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Review Article

Vitamin D status of healthy childbearing age women in South Asia: A pooled analysis of community-based studies

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ABSTRACT

Hypovitaminosis D (Vitamin D deficiency and insufficiency) is a major public health problem globally. A high prevalence of vitamin D deficiency (VDD) and vitamin D insufficiency (VDI) has been noted in South Asian (SA) women of childbearing age despite the abundant sunshine. Therefore, this study aimed to systematically review the existing data from population-based studies in this region to summate the magnitude of the problem. Articles published and reported prevalence of VDD/VDI in eight South Asian countries during period of 2010-2020 were searched and screened from PUBMED and Google Scholar using PRISMA guidelines. The study population was healthy women of childbearing age (18-45 years) and included pregnant and non-pregnant women. Fourteen population-based studies were found from SA countries India, Sri Lanka, Pakistan, Bangladesh and Nepal. No studies were available from Afghanistan, Bhutan, and Maldives pertaining to the searched period. Participant groups were from diverse socioeconomic and cultural backgrounds. The prevalence ranged from 61.5% from Pakistan to 100% from Bangladesh. This systematic review reported a significantly higher prevalence of hypovitaminosis D among SA women of childbearing age. Inadequate sun exposure, lack of consumption of good vitamin D food sources due to either illiteracy or economic constrains has been regarded as potential determinants of hypovitaminosis D among participants. The findings of this study would help pertinent stake holders to prepare suitable national level programs to enhance the Vitamin D status of women of childbearing age.

Keywords:
Vitamin D deficiency, Vitamin D insufficiency, South Asia, Females

1. INTRODUCTION

Vitamin D (VD) or calciferol is a fat-soluble steroid which is important for the maintenance of calcium and phosphorous homeostasis in blood. It is essential to promote bone mineralization and to determine the bone health status and therefore to protect against fractures[1]. It has also been related in prevention of major chronic diseases such as hypertension, cardiovascular disease, cancer, diabetes, metabolic syndrome, autoimmune and infectious diseases[2-4].

The nutrition of a woman receives before conception, during pregnancy, and during lactation affects her health and the health of her child. Therefore, women's nutrition-before, during and after pregnancy should be a special focus area in any country. Action of VD during pregnancy is needed for the stages of fetal growth and development as it provides calcium requirements for the fetal bone growth. Therefore, during pregnancy alterations occur in calcium metabolism to meet the demands of the developing foetus. Increased maternal calcium absorption and metabolism of the maternal skeleton are the two main alterations[5]. As a result, hypocalcaemia is common during pregnancy and cause adverse maternal outcomes. Pregnancy induced hypertension, recurrent miscarriages, preterm delivery, postpartum haemorrhage and postpartum depression are some of them[6-8]. A significant transplacental calcium transfer can occur during the third trimester. This can increase the risk of developing osteoporosis during pregnancy[9].

Low levels of VD during pregnancy and lactation can adversely affect the growth and dental development of

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babies. It has been reported that maternal VDD during pregnancy is a risk factor for infants[10]. Moreover, maternal VDD can leads to neurological symptoms such as hypocalcaemic seizures, increased intracranial pressure, tetany and muscle weakness in the child[11]. A case study from Bhutan has shown the severity of maternal VDD with life threatening neonatal seizures[12].

VD mainly exists in two forms i.e., vitamin D2 (ergocalciferol, produced from ergosterol) and vitamin D3 (cholecalciferol, produced from 7-dehydrocholesterol, a precursor naturally occurring in the skin of animals)[13-14].

The best source of obtaining VD is sufficient exposure to sun light. The exposure of skin to UV-B rays triggers a cascade of events leading to active VD production. Endogenous synthesis begins in the epidermal keratinocytes and dermal fibroblasts from the precursor 7-dehydrocholesterol converting to cholecalciferol, or vitamin D3. In the liver and kidney sequential hydroxylation produces 1,25-dihydroxyvitamin D3, which is also referred as calcitriol. This is the active form of VD responsible for the vitamin's physiologic effects[15].

VD is not abundant in food sources. Only a few items of food such as cod liver oil, sea fish and egg yolk contain VD in appreciable amounts[1,16]. This makes it necessary to consume VD supplements and VD fortified food.

The major circulating form of VD is 25-hydroxy vitamin D and it serves as the best biomarker for VD status. Therefore, serum levels of 25- hydroxy vitamin D is considered as the most reliable measurement of VD in any population[17]. However, there is no common definition for VDD/VDI, as the cut off values can be vary depending on the age, geographical location and several other factors[16].

