Vitamin D Deficiency: Characterization of an Overlooked Health Hazard

By

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A thesis submitted to the Department of Mathematics and Natural Sciences in partial fulfillment of the requirements for the degree of Master of Science in Biotechnology

Department of Mathematics and Natural Sciences
BRAC University
2020

Declaration

It is hereby declared that

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2. The thesis does not contain material previously published or written by a third party unless properly quoted by a complete and correct citation.

3. The thesis does not include material which has been accepted or submitted, for any other degree or diploma at a university or other institution.

4. I have acknowledged all main sources of assistance.

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Ethics Statement

The concept of this study was unique and thus mine did not have any conflict of interest. However, the study did not use any animal model and in the case of human individuals, we take permission from the BRACU ethics committee.

Acknowledgment

I would like to thank all those who helped me various times to complete this thesis work:

To our chairperson Professor A F M Yusuf Haider, Department of Mathematics and Natural Sciences, BRAC University for allowing me to continue my work and necessary assistance from BRAC University library and computer lab.

To my supervisor Dr. Mahbubul Hasan Siddiqee, senior lecturer. Department of Mathematics and Natural science, BRAC University who taught me each and every detail of research work, provided his valuable time to clear all of my doubts during working on this project, constant encouragement and guidance to complete this whole project.

To my department coordinator Dr. Ifthekar Bin Naser, Assistant Professor, Department of Mathematics and Natural Sciences, BRAC University for the inspiration he provided me as a student to complete this project.

To my teachers Mohammed Hasan Murad, Romana Siddique, Mehnaz Karim, Fahareen-Binta Mosharraf, and MHM Mubassir, Department of Mathematics and Natural Sciences, for providing their assistance to complete the survey portion of this project on our campus.

To our University assistant librarian Md. Shahajada Masud Anowarul Haque made necessary arrangements for me to use the SCOPUS database.

To Mr. Mesbahur Rahman, and Mr. Mahbub Hasan, statistical analyst, Biomedical Research Foundation (BRF) for helping me to solve the statistical portion of my thesis work.

To my juniors Mahedi, Mahmud, and Sujon for helping me in data collection from various parts of our country for completing the survey portion of this project.

To my friends Antu, Sishir, and Rezwan who helped me during the presentation of my thesis writing.

Finally, to my parents who constantly support me to complete this thesis work, without support from this two-person might be I was unable to complete this whole work.

Dedication:

To all public health workers in our country who tried hard and soul to improve the overall health status of our people.

Table of contents

List of tables

List of Figures

Figure 15: Forest plot shows country wise prevalence of Vitamin D deficiency among South Asian adult.

Figure 16: Gender wise forest plot for prevalence of Vitamin D deficiency among South Asian adult population

List of Acronyms

VDD = Vitamin D Deficiency.

25 (OH) D = 25-Hydroxy Vitamin D.

1, 25 $(OH)_2$ D = 1, 25 di hydroxyl Vitamin D.

RCT = Randomized Control Trial.

CC = Case Control.

CS = Cross Sectional.

RIA = Radioimmunoassay.

LCMS = Liquid chromatography tandem mass spectroscopy.

CLIA = Chemiluminescence immunoassay.

CMIA = Chemiluminescent microparticle immunoassay.

EIA = Enzyme Immunoassay.

RAIA = Random access Immunoassay.

AMK = Automated Kit.

ELISA = Enzyme Linked Immunosorbent Assay.

ECLIA = Electrochemiluminescence Immunoassay.

Commercial Kits = CK.

CIA = Commercial Immunoassay.

IRMA = Immunoradiomatric immunoassay.

HPLC = High performance liquid chromatography.

HPLC- MS = High performance liquid chromatography – tandem mass spectroscopy.

AFBM = Analytical facility for bio active molecule.

CMIA = Chemiluminescent microparticle immunoassay.

KAP = Knowledge, Attitude, Practice.

Abstract:

Vitamin D or sunshine vitamin is a hormone precursor, soluble in fat and plays an important role in our body by participating in several endocrine autocrine and paracrine activities. Since it has many pleiotropic health effects in our body, deficiency of this vitamin can create a negative impact on our health. Though worldwide 1 billion people were affected with vitamin D deficiency but it was quite surprising that many countries of the world, especially in South Asia, did not recognize this issue as a serious public health problem. My study results point out two important things; firstly, from systematic review results it was clear that vitamin D deficiency is highly prevalent in South Asian countries and more than 6 out of 10 South Asian individuals in respect to all age groups were affected with vitamin D deficiency. To overcome this scenario, all South Asian governments should revise their health policy and address vitamin D as an important factor to improve mass communication health status. Secondly, KAP study results showed that in Bangladesh, educated teenagers, young adults and doctors who were either studying or working in different institutions, had a lack of knowledge about vitamin D and its impact on our health. They also carried a negative attitude towards sunlight. Because of this negative notion and lack of knowledge, many of our study participants were not concerned about their vitamin D status. Our study points out that this large group of educated individuals never checked their own vitamin D level (85% from general group (College and University students) and 80% from medical group (medical students and doctors)). So it is necessary to create awareness both in medical and general students about the importance of vitamin D, how we can improve our vitamin D status easily with free of cost by sunlight exposure, and why vitamin D is essential to fight against several chronic diseases. In a society, it will be easy to improve all over mass communication health status if educated individuals of that society showed concern about certain serious health issues like vitamin D deficiency. Government and other stakeholders of Bangladesh related to public health need to come forward to address this issue.

Keywords: Vitamin D deficiency, Public health, Systematic review, KAP study, South Asia, Bangladesh.

Introduction

Macronutrients and micronutrients are essential for our body to work properly in regular life processes. Macronutrients are commonly known as energy providing nutrients which include carbohydrates, fat, protein etc. We need those things to maintain our cellular growth and development. On the other hand micronutrients are encompassing with vitamins and minerals. Those take part in several chemical reactions at cellular level as a regulatory substance or sometimes work together with enzymes and other substances to maintain normal cellular metabolism, growth and development for maintaining a healthy life [1].

Vitamin A, Iron and Iodine are described as the most important micronutrients for the global public by WHO (World Health Organization) and FAO (Food and Agriculture Organization) in the year 2004 [2]. Beside these three micronutrients Vitamin B6, Vitamin C, Vitamin E, magnesium and zinc are also considered essential micronutrients and recommended to consume regularly from Harvard medical school in the year 2016 [3]. No doubt that these micronutrients are essential but much discussion on these sometimes shadow the importance of another important micronutrients called Vitamin D.

