[44]	2019	India	Both	Community – CS	2nd trimester	NM	CLIA	177	< 20 ng/ml	15·55	7·65	To find out prevalence and outcome of hypovitaminosis of VD in pregnancy.
Nagendra et al.[45]	2018	India	NM	Hospital – RCT	3rd trimester	NM	CMIA	532	NM	21·4	4·97	To determine 25-hydroxyvitamin D (25OHD) levels in pregnant women at 28 weeks and supplement based on these levels and check maternal and neonatal levels after delivery at term.

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Table 1. (*Continued*)

Authors	Year	Country	Study area (Urban/ Rural)	Study design	Timing of measurement (vitamin D levels) during pregnancy	Socio economic status	Vitamin D estimation method	Sample size (*n*)	Reported cut-offs used (ng/ ml)	Average serum level of vitamin D (ng/ml)	Standard deviation (SD)	Overall objective of the selected studies
Marwaha et al.[46]	2011	India	NM	Hospital – CS	All three tri- mesters	Lower	RIA	541	< 20 ng/ ml	9·18	4·52	Evaluated maternal 25(OH)D levels in different tri- mesters, assessed the impact of seasonal varia- tion on serum vitamin D levels and correlated maternal and newborn serum vitamin D levels by concurrent evaluation of serum 25(OH)D levels in mother–infant pairs at 6–8 weeks postpartum.
Ullah et al.[47]	2013	Bangladesh	Urban	Hospital – CC	2nd trimester	NM	ECLIA	76	< 30 ng/ ml	24·86	1·02	Investigate the prevalence and relationship of vitamin D deficiency with both preeclampsia and eclamp- sia.
Schulze et al.[48]	2019	Bangladesh	Rural	Community – RCT	3rd trimester	Both	Immunoassay	1521	< 20 ng/ ml	18·77	5·24	Assessed the efficacy of a daily MM (15 nutrients) compared with IFA supplement, each providing approximately 1 RDA of nutrients and given begin- ning at pregnancy ascertainment, on late preg- nancy micronutrient status of women in rural Bangladesh.
Roth et al.[49]	2013	Bangladesh	Urban	Community – RCT	3rd trimester	NM	HPLC-MS	160	< 30 ng/ ml	17·8	NM	Evaluate the change in maternal and neonatal (cord blood) 25(OH) D concentration and effects on serum Ca concentration and to generate prelimi- nary data regarding pregnancy outcomes.
Roth et al.[50]	2018	Bangladesh	NM	Hospital – RCT	2nd trimester	Both	AFBM	1298	< 12 ng/ ml	10·992	5·6	Evaluated the dose-dependent effects of prenatal vitamin D supplementation, with and without post- partum supplementation, on infant growth and other maternal, new born and infant outcomes.
Anwar et al.[51]	2015	Pakistan	Both	Community – CS	NM	Lower	CLIA	269	< 20 ng/ ml	8·404	5·43	Determine the prevalence of vitamin D deficiency in pregnant women and their neonates and to find out whether vitamin D defi ciency is influenced by Gc protein polymorphisms
Khan et al.[51]	2016	Pakistan	NM	Community – RCT	1st and 2nd trimester	NM	CLIA	85	< 19·9 ng/ml	12·825	5·8	Determine if oral vitamin D supplementation to preg- nant women reduces the incidence of LBW among neonates and to determine if oral vitamin D sup- plementation improves periodontal probing depth (PD), bleeding on probing (BoP) and clinical attachment loss (AL) among pregnant women.
Karim et al.[53]	2010	Pakistan	NM	Hospital – CS	NM	Both	NM	50	< 20 ng/ ml	24·1	11·7	To estimate the prevalence of vitamin D deficiency among pregnant women in Karachi, Pakistan; correlate maternal and cord blood vitamin D deficiency and assess possible predictors of vitamin D deficiency.
Jiang et al.[54]	2005	Nepal	Rural	Community –RCT	1st trimester	NM	Immunoassay	1163	< 10 ng/ ml	20·44	9·852	Investigated the prevalence of deficiency for vitamins A, E, D, riboflavin, B_6, B_{12}, folate, Zn, Fe and Cu during early pregnancy (12 wk) in a rural popula- tion of Nepalese pregnant women.