Even though hypovitaminosis D is unexpected in tropical countries where overhead sunlight is abundant throughout the year, it is common in South Asian countries[18]. It is more prevalent among females than males. Previous studies have highlighted several risk factors for the higher prevalence of hypovitaminosis D among South Asian women[1,18-20]. The most important predisposing factor is the social and cultural practices in South Asian countries like India, Pakistan and Bangladesh which prevents the exposure of women to sunlight. Women in traditional families are not allowed to wear revealing clothes. Due to the home bound lifestyle, they are not encouraged to engage in outdoor activities[21]. Moreover, some families are fully vegetarian and thus prevents the dietary VD intake[22]. According to recent studies women with darker skin complexion are more prone to VDD[23]. Other confounding factors such as increasing urbanization and environmental pollution have also made women vulnerable to hypovitaminosis D[22].

Moreover, certain malabsorption syndromes such as Crohn's disease and celiac disease can affect the vitamin D status[24]. VDD/VDI can result from decreased endogenous synthesis due to liver insufficiency in chronic liver diseases (eg: cirrhosis), hyperparathyroidism, renal failure and 1-alpha hydroxylase deficiency. Medications such as nifedipine, phenobarbital, dexamethasone and rifampin can induce the hepatic catabolism of VD[25].

There is a scarcity of data on VD status among women in childbearing age from lower- and middle-income countries of South Asia. Few segregated studies have been conducted in Sri Lanka, Pakistan, Nepal, Bangladesh and India. However, no systematic review is available in South Asian region portraying the current burden of VDD/VDI in this special cohort. Though VDD/VDI is a global health concern, this problem has not gained considerable attention. Therefore, the aim of this report is to gather the data on VD status of healthy women of childbearing age in South Asian region. The outcome of this report would help policy makers and public health leaders to formulate relevant policies to overcome hypovitaminosis D related morbidities. Further, we hope that the findings will raise the awareness of health professionals in the region to strengthen and streamline remedial measures that are in operation to reduce hypovitaminosis D.

2. METHODS

2.1. Search strategy

A systematic review was conducted according to the PRISMA guidelines utilizing the existing literature from five South Asian countries[26]. The articles reporting VDD/VDI or hypovitaminosis D among women in childbearing age (18-45 years) were searched in Google Scholar and Pub Med. During search following key words were used; 'epidemiology', 'prevalence', 'vitamin D status', 'deficiency', 'pregnant women', 'women', 'associated factors', 'Sri Lanka', 'India', 'Pakistan', 'Nepal', 'Bangladesh', 'Bhutan', 'Maldives' and 'Afghanistan'. Moreover, we manually searched the bibliography of all selected articles in order to retrieve more articles.

2.2. Inclusion and Exclusion criteria

Inclusion criteria for this study were a) studies carried on women in child bearing age including pregnant women; b) studies focusing the vitamin D status, prevalence of VDD/VDI; c) studies discussing the outcomes of VDD; d) studies published in English language between 2010-2020; e) studies reported from South Asian countries; Sri Lanka, India, Pakistan, Nepal, Bangladesh, Afghanistan, Bhutan and Maldives f) studies with a cross-sectional, cohort, and case control trial. Following were considered as the exclusion criteria a) studies did not report data from South Asian countries; b) studies conducted among women suffering from diseases and deficiencies other than VD. c) commentary, review, letter to the editor, and case series.

Nevertheless, the data on VDD/VDI for the selected population was not available from Afghanistan, Bhutan and Maldives and hence the prevalence data pertaining to those countries are not included in this review. Yet, a high prevalence of VDD has been noted among the SA population[27].

2.3. Data extraction

We extracted data from studies conducted in five South Asian countries (Table 1). A data extraction table was developed in an Excel file using the selected data. This included a) title of the study, b) name of the journal, c) name of authors, d) year of publication, e) year/years of data collection, f) study objectives, g) study setting h) study design i) study population j) diagnostic criteria for vitamin D deficiency k) prevalence (if mentioned, gender, age, location specific) l) author's conclusion.

2.4. Quality appraisal

Two investigators (SHJ and DIU) independently determined the quality of the included studies by using Newcastle-Ottawa scale[28]. Depending on the items listed in selection, comparability and outcome/exposure domains, the studies were evaluated. If any study had scored three or four stars in selection domain, one or two stars in comparability domain and three stars in outcome domain, they were considered as "good quality". Two stars in selection domain, one or two stars in comparability domain and two or three stars in outcome domain were categorized as "fair quality". Zero or one star in selection domain or zero stars in comparability domain or zero or one in outcome domain was categorized into "poor quality" studies.

2.5. Author contribution

The authors confirm the contribution to the review report as follows. DIU contributed to the conception of the idea of the study. SHJ participated in the search for eligible studies and data extraction. Both DIU and SHJ analyzed and interpreted the results. Authors independently assessed the study quality. Both of the authors reviewed the results and contributed to the draft manuscript preparation. Any dispute that arose during the process was resolved by consensus. Final version of the manuscript was read and approved by both.

2.6. Definition of VD status

Generally, serum 25- Hydroxy vitamin D concentrations are used to define the status of VD. The laboratory methods used to assess serum 25- Hydroxy VD in each study considered in this report is elaborated in Table 2. There has been a long debate on the cutoff points for VD status. The studies included in this review have adopted different guidelines to ascertain VD status. They are Lips classification Institute of Medicine cut off points and previous studies that had used endocrine society clinical practice guideline[29-32].