Vitamin D is a fat soluble steroid hormone which was discovered in the early twenty century [4]. One interesting thing about vitamin D is that the human body does not need to take vitamin D as a diet regularly to fulfill the needs but they can synthesize it in their body by exposing their skin in sunlight. It has a wide range of functions in our body which include anti-inflammatory and immune modulating effects. It is now well recognized that vitamin D deficiency will be coming as a pandemic for twenty first century and several epidemiological and observational study suggest that vitamin D deficiency may be responsible for several non-communicable disease such as diabetes, cardiovascular disease, colon cancer and breast cancer, osteoporosis etc. These diseases are mainly responsible for increasing mortality globally. Beside non-communicable

disease it is also responsible for many communicable diseases such as tuberculosis, pneumonia, influenza etc. Vitamin D deficiency is affected both in developed and developing countries and a study report shows that nowadays 1 billion people worldwide are affected with vitamin D deficiency [5–8]. These substantial evidence from several study reports indicate that the importance of vitamin D in our body is as similar as other important micronutrients to lead a healthy life.

Review of literature

More than 200 journal articles which was published in peer reviewed journal such as British Journal of pharmacology and pharmacotherapeutics, Journal of advanced research, British journal of nutrition, Achieve of osteoporosis, Indian journal of clinical nutrition, Nature etc. were reviewed in this section and those article mainly discuss about vitamin D, its sources, risk factor associated with vitamin D deficiency, group of people who are at risk for vitamin D deficiency etc. Beside those articles published reports from world health organizations regarding global health and study on south Asian countries also reviewed in this section.

Risk factor associated with general health

We all know that old proverb “Health is wealth” and this taught us from our childhood that we should take care of our health to lead a happy and wealthy life. It’s necessary to be aware of risk factors associated with general health for taking prevention measures against them. According to a report published from the organization (WHO) “health risk” is defined as “a factor that raises the probability of adverse health outcomes”. In that report they also said that high blood pressure, high blood glucose, using tobacco, physical inactivity and obesity are the major risk factors for mortality in this world [9].

Dr Margaret Chan who was a former WHO director once said that "The threat of Non communicable diseases (NCDs) constitutes one of the major challenges for development in the 21st century, undermining social and economic progress throughout the world." Low and middle income countries are affected mostly with chronic non communicable and communicable diseases like diabetes, cancer, cardiovascular disease, tuberculosis etc [10–12].

Vitamin D is an essential micronutrient because its receptor presents almost every tissue and cells in our body and activation of vitamin D in our body is responsible for regulating up to more than hundred genes in our body. We think vitamin D deficiency acts as an important factor for developing several non-communicable and communicable diseases in human beings and we will briefly discuss it in a later section.

History of discovering Vitamin-D

In the early twenty century high incidence of rickets was observed in Scottish People and at that time the disease was known as “the English disease”. Sir Edward Mellanby tried to find out the cure mechanism from rickets and he assumed that it might be because of dietary mechanism deficiency and it might be cured by using Vitamin-A. To establish his theory he fed rickets affected dogs with cod liver oil and found that it works positively. Another scientist named E.V McCollum from John Hopkins University followed this work and checked the hypothesis whether Vitamin-A is responsible for curing rickets. He bubbled oxygen through cod liver oil which destroyed Vitamin A and discovered that this preparation is no longer able to prevent xerophthalmia and Vitamin A deficiency but still able to heal rickets. In the year 1922 he published this finding and concluding that by saying it is not Vitamin-A which is responsible for curing rickets, it’s a new Vitamin and coined the term Vitamin-D [4]

Types and Sources of Vitamin-D

Vitamin D is a fat soluble pro hormone which takes part in several endocrine, paracrine and autocrine activities in our body. It is generally two types Ergocalciferol or Vitamin D2 and Cholecalciferol or Vitamin D3. Humans can take Vitamin-D from three sources. (1) Through diet, (2) Exposing body parts through sunlight and finally (3) Via Supplement.

Human beings cannot synthesize Vitamin D2 in their body, so they take it as a diet from other sources and it is available in some sun exposed mushrooms, yeast, cod liver oil, most oil rich fish like salmon, mackerel etc. Beside this some fortified foods like milk, orange juice, yoghurt butter, cheese, and egg yolk also provide vitamin-D for people. People also can take vitamin-D in a form of capsule, tablet, liquids or drops as a supplement. There are several multivitamin drugs available in the market which contain 800-1000 IU of Vitamin D. Vitamin D3 or sunshine vitamin is the true natural source of Vitamin D for ourselves because we can synthesize it in our body by expanding sometimes in sunlight [5–7].

Vitamin D synthesis in human body

Nowadays Greek historian Herodotus' explanation about skull bone weakness is being taken as the historical reference of the physiological effect of vitamin D and sunlight. Herodotus visited the battlefield where Cambyses overcame Egyptians at the year 525 B.C. He inspected the skulls of Persians and Egyptians and found that Persians' skulls were so fragile that they could be broken by pebbles whereas Egyptians skulls were so strong that they were hardly broken when affected with stone. Herodotus' explanation about this kind of skull bone weakness was that Persians covered their head with turbans shading from sunlight whereas Egyptians where bareheaded from childhood and exposing their head to sunlight [7].

It is well established that UVB radiation responsible for synthesizing vitamin D in the human body and humans can synthesize vitamin-D naturally from sunlight when they expose their body parts at wavelength 280-315 nm or 280-320 nm. At this wavelength UVB radiation penetrate our skin and convert 7- dehydrocholesterol into active form of vitamin D which is 1,25 dihydroxyvitamin D. 7 dehydrocholesterol is the precursor molecule which present in plasma membrane and converted to previtamin D after UVB penetration. Previtamin-D which comes from the skin is biologically inert and its need two types of hydroxylation to be a biologically active form of Vitamin-D. Previtamin D comes out from plasma membrane, binds with vitamin D binding protein (VDP) and enters into liver via blood circulation where first hydroxylation happen. In the liver by the help of enzyme hepatic hydroxylase previtamin D converted to 25 hydroxy vitamin-D [25 (OH) D]. From liver 25 (OH) D enters into the kidney where second hydroxylations occur. In the kidney 25 hydroxy vitamin-D was converted to 1, 25 dihydroxy vitamin D [1, 25 (OH) 2 D] by the help of enzyme α-hydroxylase. Enzyme hydroxylase was released by the instruction of a gene named CYP27B1 (Cytochrome P450, Family 27, Subfamily B, and Member 1). Vitamin-D which comes as a form of diet is also going through this process to become biologically viable [7,13].