RCT, randomised control trial; CC, case control; CS, cross sectional; ECLIA, electrochemiluminescence immunoassay; HPLC-MS, high-performance liquid chromatography – tandem mass spectroscopy; AFBM, analytical facility for bio active molecule; CLIA, chemiluminescence immunoassay; RIA, radioimmunoassay; ELISA, enzyme linked immune sorbent assay; CMIA, chemiluminescent micro particle immune assay; NM, not mention.

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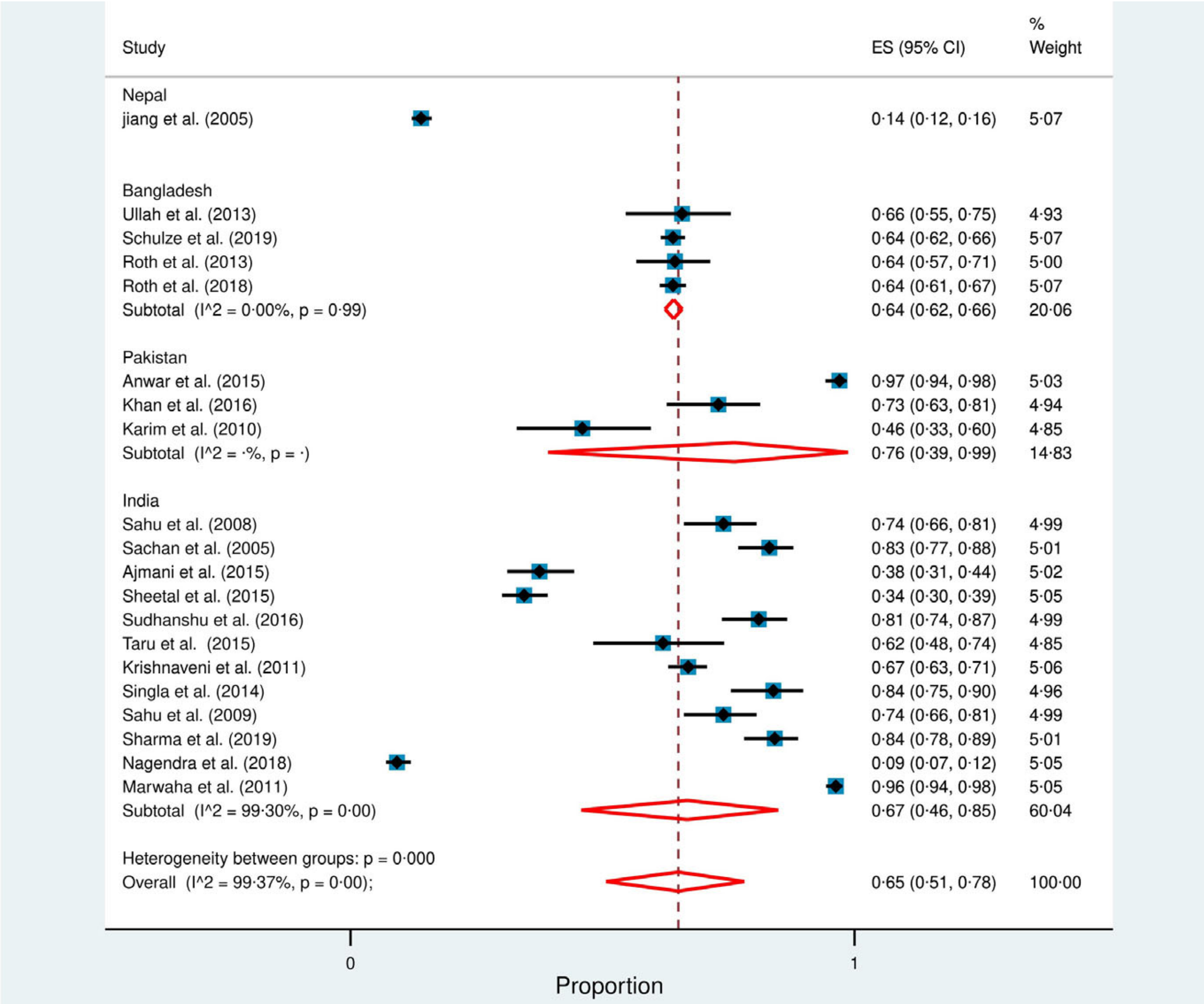