Accordingly, most of the studies have used <10 ng/ml as the cut off to define VDD and <20 ng/ml to define VDI (<25 nmol/L; VDD, <50 nmol/L VDI). However, Garg et al., (2018) has used previous Indian studies to derive VD status and has considered <35ng/ ml as the VDI[22]. Details on cut off points used in different studies are summarized in Table 2.

3. RESULTS

3.1. Search results

The initial screening brought up 750 articles from PubMed (n=206) and Google Scholar (n=544). Following title and abstract screening 45 articles remained for full text assessment. Then 32 studies were excluded after full text review. Finally, 14 articles that met the eligibility criteria were reviewed and included in synthesizing the review article (Figure 1). Articles on VDD/VDI of women in childbearing age were found from five South Asian countries. They were from Pakistan (n=4), India (n=3), Sri Lanka (n=5), Bangladesh (n=1) and Nepal (n=1). No studies were found from Afghanistan, Bhutan, and Maldives. Eligible articles relevant to the selected title were published after 2010. Number of participants ranged from 50 to 1502 in two studies from India.

3.2. Quality of studies

Among 14 studies included in this systematic review, two were fair quality[10,33] and twelve were good quality[1,16,18-20,22,34-35] based on the Newcastle-Ottawa scale[28]. Detail of the study quality is illustrated in additional file 1.

3.3. Description of studies: design, setting and population

3.3.1. Sri Lanka

We found five studies from Sri Lanka[10,18,20,33-34]. Three were cross sectional studies while one study was a secondary analysis of existing data from a prospective cohort study and the other study was a prospective cohort study from the same author. There is an overlap between the three studies published by Anusha et al., since all three reports publish the VD status of the same cohort (pregnant mothers) in three different prevalence rates[20,33-34]. The number of participants from Sri Lankan studies ranged from 89 to 434[33,20]. Studies by Anusha et al.,