Many journal articles refer that 10 a.m. to 3p.m is the best suitable time to synthesize vitamin D in human body and we can synthesize vitamin D by exposing our arms and feet from 5 minutes to 30 minutes twice in a week during this time schedule mention above [6]

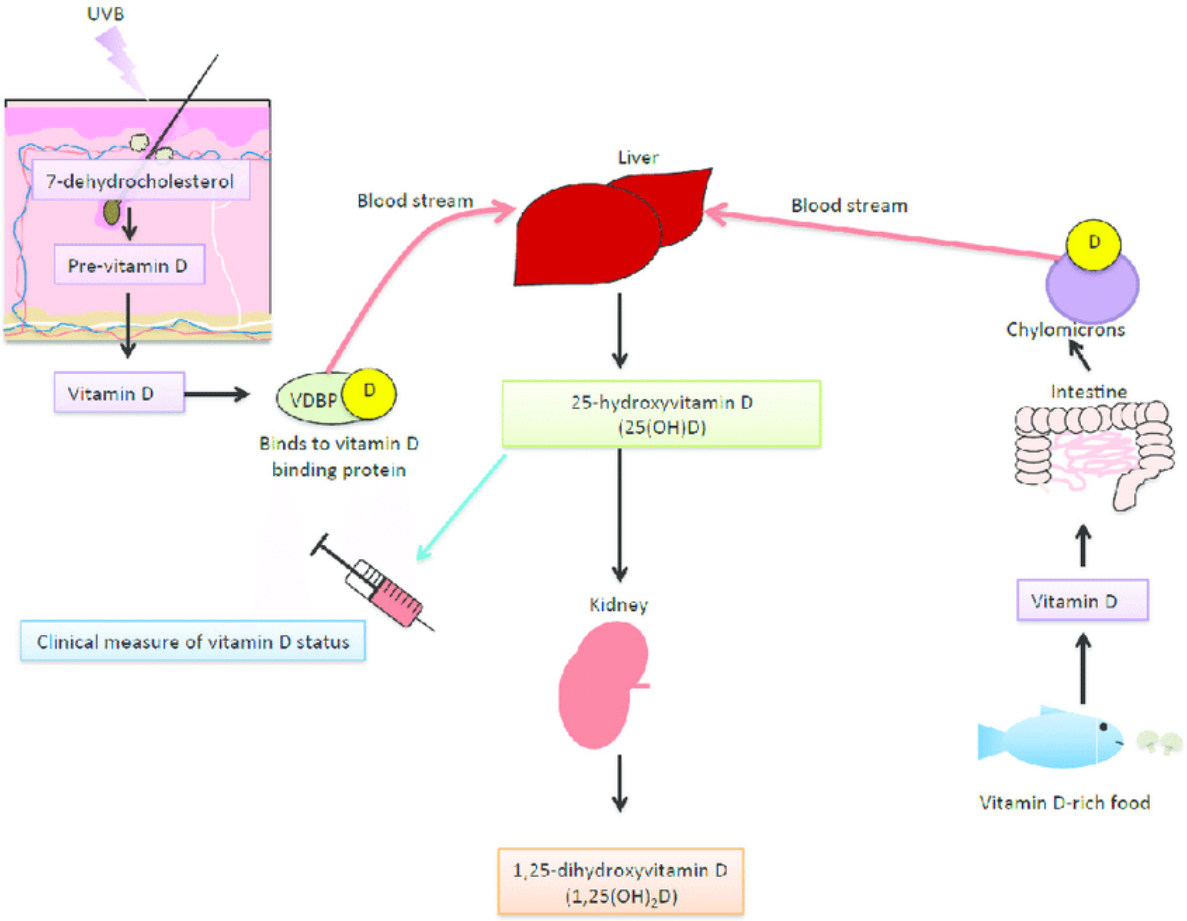

Figure 1: Synthesis of vitamin D in human body.

Physiology of Vitamin-D

Active form of vitamin D [1, 25 dihydroxyvitamin D; {1, 25 (OH) 2 D}] has several anti-inflammatory and immune modulating effects which include endocrine paracrine and autocrine activity. The endocrine effect of vitamin is mainly maintaining calcium and phosphorus homeostasis for bone metabolism. Only 10-15 % of calcium and 60% of phosphorus were absorbed without vitamin-D whereas sufficient levels of vitamin D increase the number about 30-40% calcium and 80 % for phosphorus [5].

Inactive form of Vitamin D has a half-life of about 15 days [25 (OH)D] On the other active form of Vitamin D [1, 25 (OH) 2 D] has a half-life of about only 15 hours but it has a wide range of biological actions. Because of this reason [25 (OH)D] concentration is taken to measure the level

of vitamin D in the human body as it is present much more time in blood serum concentration than [1, 25 (OH) 2 D] [5,7].

Active form of vitamin D [1, 25 (OH) 2 D] circulates much lower concentration at serum level but has higher affinity for vitamin D receptor gene and its local production is responsible for regulating up to 200 genes which has several pleiotropic health benefits, before being converted to biologically inactive calcitroic acid. Vitamin D receptor gene (VDR) is present in most tissues and cells in our body and those takes part in wide range of biological action which include both paracrine and autocrine activity such as inhibiting cellular proliferation and inducing terminal differentiation, suppressing angiogenesis, stimulating insulin production, inhibiting renin production, and activating macrophage cathelicidin production. Regulation of α-hydroxylase which is an essential enzyme for converting previtamin D to vitamin D maintaining various immunological conditions. For example extra renal production 1, 25 dihydroxyvitamin D takes part in the innate immune system against intracellular bacteria. During wounds it increases the production 1, 25 dihydroxyvitamin D by keratinocytes and helps in wound healing. Vitamin D receptor is also found in the brain which helps vitamin D to cross the blood brain barrier but its exact role in brain tissue is still unknown [5,7].

Factors influence on Vitamin D status:

Vitamin D status varies because of several kinds of underlying variables such as sunlight, skin colour, diet, poverty, illiteracy, age etc. Individual sunlight exposure in a region influenced by sunlight availability at that region of the world. Usually countries located in tropical regions have high level of sunlight intensity and availability throughout year compared to subtropical region. Moreover according to fitzpatrick scale people of different ethnicities experience six different types of skin colour (Type I to Type VI) and it differs region to region throughout the world. A

black people need to spend five times longer in sunlight to produce the same amount Vitamin D as a person with white skin. However illiteracy and poverty in together also influence on Vitamin D status because an illiterate person does not had the knowledge about healthy diet and that's why usually they were not much concern about their Vitamin D status. Finally elderly adult person generally does not spend much time in sunlight and they lived with several kinds of comorbidities which influence on their Vitamin D status [5,7,14,15].

Vitamin D deficiency

Serum 25 (OH) D level was considered to measure vitamin D level in the human body and previously the cut off values varied from study to study which was conducted by many researchers. Previously few Indian studies define vitamin D deficiency (VDD) as serum level <10 ng/ml or <25nmol/l and vitamin D insufficiency was defined by serum level within 10-20ng/ml or 25-35 nmol/l [16,17]. Some studies also define vitamin D deficiency at serum level below 37.5 nmol/l or 15 ng/ml [18]. But now a days it is well established that serum concentration of 25(OH) D level <20 ng/ml or 50 nmol/l define as deficiency and insufficiency is defined by 25(OH) D level 21-29 ng/ml or <75nmol/l [19] Because of vitamin D deficiency many health related complexion is started which include several polygenic and infectious disease.