Fig. 2. Forest plot represent overall and country wise prevalence of vitamin D insufficiency among South Asian Pregnant women. In this forest plot, all the diamonds, except the last one (overall pooled prevalence), represents polled prevalence for individual country: (1) Nepal (2) Bangladesh, (3) Pakistan, (4) India. Each horizontal line of the forest plot represents an individual study and the box plotted as prevalence for that study. The horizontal points of the diamond represent the limit of 95 % CI.

degree of heterogeneity was found in both studies setting ($I^2 = 99$ %; $P = 0{\cdot}00$) (Fig. 3).

Quality assessment

Among these selected studies, no study was found with a high risk of bias, thirteen studies with moderate risk of bias and the reminder with low risk of bias. Risk of bias table available in supplementary file (online Supplementary Table S2).

Publication bias

The funnel plot indicated the existence of asymmetry and publication bias for the prevalence of vitamin D insufficiency (online Supplementary Fig. S2). Eggers's test was found statistically insignificant, which means publication bias was small in case of this meta-analysis ($P = 0{\cdot}84$).

Discussion

Results from this study reveal that as much as 65 % (95 % CI: 64 %, 72 %) of the SA pregnant women could be affected with vitamin D insufficiency (Fig. 2). Our findings parallel with a systematic review and meta-analysis conducted on Iranian pregnant women reporting approximately 68 % of the study participants being vitamin D insufficient (using < 20 ng/ml cut-off)[55]. Comparison of this insufficiency to the other parts of the world implies that this problem might be worse in SA compared with Africa (around 34 %; using < 20 ng/ml cut-off)[56]. We speculate that such widespread insufficiency of vitamin D could be linked to the high prevalence of some of the health problems and pregnancy-related complications in this region. Indeed, this speculation is supported by high prevalence and the rising trend of pregnancy-related complications, communicable and non-communicable diseases in SA[23–28].

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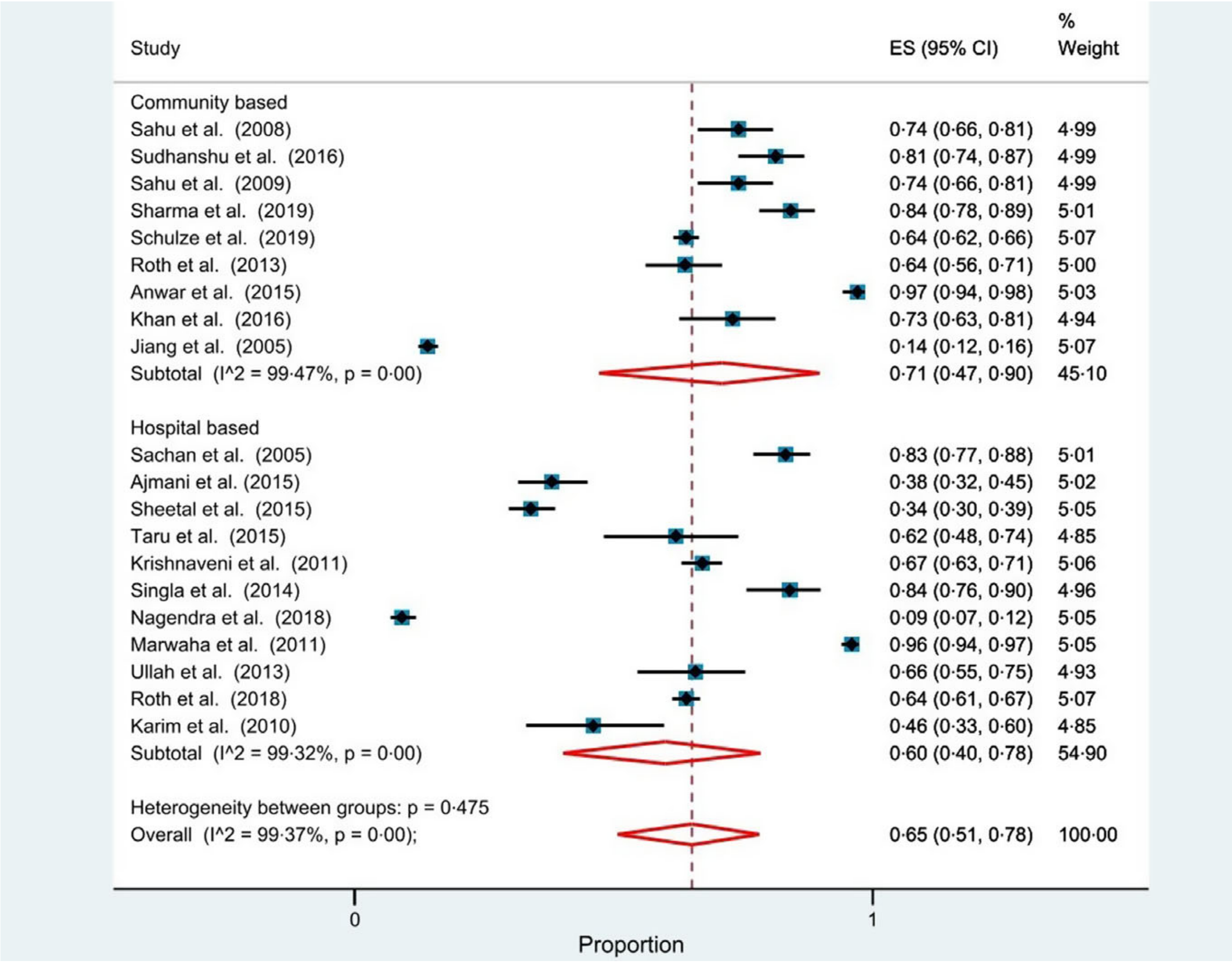