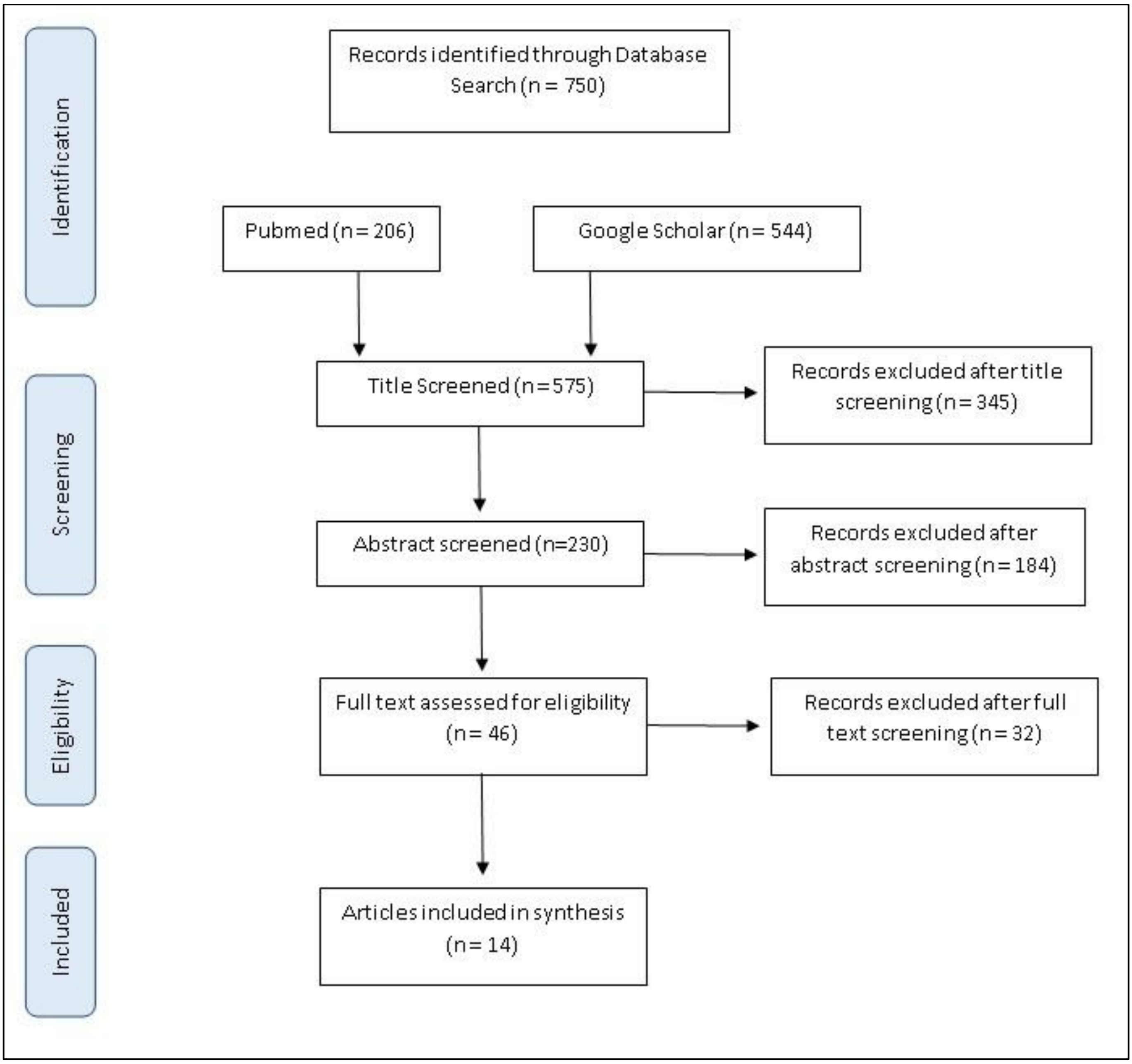

Figure 1. Flowchart showing steps of selecting articles.

recruited healthy non vitamin D supplemented pregnant women of their 3rd trimester who are attending the antenatal clinic of Colombo South Teaching Hospital[20, 33-34]. These studies recruited the participants using convenient sampling technique. The study by Anusha et al., (2019) examined the VD levels of pregnant mothers and in a follow-up visit mother-baby pair to ascertain the VD status of those lactating mothers and their babies[10]. The other two studies recruited healthy community dwelling women between 20-40 years[18,20]. Rodrigo et al., (2013) selected the participants employed in the Southern province (Galle district) of Sri Lanka by using multistage cluster sampling method[20]. The study by Subasinghe et al. (2019) selected participants from two Grama seva divisions (smallest administration unit) of Matara and Kandy districts[18]. Three studies have collected data on the dietary history of the participants[18,20,34].

3.3.2. Pakistan

Four studies were found from Pakistan and all were cross sectional studies[16,19,35-36]. The number of participants ranged from 60 to 360[16,35]. Studies by Rabbani et al., 2015 and Ali et al., 2013 have recruited healthy pregnant women and the other two studies were conducted among healthy women of childbearing age[16,30]. The pregnant women were recruited from the departments of obstetrics and gynecology of hospitals. They have been given data collection pro forma to gather the demographic information. Akhtar et al. (2019) carried out their study using female university students in Pakistan while the study of Junaid et al. (2015) recruited university students, students or employees of Madrasas or Islamic Institutes, and employees working in office, hospital or domestic settings for their studies[16,35]. These two studies have used detailed interviews to collect the demographic data of the participants[16,35]. All studies measured serum 25-hydroxy vitamin D in order to estimate the VD status of the selected study populations.

3.3.3. India

There were three cross sectional studies from India[22, 37-38]. Sample size varied from 55 to 1502[38,22]. One study has recruited healthy women between 32 and 36 weeks of uncomplicated singleton pregnancy from a fee-paying nursing home (affluent) and non-fee-paying hospital (nonaffluent)[37]. They were aged between 20-35 years. The study of Garg et al., (2018) recruited women (aged between 15-60 years) attending the gynae clinic[22]. Both these studies collected detailed information about the socio demographic status and the dietary history of the participants. The respondents of the study of Harinarayan et al., (2011) were healthy women of reproductive age and postmenopausal women[38]. In this report we have included the data pertaining to the participants in the reproductive age. These subjects were relatives of patients attending hospital and healthy hospital staff. In all three studies blood samples were collected to measure the serum 25 Hydroxy vitamin D level.

3.3.4. Bangladesh

We found one case control study from Bangladesh[1]. The study recruited 40 female garment workers as the case group and 40 general female workers as the control group. The general female workers were mainly agricultural and construction workers who worked at sufficient sun light. The participants were aged between 20-40 years. To establish the possible correlation between serum 25-hydroxy vitamin D level and food consumption in the cohort, a short food frequency table was used in the study.

3.3.5. Nepal

Only one cross sectional study was identified from Nepal[39]. The study setting was a local non-governmental maternal and children hospital. Pregnant women (79) admitted to the hospital for their delivery were recruited for the study. Demographic data and clinical data of the participating mothers were collected using a standardized questionnaire. Venus blood samples were collected to estimate the serum VD level, before delivery. VD levels of their new born babies were assessed by obtaining umbilical cord blood after delivery. The characteristics of the studies from all the five selected countries are summarized in the Table 1.

3.4. Prevalence

Studies on VD status in SA population is scarce. However limited data shows a high prevalence of VDD/VDI in women of childbearing age in SA countries (Table 2). All studies except one included in the current report stated a very high degree of hypovitaminosis D ranging from 61.5% (Pakistan)-100% (Bangladesh)[19,1].