Disease causes because of Vitamin D deficiency

Vitamin D may act in determining mortality because of its anti-inflammatory and immune modulating effects. Studies suggest that it acts as a factor both in several kinds of noninfectious and infectious disease. Few observational and randomized trial show a mountain of evidence that law level of vitamin D is act as a responsible causing factor in cardiovascular disease, colon

cancer and breast cancer, diabetes, autoimmune disease, Osteoporosis, influenza, bacterial vaginosis, tuberculosis, autoimmune disease, Parkinson's disease etc. [20]

Non Infectious disease:

Vitamin D receptors are present in the cardiac system and maintain renin-angiotensin hormone system, inhibit excessive proliferation in cardiomyocytes. Framingham study suggests that people with lower concentration vitamin D (<15 ng/ml) increase the risk of heart disease at about 60 %.

Vitamin D inhibits cellular proliferation and promotes terminal differentiation which in result stopping growth of new blood vessels. This kind of anti-inflammatory effects has a role in suppressing different kinds of cancer and studies suggest that people with low concentration of vitamin D are at high risk of developing colon cancer and breast cancer.

Several randomized trials show substantial evidence that low vitamin D may be responsible for developing type 1 diabetes in children and type to diabetes in older adults. This may happen because 1, 25 dihydroxyvitamin D acts as a positive regulator of secreting insulin from pancreas β cells and pancreas cells are associated with CYP27B1 activity. So low serum concentration of 25 (OH) D may be responsible for impaired β cells function.

The main function of vitamin D is maintaining calcium phosphorus absorption in our body and its deficiency can cause various bone related diseases. Studies suggest that low concentration of vitamin D is responsible for osteoporosis, fracture and falls in adults, rheumatoid arthritis, rickets etc [5,8,21].

Infectious disease and autoimmune disease:

Besides those noninfectious diseases vitamin D deficiency can also cause a few infectious diseases and autoimmune disease like bacterial vaginosis, influenza, Parkinson's disease, age related macular degeneration, multiple sclerosis, tuberculosis etc.

Data from a national health and nutrition examination survey show that pregnant women with low levels of vitamin D are at risk of 3 times higher to develop bacterial vaginosis. Because low concentration of vitamin D inhibits the innate immune system properly against pathogenic bacteria. A study conducted on white people shows that sufficient amounts of vitamin D decrease the risk at about 62 % to develop multiple sclerosis. A Japanese randomized trial shows that children supplemented with vitamin D decrease the rate at about 40 % to develop influenza. Studies suggest that higher levels of vitamin D are associated with diminishing the chance of acquiring age-related macular degeneration in women who are younger than 75 years. A cohort study based on mini Finland health surveys show that inadequate levels of vitamin D may act as a responsible factor for pathogenesis of Parkinson's disease which is the major cause of disability in elder population. A review study which included more than 150 studies by Ludovica Facchini et al found that there has been a significant association between low vitamin D levels and susceptibility to mycobacterium tuberculosis or TB infection [5–7,22].

Group of people at risk of Vitamin D deficiency

Sunlight is the most abundant natural source of vitamin D for human beings. So people who have less exposure to sunlight or who are sensitive to sunlight exposure are at risk of getting affected with vitamin D deficiency. Generally breast fed infants do not spend much time in sunlight at pick time (10a.m to 3p.m) of vitamin D synthesis. They usually fully fill their need of vitamin D from mother milk but studies show that human milk provides only <25 IU/L to 78 IU/L vitamin D and level of vitamin D in human milk is proportional to mothers vitamin D status. American

association of pediatricians recommended that a breastfeed infant should be supplemented with 400 IU/L vitamin D per day. Besides breast feeding infants, older adults are also at risk of developing vitamin D deficiency as most of them prefer spending much time indoors or avoid getting exposed to sunlight. However, sometimes the skin of older adults is not effectively synthesizing vitamin D because of aging. So they need supplementation of vitamin D [5,6].

People who are indoor employees and do not get time to be exposed to sunlight are also at risk of growing vitamin D deficiency if they don't take supplements. Black people need to spend more time in sunlight then do white people as they absorb more UVB light in the melanin of their skin. Since vitamin D is a fat soluble prohormone, it needs fat in the gut for absorption. So people who are suffering from fat malabsorption or certain kinds of medical conditions such as liver disease, kidney disease, and cystic fibrosis are also at risk of growing vitamin D deficiency. People who are using sun protection cream in sunlight which reduces UVB penetration in the scene are too at risk of getting affected with vitamin D deficiency [5].

Endocrine society of clinical practice (ESCP) suggests that children and adults need 10000IU/D units of Vitamin D to correct vitamin D deficiency. So if people who are suffering with vitamin D deficiency they need to take this amount of vitamin D as supplement or diet or from sunlight exposure to get rid of vitamin D deficiency [5].

Global picture of vitamin D deficiency

Approximately 50% of the world population now have vitamin D insufficiency and around 1 billion people worldwide are now affected with vitamin D deficiency [6]. This kind of data indicates alarming evidence that vitamin D deficiency is now becoming pandemic for the 21st century, since its deficiency acts as an important factor to develop various kinds of chronic medical conditions such as cardiovascular disease, various types of malignancy in human beings. Study reports show that prevalence of Vitamin-D deficiency was 42% in Europe, 33% in the

U.S.A, 35% in Iran, 81% in Saudi Arabia and in Korea it was 68%. High prevalence >70% has been observed in Asian countries [23]. So it is clear that not only developing countries but also various developed countries are also affected with vitamin D deficiency. A systematic review published in 2014 which conducted on worldwide population to assess the vitamin D status. This systematic review consisted 195 peer reviewed journal articles which covered most of the countries in the world observe that 88.1% of study samples had mean serum 25 (OH) D level below 30ng/ml or 75nmol/l and 37.1% of study samples had mean value of serum 25 (OH) D below 50nmol/l or 20ng/ml [24]. Beside this a meta-analysis published in 2007 which includes articles only on randomized control trials to see the effect of vitamin D supplementation on mortality. Their study data included 57311 participants and they found that taking ordinary doses of vitamin D as supplements seems to have an association with decreasing total mortality rates [8]. From the above discussion it's indicating that the global picture of vitamin D deficiency is quite alarming but still in many developed and developing countries people are not much aware of vitamin D deficiency. Sometimes data regarding vitamin D is not available in many countries. For example a meta-analysis conducted in low middle income countries revealed that there are 54 countries where no published study regarding vitamin D is available for inclusion in meta-analysis [25]. A knowledge attitude and practice based study (KAPs study) conducted among health care professionals in Riyadh, Saudi Arabia found that there is a gap in knowledge and practice among primary health care physicians about vitamin D [26]. A Chinese KAPs study on University students showed that below 50% of students have correct knowledge about vitamin D, 82.7% of students using sunscreen [27].