Fig. 3. Forest plot represents prevalence of vitamin D insufficiency in accordance with study settings (community-based *v.* hospital-based). In this forest plot, all the diamonds, except the last one, represents polled prevalence on the basis of study settings: (1) community-based and (2) hospital-based. Each horizontal line of the forest plot represents an individual study and the box plotted as prevalence for that study. The horizontal points of the diamond represent the limit of 95 % CI.

For instance, like many other non-communicable diseases, the rate of cesarean section is increasing significantly in SA countries, especially in India, Pakistan, Bangladesh and Maldives. The overall cesarean rate has been found more than 15 % in these countries which have crossed the WHO recommended range (10–15 %)[25]. In this regard, some studies reported the association between low serum level of vitamin D and the risk of cesarean section 26, 57. Besides this, some study reports also suggested that gestational diabetes, eclampsia and preeclampsia and various non-communicable diseases are increasing among different SA countries[24,27,28,58,59]. Therefore, the causal association of high insufficiency of vitamin D and the rising trend of these diseases should be considered seriously for better health care delivery in SA.

While the highlight of this study was high vitamin D insufficiency, we also found a high degree of heterogeneity in overall results ($I^2 = 99·37$ %). We hypothesise that geographical location could be a factor for such a large-scale heterogeneity.

Country-wise comparison showed that Pakistan had the highest prevalence (76 %; 95 % CI: 39 %, 99 %), followed by India (67 %; 95 % CI: 46 %, 85 %) and Bangladesh (64 %; 95 % CI: 62 %, 66 %) (Fig. 2). It is hypothesised that variability in the degree of sunlight exposure due to differences in geographical locations could be a probable reason for this. Throughout the year, people living in tropical areas get more sunlight exposure than those living in subtropical regions. Vitamin D synthesised naturally in our body when UVB from sunlight penetrates our skin and undergoes some physiological changes[1,2,13]. Pakistan is situated in a subtropical region where there is relatively low sunlight availability compared to tropical regions. The national boundaries of Bangladesh and India both share tropical and subtropical regions in their national map[60]. Our hypothesis can be bolstered by the fact that a high prevalence of vitamin D insufficiency was also observed in countries like Iran (56 %) and China (70 %) (using < 20 ng/ml cut-off), which share similar geographical locations on their national map[55,61]. Additionally, this hypothesis is also corroborated by intra-country study reports. For instance, geolocation hinted that northern part of India is placed in sub-tropical zone, whereas southern section is in tropical zone[60]. Study reports suggested that prevalence of vitamin D insufficiency is higher amid north Indian pregnant women (93 %) in comparison with pregnant women (65 %) from south India[38,62].