Among Pakistani studies the highest prevalence (73%) was reported from a study that admitted participants of age 15-50 years and had VD levels <50 nmol/L[35]. This could be attributed to wide range of age distribution of participants that had been set as eligibility criteria of the study. However, two other studies conducted among pregnant women of age 20-30 years and 20-40 years also showed a higher prevalence of VDD[19,36]. In these two studies, analysis of the cord blood samples collected at the time of delivery reported a 58.2% and 99.5% prevalence of VDD in newborns respectively.

Sri Lankan studies also reported a higher prevalence rate of VDD/VDI. The highest prevalence (66.3%) was reported by Kaneshapillai et al., (2018) among pregnant women in their third trimester and the age was not mentioned[34]. The same author had reported slightly different values for the VDI in other two reports from the same tertiary care center in the capital of Sri Lanka[10,33]. It is not clear that these findings are from the same group or different groups. Another two studies that have recruited participants (20-40 years) - from southern and central provinces of Sri Lanka also reported a higher prevalence of hypovitaminosis D (>55%) among participants[18,20].

Considering studies conducted among Indian women, the highest prevalence of VDD (94%) was detected in a study that enlisted woman of the age group of 20-35 years[37]. The other two Indian studies also reported a significantly higher prevalence of VDD as 64.06% and 76%[22,38]. It is noteworthy to mention that VD deficient mothers have given birth to VD deficient babies too[37].

The prevalence of VDD (<20 ng/ml) and insufficiency (20-30 ng/ml) was 81% and 11.39% respectively among Nepal pregnant mothers at the time of the delivery[39]. Bangladesh study reported the highest prevalence of VDD (100%) across the SA region (100%, among garment factory workers)[1]. According to the data shown in Table 2 it is evident that pregnant women are at a higher risk of VDD/VDI status when compared with the VD status of non-pregnant women from each country.

However, the data from six countries of the region doesn't put any strong evidence of prevalence of VDD/VDI restricted to special age category. Despite all women of childbearing age appear of being deficient. No data were available to assess the VD status of this cohort from Afghanistan, Bhutan and Maldives.

Table 1. Characteristics of studies.

Country	Author Year[Ref]	Setting	Study population, Study design	Number of participants, Age limit/Mean age
Sri Lanka	Subasinghe et al. 2019[18]	Two Grama sewa divisions (Smallest administration unit)	Community dwelling healthy women in Matara and Kandy, Cross-sectional study	132, 20-40 years
	Rodrigo et al. 2013[20]	Institutions located in the Galle district	Females who were employed in southern Sri Lanka, Cross-sectional study	434, 20-40 years
	Anusha et al. 2018[33]	Obstetric Department of Colombo South Teaching Hospital	Healthy and non-vitamin D supplemented Sri Lanka-based pregnant mothers in third trimester, Secondary analysis of existing data from a prospective cohort study	89, 29±6 years
	Anusha et al. 2018[34]	Obstetric Department of Colombo South Teaching Hospital	All mothers attending the antenatal clinic in their 3rd trimester, Cross-sectional study	91, Not mentioned
	Anusha et al. 2019[10]	Tertiary care Teaching hospital, Southern part of Colombo district	Pregnant mothers in the third trimester (mean gestational age 39±1 weeks) Prospective cohort	115, ≤18 years
Pakistan	Akhtar et al. 2019[16]	University	Female students of Bahauddin Zakariya University, Cross-sectional study	60, 20-25 years
	Junaid et al. 2015[35]	University, Islamic institutes, offices, Hospitals, Domestic setting	Female students from University of the Punjab Campus, Students and staff of the Islamic institutes, Employees in offices, hospitals, domestic setting, Cross-sectional study	215, 15-50 years
	Rabbani et al. 2020[19]	Hospital	Healthy pregnant women attending Department of Obstetrics and Gynaecology, Military Hospital Rawalpindi, Cross-sectional study	213, 27.8±4.1 years
	Ali et al. 2013[36]	Hospital	Healthy pregnant women attending Department of Obstetrics & Gynaecology, Liaquat National Hospital, Cross-sectional study	360, 21-30 years/mean 28.52±3.4 years.
India	Garg et al., 2018[22]	Gynae clinic	All women attending the Gynae clinic, Cross-sectional study	1502, 15-60 years
	Jani et al., 2014[37]	A private, fee-paying nursing home (affluent) and A non-fee-paying hospital (nonaffluent)	Healthy women between 32 and 36 weeks of uncomplicated singleton pregnancy, Cross-sectional study	150, 20-35 years
	Harinarayan et al., 2011[38]	Hospital	Women of reproductive age, Cross-sectional study	55, 38+0.7 years (mean±SEM)
Bangladesh	Mahmood et al., 2017[1]	Garment factory	Female garment workers of export-oriented garment factory in Dhamrai, Dhaka (Case group) and general female workers (Control group), Case control study	80, 27.2±5.5 years (Case group), 28.3±4.8 years (Control group)
Nepal	Shrestha et al., 2019[39]	Hospital	Pregnant women admitted to the Siddhi Memorial Hospital, Bhaktapur, Nepal, Cross-sectional study	79, 18-38 years

Table 2. VD status in South Asian women of childbearing age.