South Asia

South Asia is located in the southern region of Asia which consists of sub Himalayan countries and these countries are Bangladesh, India, Pakistan, Nepal, Bhutan, Maldives, Sri Lanka and Afghanistan. These eight nations belong to an intergovernmental institution which act as a geopolitical union of state for south Asian countries called SAARC.

Figure 2: Map of south Asia

Together South Asian countries cover up 5131.1 thousand square kilometers area and have around 1.8 billion population which is over 24% of total world population. This makes it the most densely populated region in the world. Physiologically and culturally people of this region have some common characteristics [28–30].

South Asian Scenario of Vitamin D deficiency

In south Asia several kinds of study are conducted regarding vitamin D which includes cross sectional, case control, randomized control trial, observational cohort, hospital based or community based, awareness based and more than half of these studies are conducted in India. Then come Pakistan, Bangladesh, Nepal and Afghanistan respectively. Bhutan and Maldives are two south Asian country which have no published literature about vitamin D. These studies covered all groups of population, starting from neonates to older adults and the maximum of these studies were conducted on adult women and men, newborn infants, pregnant women, postpartum mothers, premenopausal or post-menopausal women and teenagers. These study results indicate that vitamin D status in south Asian countries is not so good. For example, A hospital based Indian study which conducted for three years from 2011-2014 among all age groups of population with a sample size of near about 25000 showed that the 59% of study population had vitamin D deficiency and 69% of them were male and 31 % of them were female [31]. On the other hand a community based cross sectional study reported that 96% of Afghani children were Vitamin D deficient with a mean 5 ng/ml [32]. Moreover, a community based cross sectional study conducted on rural and urban Pakistani pregnant women, showed that 97% of study participants were Vitamin D deficient with a mean 8 ng/ml [33]. In Bangladesh, a case control study among working women showed that 100% of indoor workers had vitamin D deficiency [34].

Beside those observational studies few awareness based studies also suggested that people in south Asia are not much concerned about the effect of vitamin D deficiency. A study from Bangladesh concluded that there is a lack of knowledge in undergraduate pharmacy students and the scenario might be worse for general students [35]. An Indian study also concluded almost similarly with an extra point that students had a negative approach towards direct exposure to sunlight [36].

Purpose of study

From the discussion in literature review it is clear that vitamin D deficiency is now becoming a global phenomenon. Vitamin D status of people living in south Asia is not so good. Moreover, knowledge and attitude towards sunlight and vitamin D is not convincing among students living in different south Asian countries.

In this study our purpose is to see the image of vitamin D deficiency among the South Asian population by the help of a systematic review and meta-analysis. We also want to evaluate the knowledge, attitude and practice (KAP) regarding vitamin D and sunlight among Bangladeshi students and doctors. We think findings of this study will help to give a complete picture about vitamin D deficiency in this region among all groups of population. Beside this it will also help to create an awareness among Bangladeshi population regarding vitamin D, it's important and negative effect of its deficiency.

Objective

In this study our primary objective is to see the "prevalence of Vitamin D deficiency among apparently healthy south Asian populations by a systematic review and meta-analysis". Secondly we also check the knowledge, Attitude and Practice (KAP) regarding vitamin D and sunlight among Bangladeshi college, university and medical students and also among health care professionals or doctors.

Hypothesis

We assume that pooled prevalence will show a high percentage of vitamin D deficiency among the South Asian population. KAPs study will evaluate that Bangladeshi students and healthcare professionals have significant lack of knowledge, negative attitude and practice towards vitamin D and sunlight.

Chapter 1:

Systematic review and meta-analysis of Vitamin-D deficiency among south Asian population.

From our review of literature it is clear that Vitamin D deficiency is prevalent in South Asian countries. However individual study reports on people living in south Asian countries does not show a complete picture of this region. For example, in Sri Lanka, a community-based analysis of adults found that 48 per cent of their study participants were deficient in vitamin D. However, a community-based study of Pakistani adults showed that 89 % of their study participants had deficient vitamin-D [37,38]. On the other hand, a community-based analysis of pregnant women in Bangladesh found that 64 % of participants in their study were deficient in vitamin D. But a related study in Pakistani pregnant women recorded that 97 % of their study participants had a

deficiency in vitamin D [33,39]. Moreover, a community-based study on Nepali children who were above six years of age reported that 17% of their study participants were vitamin D deficient. But a similar kind of study in Indian children reported that 92% of their study participants had vitamin-D deficiency [40,41].

Sufficient systematic review on the South Asian population regarding prevalence of Vitamin-D deficiency are rarely present in these regions. A systematic review and meta-analysis is a kind of research analysis which presents results through the combination and analysis of data from various studies on similar research topics [42]. In our literature search we found only three systematic reviews which were conducted with a limited number of sample sizes and does not include people from other south Asian countries except India and Pakistan. So a thorough systematic review is necessary to understand the underlying variables and adopting appropriate national policies in this region regarding Vitamin D deficiency. In this regard, we perform a systematic review and meta-analysis on the prevalence of vitamin D deficiency among the South Asian population.

Methodology:

We used recommendations and guidelines provided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P 2015) to conduct this study [43].

Search strategy:

PubMed (basic and advanced), Scopus, Google Scholar were three main electronic search engines used in this study. (After being logged off from all Google accounts to avoid customized results). These three databases were independently explored by two researchers from 20 October, 2019 to 21st January 2020. The following MeSH terms were used for literature search:

Table 1: Search strategy for literature search

PubMed	Scopus	Google Scholar
• ("Vitamin D Deficiency"[MeSH]) AND Bangladesh[MeSH] AND pregnant women [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND pregnant women [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Children [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Prevalence [MeSH] AND Children [MeSH] • ("Vitamin D Deficiency"[MeSH]) AND Bangladesh[MeSH] AND Neonates [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Neonates [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Prevalence [MeSH] AND Neonates [MeSH] • ("Vitamin D Deficiency"[MeSH]) AND Bangladesh[MeSH] AND Infants[MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Infants [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Prevalence [MeSH] AND Children [MeSH] • ("Vitamin D Deficiency"[MeSH]) AND Bangladesh[MeSH] AND Newborn [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Newborn [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Prevalence [MeSH] AND Newborn [MeSH]	• (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(Pregnant women)) OR (INDEXTERMS("Vitamin D") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(Pregnant women)) OR (TITLE-ABS-KEY("Prevalence") AND (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Pregnant women)) • (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(Children)) OR (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Children)) OR INDEXTERMS(prevalence)) AND (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Children)) • (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(Neonates)) OR (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Neonates)) OR INDEXTERMS(prevalence)) AND (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Neonates)) • (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(Infants)) OR (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Infants)) OR INDEXTERMS(prevalence)) AND (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Infants))	• (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (Bangladesh) AND (Pregnant women) • (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (Bangladesh) AND Children • (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (Bangladesh) AND Newborn • (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (Bangladesh) AND Neonates • (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (Bangladesh) AND Infants • (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (Bangladesh) AND Pediatrics