While a high degree of heterogeneity cannot be fully explained with variation in geography, several other factors such as skin colour, clothing practice, cultural aspects and diet may also influence variation among prevalence in this region[1,2,13]. For instance, in this review, we found only a single study from Nepalese pregnant women that reported pregnant women from Nepal had the lowest percentage (14 %) of prevalence than people in the Bangladesh, India and Pakistan (Indian subcontinent). In this regard, we hypothesise that this could be related to some of the cultural aspects and skin colour. According to the Fitzpatrick skin type, most Nepalese belong to lighter skin in comparison with Indian subcontinent women[63]. Despite Nepal being situated in a subtropical region[60], this lighter skin complexion could be an important factor behind the lowest observed prevalence of vitamin D insufficiency, in comparison to rest of the Indian sub-continent. Hence, we hypothesise that the disparity of skin complexion among SA population might be a potential confounding factor for the heterogeneity of serum vitamin D in SA.

Furthermore, we hypothesise that clothing practice may also act as a factor behind such a high prevalence of insufficiency in the Indian subcontinent. The use of burqas (traditional full-body covering), hijab (Muslim wearing that covers the upper part of the body), similar to other non-religious body coverings (traditional clothes) block direct sunlight exposure event in the outdoor setting. These types of clothing practices are very common in many states of India, Pakistan and Bangladesh. A recent media report also suggests that these practices have increased exponentially in this region over the past three decades[64]. We argue that this could be linked to the high prevalence of vitamin D in this region and also the high heterogeneity observed in this study.

Our argument is bolstered by the fact that people from the European countries have quite opposite skin colour and dressing practices from the Indian sub-continent[63]. A study report from a large observational data suggested that insufficiency rate is lower among Europeans in comparison with SA (using < 20 ng/ml cut-off – 40 % of Europeans are vitamin D insufficient)[65]. Therefore, clothing practice might be a confounding factor for such a high prevalence of insufficiency in this region.

Besides this, we also hypothesise that the cultural aspect of this region may also act as a factor for such a high prevalence of insufficiency. A lesser number of SA women spend their time in outdoor environment for work purpose (meaning the majority stay in the households), which effectively limits their exposure to direct sunlight for the majority. In the year 2020, World Bank reported that the participation rate of female labour is close to 24 %, whereas the participation rate of male labor is 80 % in SA[66]. Similar trends have been found in Middle East women. The World Bank stated in 2020 that female labor participation in Middle East countries is close to 20 % only[67]. As a majority of SA women spend more time in household jobs, they are more likely to receive lesser exposure to sunlight. Perhaps, this partially explains 60 % of Saudi Arabian women residing in Riyadh city being vitamin D insufficient[68].

Additionally, in our study, we also found that studies that are designed on community-based setting (71 %; 95 % CI: 47 %, 90 %) showed a high prevalence of insufficiency in comparison with hospital-based setting (60 %; 95 % CI: 40 %, 78 %) (Fig. 3). According to the iceberg phenomenon[69], our findings suggest that a substantial number of pregnant women who lived in SA countries are affected with vitamin D insufficiency that is either subclinical, unreported or concealed from view. Therefore, community-based study settings demonstrated such a high prevalence of insufficiency in SA pregnant women.

Furthermore, a high percentage of early marriage (meaning likely early pregnancy) which has been implicated with insufficiency of essential nutrients for the young adults could be another factor behind high-level vitamin D insufficiency in SA. During pregnancy, women require more vitamin D than usual for fetus development[3–5]. UNICEF reported that more than half (56 %) of the SA women get married before the age of 18. The child marriage rate is higher in Bangladesh (74 %), then followed by India (58 %) and then Nepal (52 %)[70]. Consequently, this early pregnancy and lack of nutrition[71] might be also acting as a factor for such a high prevalence of vitamin D insufficiency with high degree of heterogeneity among the pregnant women in SA.