Country	Population	Author, Year[Ref]	Methods used for measurement of blood Vitamin D	Citing literature for cutoff values	Cut off values for VD status /Serum 25(OH)D concentration	VD status	Contributory factors for Vitamin D status
Sri Lanka	Non-pregnant women	Subasinghe et al., 2019[18]	Chemiluminescence Binding Assay	Lips classification	<10 ng/ml; deficiency 10-20 ng/ml; insufficient >20 ng/ml; adequate	Deficiency; 6.1% Insufficiency; 51.5% Sufficiency; 42.4%	Reduced sun exposure time, Low intake of dairy and non-dairy vitamin D rich foods
		Mahinda Rodrigo et al., 2013[20]	Liquid phase radioimmunoassay	Lips Classification	<12.5 nmol/L; severe deficiency 12.5-25.0 nmol/L; moderate deficiency 25.1-35.0 nmol/L; mild deficiency	Severe deficiency; 21.4% Moderate deficiency; 19.1% Mild deficiency; 15.7%	Not mentioned
	Pregnant women	Anusha et al., 2018[33]	Enzyme linked fluorescent assay (ELFA)	Institute of medicine (IOM) reports and Consensus report on Nutritional rickets	<10 ng /ml; deficiency 10-20 ng /ml; insufficiency >20 ng /ml; sufficiency	<10 ng /ml; 18.5% <20 ng /ml; 66.3%	Socio-economic status (a mixed of education, income and occupation), Low dietary intake of vitamin D and Calcium
		Anusha et al., 2018[34]	Enzyme linked fluorescent assay (ELFA)	Institute of Medicine (IOM) classification	<10 ng /L; deficiency >20 ng /L; sufficiency	Deficiency; 12.4% Insufficiency; 50.6% Sufficiency; 37%	Reduced exposure to sun, Less affordability to vitamin D rich foods and to compensate high demand for vitamin D during pregnancy, genetic factors
		Anusha et al., 2019[10]	Enzyme linked fluorescent assay (ELFA)	Guide for Vitamin D in Childhood, Royal College of Pediatrics and Child Health, Vitamin D and Bone Health, A practical clinical guideline for management in children and young people	<25 nmol/L; deficiency <50 nmol/L; insufficiency	Deficiency; 12% in pregnant mothers 5% in lactating mothers Insufficiency; 51% in pregnant mothers 43% in lactating mothers	Reduced sun exposuretime
Pakistan	Non-pregnant women	Akhtar et al., 2019[16]	Enzyme Linked Immunosorbent Assay (ELISA)	Consensus of International Experts	<12.5 nmol/L; severe deficiency 12.5-25 nmol/L; moderate deficiency 25-50 nmol/L; Mild deficiency >50 nmol/L; Insufficiency >75 nmol/L; sufficiency	Deficiency status are not severe	Skin pigmentation, Reduced sun exposure (veil status), poor dietary patterns

Table 2. VD status in South Asian women of childbearing age. (cont.)

Country	Population	Author, Year[Ref]	Methods used for measurement of blood Vitamin D	Citing literature for cutoff values	Cut off values for VD status /Serum 25(OH)D concentration	VD status	Contributory factors for Vitamin D status
Pakistan	Non-pregnant women	Junaid et al., 2015[35]	IDS enzyme Immunoassay (Immunodiagnostic Systems Boldon,UK)	Endocrine society clinical practice guidelines	<50 nmol/L; deficiency	Deficiency; 73%	Demographic, social and behavioral factors Poor literacy, reduced sun exposure time
	Pregnant women	Rabbani et al., 2020[16]	Electro-chemiluminescence immunoassay (ECLIA)	Previous literature	<50 nmol/L; deficiency ≥50 nmol/L; sufficiency	Deficiency in mothers; 61.5% Deficiency in babies; 99.5%	Reduced sun exposure
		Ali et al., 2013[36]	Electrochemiluminescence technique	Not mentioned	<32 ng/ml; deficiency	Deficiency in mothers; 69.6% Deficiency in cord blood; 58.2%	Veil/parda observance leading to sun exposure
India	Non-pregnant women	Garg et al., 2018[22]	Electrochemilumine	Previous Indian studies	<20 ng /ml; severe deficiency 20-30 ng /ml; moderate deficiency <35 ng /ml; mild deficiency	severe deficiency; 64.06% moderate deficiency; 34.69%	Poor literacy, being a working women/ house wife, living in a rural/urban area
		Harinarayan et al., 2011[35]	Radioimmunoassay (RIA) and Immunoradiometric assay (IRMA) kit	According to the recent reports	<20 ng/ml; deficiency 20-30 ng/ml; insufficiency >30 ng/ml; sufficiency	Deficiency; 76%	Not mentioned
	Pregnant women	Jani et al., 2014[38]	Chemiluminescent microparticle immunoassay	Institute of Medicine (IOM) guidelines	<20.0 ng/ml (<50 nmol/L); deficiency 20.0-29.9 ng/ml (50-74.9 mol/L); insufficiency ≥30.0 ng/ml (≥75 nmol/L); Adequate	Deficiency; 94%	Reduced sun exposure
Nepal	Pregnant women	Shrestha et al., 2019[39]	Fluorescence Immunoassay	Endocrine society of clinical guidelines	>20 ng/ml (<50 nmol/L); deficiency, 20-29 ng/ml (50-75 nmol/L); insufficiency, 30-100 ng/ml (75-250 nmol/L); sufficiency	Deficiency in mothers; 81% Insufficiency in mothers: 11.39% Deficiency in babies; 35.8	Not mentioned
Bangladesh	Non-Pregnant women	Mahmood et al., 2017[1]	Chemiluminescence microparticle immunoassay	Institute of Medicine guidelines	>20 ng/ml; deficiency, 21-29 ng/ml; insufficiency	Deficiency; 100% in case group Deficiency; 17% in control group Insufficiency; 80% in control group	Reduced exposure sunshine, air pollution status, skin pigmentation, Covering types of dresses