PubMed	Scopus	Google Scholar
• ("Vitamin D Deficiency"[MeSH]) AND Bangladesh[MeSH] AND Adolescents [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND	• (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(Pediatrics)) OR (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Pediatrics)) OR INDEXTERMS(prevalence)) AND (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-	• (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND

Adolescents [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Prevalence [MeSH] AND Adolescents [MeSH] • ("Vitamin D Deficiency"[MeSH]) AND Bangladesh[MeSH] AND Pediatrics [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Pediatrics [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Prevalence [MeSH] AND Pediatrics [MeSH] • ("Vitamin D Deficiency"[MeSH]) AND Bangladesh[MeSH] AND healthy adults [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND healthy adults [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Prevalence [MeSH] AND healthy adults [MeSH] • ("Vitamin D Deficiency"[MeSH]) AND Bangladesh[MeSH] AND young adults[MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Prevalence [MeSH] AND young adults [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND young adults [MeSH] • ("Vitamin D Deficiency"[MeSH]) AND Bangladesh[MeSH] AND adults Males [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND adult Males [MeSH • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Prevalence [MeSH] AND adult Males [MeSH]	KEY(Pediatrics)) • (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(Newborn)) OR (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Newborn)) OR INDEXTERMS(prevalence)) AND (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Newborn)) • (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(Adolescents)) OR (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Adolescents)) OR INDEXTERMS(prevalence)) AND (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Adolescents)) • (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(Healthy adults)) OR (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Healthy adults)) OR INDEXTERMS ("Vitamin D") AND INDEXTERMS(BANGLADESH) AND TITLE-ABS-KEY (Prevalence) AND TITLE-ABS-KEY (Healthy adults) • (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(Young adults)) OR (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Young adults)) OR INDEXTERMS ("Vitamin D") AND INDEXTERMS(BANGLADESH) AND TITLE-ABS-KEY (Prevalence) AND TITLE-ABS-KEY (Young adults) • (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(adult Males)) OR (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(adult Males)) OR INDEXTERMS ("Vitamin D") AND INDEXTERMS(BANGLADESH) AND TITLE-ABS-KEY (Prevalence) AND TITLE-ABS-KEY (adult Males)	(Bangladesh) AND Adolescents • (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (healthy adults) AND (Bangladesh) • (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (young adults) AND (Bangladesh) • (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (elderly) AND (Bangladesh) • (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (adult Males) AND (Bangladesh) • (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (adult Females) AND (Bangladesh)
PubMed	**Scopus**	**Google Scholar**
• ("Vitamin D Deficiency"[MeSH]) AND Bangladesh[MeSH] AND adults Females [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND adult Females [MeSH • ("Vitamin D"[MeSH]) AND	• (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(adult Females)) OR (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(adult Females)) OR INDEXTERMS ("Vitamin D") AND INDEXTERMS(BANGLADESH) AND TITLE-ABS-KEY (Prevalence) AND TITLE-ABS-	• (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (Premenopausal

Bangladesh[MeSH] AND Prevalence [MeSH] AND adult Females [MeSH] • ("Vitamin D Deficiency"[MeSH]) AND Bangladesh[MeSH] AND Premenopausal women [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Premenopausal women [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Prevalence [MeSH] AND Premenopausal women [MeSH] • ("Vitamin D Deficiency"[MeSH]) AND Bangladesh[MeSH] AND Postmenopausal women [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Postmenopausal women [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Prevalence [MeSH] AND Postmenopausal women [MeSH] • ("Vitamin D Deficiency"[MeSH]) AND Bangladesh[MeSH] AND Lactating women [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Lactating women [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Prevalence [MeSH] AND Lactating women [MeSH] • ("Vitamin D Deficiency"[MeSH]) AND Bangladesh[MeSH] AND Elderly[MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Elderly [MeSH] • ("Vitamin D"[MeSH]) AND Bangladesh[MeSH] AND Prevalence [MeSH] AND Elderly [MeSH]	KEY (adult Females) • (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(Premenopausal women)) OR (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Premenopausal women)) OR INDEXTERMS ("Vitamin D") AND INDEXTERMS(BANGLADESH) AND TITLE-ABS-KEY (Prevalence) AND TITLE-ABS-KEY (Premenopausal women) • (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(Postmenopausal women)) OR (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Postmenopausal women)) OR INDEXTERMS ("Vitamin D") AND INDEXTERMS(BANGLADESH) AND TITLE-ABS-KEY (Prevalence) AND TITLE-ABS-KEY (Postmenopausal women) • (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(lactating women)) OR (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(lactating women)) OR INDEXTERMS ("Vitamin D") AND INDEXTERMS(BANGLADESH) AND TITLE-ABS-KEY (Prevalence) AND TITLE-ABS-KEY (Lactating women) • (INDEXTERMS("Vitamin D Deficiency") AND INDEXTERMS(BANGLADESH) AND INDEXTERMS(Elderly)) OR (TITLE-ABS-KEY("Vitamin D") AND TITLE-ABS-KEY(BANGLADESH) AND TITLE-ABS-KEY(Elderly)) OR INDEXTERMS ("Vitamin D") AND INDEXTERMS(BANGLADESH) AND TITLE-ABS-KEY (Prevalence) AND TITLE-ABS-KEY (Elderly)	women) AND (Bangladesh) • (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (Postmenopausal women) AND (Bangladesh) • (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (Lactating women) AND (Bangladesh) • (("Vitamin D") OR ("Vitamin D3")) AND ((prevalence) OR (deficiency)) AND (Elderly) AND (Bangladesh)

Same types of search terms was used for all other seven South Asian countries to complete search procedure

The search was repeated with the following alternative terms: '25(OH) D', '25-hydroxy vitamin D', 'sunshine vitamin', 'insufficiency', 'frequency', and their Bengali equivalents to minimize the chance of exclusion of relevant studies.Later, to identify any studies that were not published

online (or, not indexed in any of the sources listed above) the reference lists for all articles deemed relevant were explored.

Searches were conducted in English. The personal profiles (in current organizations of the authors if found after Google search) available online as well as their profiles on Google Scholar, Research Gate, and Orchid were further explored for information on ongoing and unpublished works.

To ensure inclusion of grey literature in this review, online archives of newspapers, government reports and published abstracts (in printed version) from conferences held in South Asian countries were also explored for relevant literature. Finally, scholars, doctors, and experts in the field of biomedical research were consulted for their knowledge on published/unpublished studies/reports relevant to vitamin D deficiency in south Asian countries.

Study selection/inclusion criteria:

The criteria applied to for inclusion of the studies were:

(1) Original studies conducted in South Asian Countries (Bangladesh, India, Pakistan, Nepal, Bhutan, Maldives, Sri Lanka and Afghanistan)

(3) Studies which conducted on apparently healthy individuals regarding all age groups both in community level and hospital level.