While all of the hypotheses proposed above could be contributing to the observed heterogeneity, slightly different cut-off values (other than < 20 ng/ml) used by some of studies that were included in this systematic review[36,38,40,47,49,50,54] might have influenced the degree of heterogeneity in our analysis. However, such heterogeneity may not be uncommon as we have demonstrated in one of the similar studies on SA adult population[72]. However, it is clear that further study is required to reveal the true source and extent of heterogeneity.

Limitations

While this study highlights critical health issues, it also has a few limitations. First, most of the studies that match with our selection criteria (15 out of 20) did not mention socio-economic conditions (income status, urban *v.* rural differences). Therefore, because of inadequate data, we could not test the effect of these factors in our study. Furthermore, we did not find any study from Sri Lanka, Bhutan, Maldives and Afghanistan. About 95 % (19 out of 20) of our selected studies were conducted among pregnant women from the Indian sub-continent. We only got a single study from Nepal. As such, because of insufficient data, we could not find the weighted mean level of vitamin D status for that country. Moreover, studies included in this review used various methods to assay the status of vitamin D in serum. While this might have introduced assay bias to our findings, this limitation is present in similar studies and was indeed inescapable. Another limitation is that, in this study, we used cut-off < 20 ng/ml to define vitamin D insufficiency. However, due to lack of studies among SA pregnant women, a few of studies were also included in our analysis that used different cut-offs[36,38,40,47,49,50,54]. Furthermore, due to poor economic condition, vitamin D assessments are often expensive for SA pregnant women. Therefore, only pregnant women with suspected deficiency or who participated in a study or a trial that included assessment of vitamin D may be assessed.

This is an inherent limitation of any such study on secondary data, and, therefore exercise of caution is recommended before generalising the results of this study.

Recommendations

Our study revealed high rise of vitamin D insufficiency among SA pregnant women. We recommend that further study is needed to see if our findings apply to a wider group of the general population. While some researchers argue that deficiency of vitamin D should be treated similar to an ongoing pandemic[7,65]. However, our search did not unveil any policies or national-level nutritional guidelines for vitamin D except in India[73]. While the existing guidelines as such supplementation and food fortification program from other countries[73,74,75,76] can be helpful for SA, we argue that the socio-cultural scenario of the individual countries (e.g. clothing practice, skin complexion and economic status) needs to be taken into consideration. Women, who wear heavy clothes and spend more time in indoor activities, can be advised to check their serum level of vitamin D regularly and take proper supplements. It has been suggested that an adult without adequate sunlight exposure should take 800–1000 IU of vitamin D per day[1]. In addition, women can be encouraged to spend time in direct sunlight exposure to prevent themselves from vitamin D insufficiency. Moreover, some other challenges need to be addressed in SA. A negative attitude towards sunlight exposure can be a big challenge. It has been reported that Indian and Pakistani students had a lack of knowledge about vitamin D and a negative attitude towards sunlight exposure[77,78]. This lack of knowledge and a negative attitude could be a major factor behind staying away from sunlight that can lead to vitamin D insufficiency. While further research is necessary to understand this. However, launching mass campaigns about the relationship between sunlight exposure and vitamin D insufficiency can be effective for SA governments.

Apart from the policies focusing on supplementation and encouraging natural synthesis, necessary measures should be taken to increase the number of diagnostic tests for detecting the serum level of vitamin D status. For achieving this, increasing the number of diagnostic centres and reducing the price for testing by offering subsidies can also be considered by the governments in the SA region.

Conclusions

Our findings reveal that more than six out of ten SA pregnant women could be suffering from vitamin D insufficiency. To our knowledge, this is the first systematic review and meta-analysis that discusses the prevalence of vitamin D insufficiency among SA pregnant women. While this study focused solely on a small group of SA pregnant women, further research is needed to check if our findings represent a wider group of general population in SA. Furthermore, strategies for prevention, diagnosis and treatment of vitamin D deficiency need to be integrated into public health policy by SA policymakers.

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The authors declare that they have no competing interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114521004360

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