3.5. Contributing factors leading to VDD/VDI in the included studies

Table 2 summarizes the possible factors that may lead to low serum VD levels in each study. In most of the studies reduced exposure to sun light, poor dietary sources and illiteracy were identified as major contributing factors leading to VDD among the reference populations.

4. DISCUSSION

To the best of our knowledge, this systematic review is the first of this type portraying the prevalence of hypovitaminosis D in South Asian women of childbearing age. We hope that this study will bring attention of international, regional and national stakeholders to the magnitude of the problem and to implement measures to reduce the future burden.

This study revealed that there is a scarcity of population-based data on VD status of SA countries pertaining to this group. Nevertheless, for the other age-community groups also no sufficient data was available. Due to numerous inconsistencies in study population characteristics, study design, sampling technique, and methods used to determine VD status and cut-off points to define VDD and VDI, it is difficult to depict an exact figure for prevalence of hypovitaminosis D and to provide convincing comparisons of prevalence estimates in these countries. Even though, the segregated studies considered in this report confirm that the prevalence of hypovitaminosis D among childbearing age women is comparatively higher and needs national level attention and remedies to overcome this important health issue.

The majority of the selected studies have discussed the associated factors for the widespread hypovitaminosis D among SA women in child bearing age. All studies from Pakistan have reported that lack of sun exposure is significantly associated with VDD among the participants[16,19,35-36]. Due to cultural constrains, it is possible to assume that the restricted clothing pattern among Pakistani women (veil/ parda observance) might have led to reduced VD levels. However only three studies supported this argument[16,19,36]. The study conducted by Junaid et al., (2015) did not demonstrate any association between veiling and risk of VDD[35]. That was in line with another study conducted in Bangladesh reporting that hypovitaminosis D is common among women of that setting irrespective of veiling[40]. A Pakistani study has reported that low VD levels are significantly correlated with the participants education level[35]. This study demonstrated that illiterate or women with primary education were greatly suffered from VDD compared with women who had secondary education level[35]. Dark skin, consumption of food poor in VD and lack of multivitamin intake were also identified as predisposing factors for VDD/VDI among Pakistani women[16]. Polymorphism of the gene encoding for VD binding protein tended to have lower VD concentrations of women from Pakistan[35].

A study from Sri Lanka has shown that majority of women with hypovitaminosis D had exposed to sun light for less than two hours/day[18]. Most of the participants recruited for this study were office workers with limited sun exposure (5-10 minutes, mostly in the early morning or late evening where UV-B exposure is minimal). Covered clothing pattern (saree) and dark skin of the participants were identified as the determinants for the reduced VD synthesis in the skin. In addition, low intake of VD sources from dairy or non-dairy foods were also associated with lower serum VD levels in these women[18]. Sufficient dietary VD intake and serum VD level was significantly correlated among a cohort of Sri Lankan pregnant women[33-34]. However, the data revealed that, diet alone may not be enough to achieve good VD status among pregnant women in the recruited sample. Hypovitaminosis D was more pronounced in these urban pregnant housewives with low educational and socioeconomic levels. Optimal dose of VD and the counterpart calcium for pregnant women is controversial[33]. Institute of Medicine recommends a safe upper level of VD and the calcium in the diet as 4000 IU and 2500 mg respectively[41]. Few other reports of randomized controlled trials indicate that a safe dose of 2000-4000 IU/ day VD supplementation in pregnancy is useful to maintain adequate levels[42-43].