(4) In case of hospital based studies people come with minor illness or for normal health checkup and whose physical condition were not related to any chronic disease.

(5) Observational study such as cross sectional, cohort, case control studies, randomized controlled trial, studies design with baseline information on vitamin D levels irrespective of age, gender, occupation, or socioeconomic grouping studies estimating prevalence of vitamin D deficiency of South Asian population

(6) In case of randomized trial we take the placebo data where baseline data is not available.

(7) Studies conducted from 1st January 2001 until 31st December 2019.

Exclusion criteria:

The criteria applied to for exclusion of the studies were

1. Previously the minimal sample size considered for this kind of systematic review was 30 and 50 [44,45]. To minimize the risk of potential bias, we consider minimal sample size 50 for our study. We exclude studies with sample size <50.
2. Studies reporting vitamin D after any kind of intervention or supplementation was excluded.
3. Studies that reported prevalence of vitamin D deficiency associated to any kind of disease such as chronic kidney, liver and heart disease, Cancer, Diarrhea, Anemia, Diabetes or disease related to any coexisting morbidity such as body aches and pain, Proximal muscle weakness, Osteoporosis or other bone related disease were excluded from this study.
4. Studies which conducted on special population such as people with short stature or mentally retarded were also excluded.
5. Studies which did not show Vitamin D status with mean, standard deviation and prevalence of deficiency or insufficiency.
6. Review article, editorial article, letter to the editor without original text.
7. Studies which satisfied selection criteria but full-text could not be obtained from the authors after request were excluded.

Mendeley Desktop software was used to manage the references and to avoid duplications.

Data extraction:

In this review, deficiency of vitamin D is defined by the serum concentration of 25(OH) D level <20 ng/ml and [19] Where values of 25(OH)D were presented in nanomol per liter (nmol/L) unit, they were converted to nanogram per milliliter (nM/L) by dividing with 2.5 (according to international system of unit conversion).

As prevalence of vitamin D deficiency in South Asian countries comprised the outcome of interest of this study, Prevalence, mean, and standard deviation of vitamin D was extracted after the selected articles were read in full. Information on external components of studies (first author's name, year of publication, study design, country, and location) and internal associated variables (age, sex, and socioeconomic status, rural/ urban) of the participants were also extracted. A standardized sheet was used for data extraction of the selected articles that met eligibility criteria.

Evaluation of study quality

Risk of bias for the selected articles was determined (as low, moderate, and high) using the checklist of 10 criteria validated by Hoy et al. [46]. The ten criteria considered for this evaluation were- (i) if the target population of the study representative of national population, (ii) if the sampling frame was representative of the national population, (iii) if census or random selection was used during selection of respondents, (iv) if the chance of non-response bias was minimal, (v) if data was collected directly from subjects, (vi) if accepted case definition was used in the study, (vii) if the assay methods were reliable, (viii) if data collection mode was uniform for all subjects, (ix) if the length of the shortest prevalence period appropriate, (x) if numerator(s) and denominator(s) were appropriate for the parameter of interest. Finally, Cochrane standards (Higgins and Altman, 2008) were followed to categorize the overall study quality into three groups; *low risk* (all 10 criteria presenting low risk), *moderate risk* (at least two criteria showing high risk), and *high risk* (more than two criteria showing high risk). If studies full fill these criteria score 0 which means low risk of bias and if studies did not full fill these criteria then score 1 which means high risk of bias. Risk of bias was assessed for all original articles.

Statistical analysis

Mean, standard deviation and prevalence of vitamin D deficiency in South Asian countries were considered as summary measurement. The weighted pooled prevalence with 95% confidence interval was obtained by using a Random-effects model [48]. Heterogeneity was determined using Cochran's Q test and the I^2 statistics. Country wise and gender wise analysis was also conducted according to the vitamin D deficient participants. Substantial heterogeneity was indicated with an I^2 more than 75% [49]. All statistical analyses were conducted by Stata version 15 (Stata Corp, College Station, TX) using the metaprop, metabias, metafunnel commands.

Result:

A total of 4085 study articles were retrieved from these three databases by using search strategy which describe above. Among these 4085 studies 3959 study articles were excluded because of being unable to fully fill our inclusion criteria. Finally 126 study articles were selected for our study. Among these 126 study articles 10 from Bangladesh, 83 from India, 23 from Pakistan, 5 from Nepal, 4 from Sri Lanka and 1 from Afghanistan. No studies were found from Bhutan and Maldives regarding Vitamin D status. Study article selection process is shown in (Figure 1). A summary outlining the features of selected studies was available in (Table 1). Google map displays country wise locations for our selected studies (Figure 2).

Out of 126 studies, almost half of the studies (60) studies did not mention the demographic area for study population. Half of the studies were hospital based (63 out of 126) and rest of them were community based. Socio economic status for the study population was not mentioned in most of the studies (76 out of 126). Maximum number of study designs was cross sectional (96 out of 126), 18 studies were case control and the rest of them were randomized control trials. Several kinds of measurement methods were used to determine vitamin D status like ELISA (Enzyme linked Immunosorbent assay) RIA (Radioimmunoassay), Chemiluminescent Immunoassay (CLIA), Chemiluminescent Microparticle Immunoassay (CLMA), HPLC (High

performance liquid chromatography), Electrochemiluminescent immunoassay etc. Among these RIA and ELISA was mostly used (60 out of 126). Only six studies did not mention any name about their procedure of vitamin D estimation method.