Studies from India reported that lack of sun exposure and poor economic status have led to low VD levels among pregnant women[37]. Garg et al., (2018) has shown that educational, social and economic background also determines the VD status among Indian women[22]. Hypovitaminosis D was observed in illiterate (89.92%), housewife women (70%), residing in rural areas (69.94%) with an income less than 10,000 Indian rupees (61.96%).

The only eligible study from Bangladesh reported that the major determinant of VD status among female garment workers is the time duration of sun exposure[1]. They spent a major part of the daytime (10-12 hours/day) in the office building with covered up dress styles. They are exposed to regular sunshine (5-15 minutes/day) in the very early morning on their way from living places to work.

It is unexpected to observe a high prevalence of VDD/VDI in SA countries as VD is a sunshine vitamin and all the countries considered in this report are tropical countries with abundant sun light comparatively throughout the year. However, critical analysis of factors associated with VD status of women in SA region demonstrates that sun exposure is a major determinant, that governs the VD status of the selected population. In fact. the most important determinant of VD status in any population is the exposure to ultraviolet-B (UV-B) rays. VDD/VDI is associated with limited outdoor activity during the midday owing to hot climate or burning sun, dark skin pigmentation and covering up of the body due to the cultural reasons reported in the study population.

The time of the year is an important factor in measurement of VD levels in diagnosis of VDD or VDI. Variation in sampling season of the studies may have an impact on the participant's VD status. Nevertheless, most of the studies included in this report haven't considered this fact. Only two studies, one from Pakistan and the study from Bangladesh has collected the samples in the summer season[35,1]. These studies have assumed that the samples were collected in the most appropriate season where the highest serum VD levels could be evident. In fact, Junaid et al., (2015) has reported that VDD was more pronounced among participants recruited in January to March compared with that of April to July participants[35].

Most of the VD in human body is derived from exposure to sunlight. This is the most cost-effective means of acquiring VD. However, people avoid sun exposure due to high temperature especially in hours where VD production is maximum. Conversely, this solution is not viable in working population where most of the daytime they spent in office buildings and hardly exposed to sun light. Not only the duration of exposure to sunlight, but also the body surface area exposed is an important for adequate VD synthesis. Yet, attention should be paid to the detrimental effect of sun exposure due to the possibility of skin malignancies[18].

Approach to different dietary sources of VD seems sustainable and calls no external support. Fatty fish is the richest natural food source of VD, while egg yolk and cod liver oil are also rich in VD. VD content in other dietary sources are minimal and strict vegetarians are at a higher risk of hypovitaminosis D. In this context the other feasible approach to overcome hypovitaminosis D is to identify food items that can be fortified with VD. However, fortified food items are expensive and they are not very popular in Sri Lanka and other developing countries[18]. It is important to identify low-cost staple food items to fortify and these food items should be freely available, affordable and acceptable to poor communities.

VD supplementation targeting pregnant and lactating women is another remedy that has been discussed in the studies included in this report. The studies conducted among pregnant women has shown that VD supplementation is not an integral part in the antenatal or post-natal care programmes[33-34]. This could be well-suited considering the widespread VDD noted throughout the selected studies. Adequate maternal VD levels prevent neonatal rickets and associated complications in the newborn and maintain the bone health in mothers also. Therefore, yet this measure is practically feasible it has been reported that VD supplementation should be considered in failing with the implemented inexpensive lifestyle modifications[18]. However, supplementation is regarded as the most effective strategy though it is not widely practiced in SA countries may be due to possible implemented cost.

There are several limitations of the present report. Though VD was measured based on chemiluminescent immunoassay, there might be variations between laboratories even with the same method. Variations in the cut off values and different units used in interpretation of VD status also interfered with analysis into some extent.

The studies considered in this report were conducted among different socio-economic groups and this would have led to variations of VD status among the study populations. Poverty and lack of knowledge will hinder the ability to access foods which are rich in VD (specially, animal products and fortified foods). However, this might not be the case with affluent members of this group. In addition, there is lacking representative data from all countries which is included in this report. Furthermore, the report was based on few available studies undertaken in South Asian countries. Therefore, the findings obtained may not accurately represent the VD status of the target population of the entire country.

Data from three countries (Afghanistan, Bhutan and Maldives) are not included in the report due unavailability of current studies. This precludes the ability to accurately assess VD status in this study population. In fact, a comparison of obtained data with studies may not be entirely appropriate as study cohorts, sampling period and many other factors varied among different studies.

5. CONCLUSION

In conclusion, the available data indicates that hypovitaminosis D is a major public health problem among women of childbearing age in SA countries. It is a widespread nutritional deficiency in this region, yet it has been widely undiagnosed and untreated. A diet low in consumption of meat, fish dairy products and eggs, reduced exposure to sunshine and illiteracy have been identified as determinants of VDD/VDI. Strategies entailing mandatory food fortification of staples with VD, VD supplementation programmes for pregnant women, developing awareness on health damaging effects of sub optimal VD levels and sagacious sun exposure. Health education on dietary sources rich in vitamin D are mandatory to improve the VD status in the childbearing age women.

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