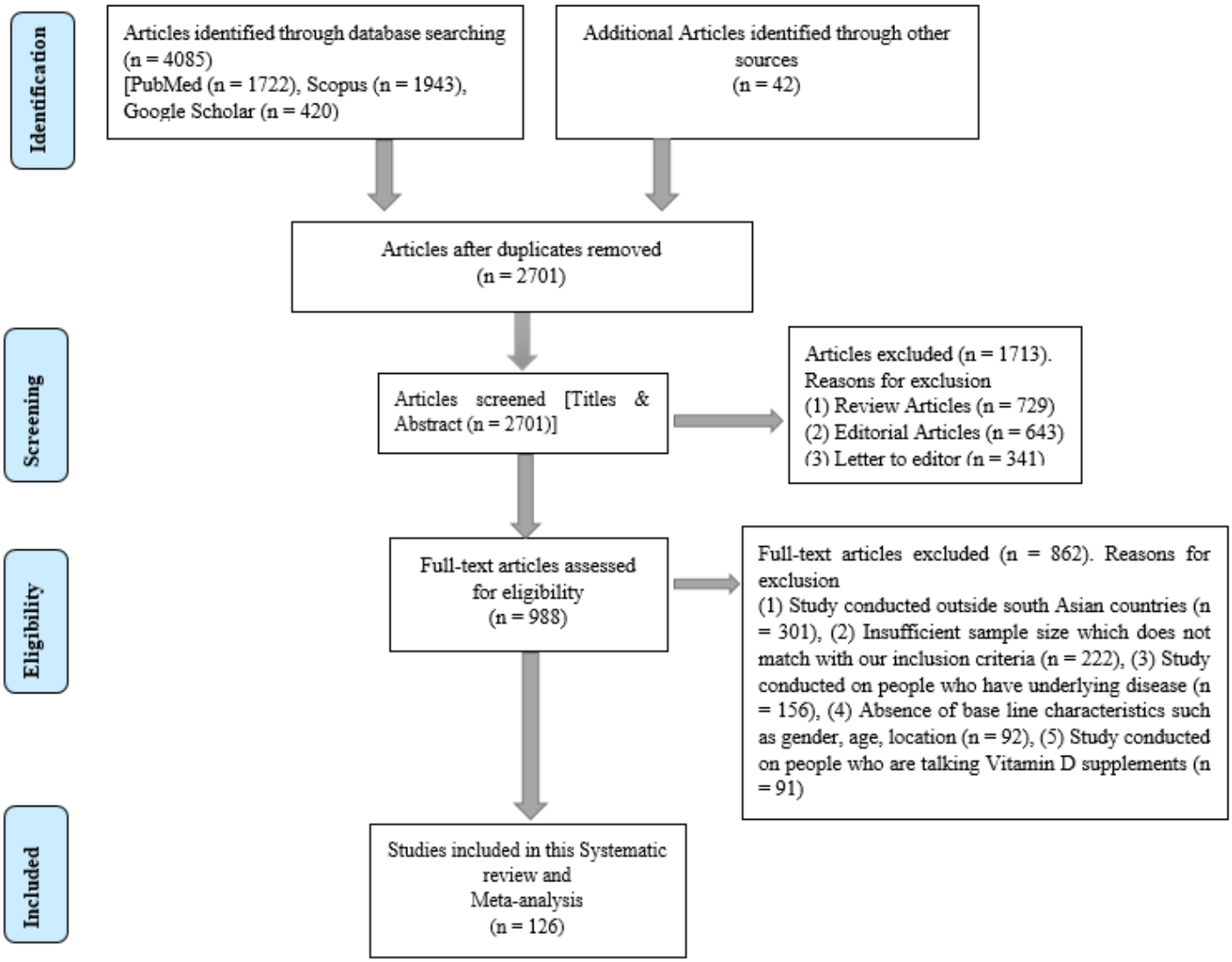

Figure 1: PRISMA chart showing the summary of search result and selection of studies for final analysis

Table 2: Characteristics of selected study articles

Authors	Year	Country	Study Area (Urban / Rural)	Study design	Age	Gender	Socio Economic status	Vitamin D estimation method	S S (I
Jiang et al [50]	2005	Nepal	Rural	Community - RCT	Mean age 23.6 years	Female	NM	Immunoassay	1
Ullah et al [51]	2013	Bangladesh	Urban	Hospital - CC	Mean age 21.5 years	Female	NM	ECLIA	7
Schulze et al [52]	2019	Bangladesh	Rural	Community - RCT	Mean age 23 years	Female	Both	Immunoassay	1
Roth et al [53]	2013	Bangladesh	Urban	Community - RCT	18 - 35 years	Female	NM	HPLC-MS	1
Roth et al [39]	2018	Bangladesh	NM	Hospital - RCT	NM	Female	Both	AFBM	1
Anwar et al [33]	2015	Pakistan	Both	Community - CS	18 - 40 years	Female	Lower	CLIA	2
Khan et al [54]	2016	Pakistan	NM	Community -RCT	Mean age 27 years	Female	NM	CLIA	8
Karim et al [55]	2010	Pakistan	NM	Hospital - CS	Mean age 28.1 years	Female	Both	NM	5
Sahu et al [56]	2008	India	Rural	Community - CS	Mean age 26.7 years	Female	Lower	RIA	1
Sachan et al [57]	2005	India	Both	Hospital – CS	Mean age 24 years	Female	Both	RIA	1
Ajmani et al [58]	2015	India	NM	Hospital – CS	18 - 40 years	Female	Both	ELISA	2
Sheetal et al [59]	2015	India	NM	Hospital – CS	Mean age 23 years	Female	Both	ELISA	4
Sudhanshu et al [60]	2016	India	Rural	Community - CS	NM	Female	Lower	RIA	1
Taru et al [61]	2015	India	NM	Hospital - CC	NM	Female	NM	NM	5
Krishnaveni et al [62]	2011	India	NM	Hospital - CS	NM	Female	Both	RIA	5
Singla et al [63]	2014	India	Both	Hospital - CC	Mean age 25. 1 years	Female	NM	ELISA	1
Sahu et al [64]	2009	India	Rural	Community - CS	NM	Female	Lower	RIA	1
Sharma et al [65]	2019	India	Both	Community - CS	Mean age 26.7 years	Female	NM	CLIA	1
Nagendra et al [66]	2018	India	NM	Hospital - RCT	18 - 35 years	Female	NM	CMIA	5
Marwaha et al [67]	2011	India	NM	Hospital - CS	19 - 30 years	Female	Lower	RIA	5
Schulze et al [40]	2014	Nepal	Rural	Community - RCT	6 - 8 years	Both	NM	CIA	1
Marwaha et al [68]	2005	India	Urban	Community - CS	10 - 18 years	Both	Both	RIA	5
Sahu et al [56]	2008	India	Rural	Community - CS	10 - 20 years	Both	Lower	RIA	1
Mandlik et al [69]	2018	India	Rural	Community - CS	6 - 12 years	Both	NM	ELISA	3
Kapil et al [70]	2017	India	NM	Community - CS	6 - 18 years	Both	Both	CLIA	6
Basu et al [71]*	2014	India	Both	Hospital - CS	6 - 16 years	Both	NM	CLIA	1
Puri et al [72]	2007	India	NM	Community - CS	6 - 18 years	Girls	Both	RIA	4
Kadam et al [73]	2011	India	NM	Community - CS	8 - 12 years	Girls	Lower	RIA	2
Khadgawat et al [41]	2013	India	NM	Community - RCT	10 - 14 years	Both	NM	CLIA	7
Chaudhuri et al [74]	2016	India	NM	Hospital - CC	8 - 18 years	Both	NM	CMIA	5
Sharawat et al [75]	2019	India	Rural	Community - CS	5 - 10 years	Both	Lower	IRMA	1
Marwaha et al [76]	2015	India	NM	Community - CS	10 - 15 years	Both	NM	CLIA	2
Sarma et al [77]	2019	India	Both	Community - CS	8 - 14 years	Both	NM	RIA	5
Sanwalka et al [78]	2012	India	NM	Community - CS	15 - 18 years	Girls	NM	RIA	1
Mandlik et al [79]	2017	India	Rural	Community - RCT	6 - 12 years	Both	NM	ELISA	1
Borker et al [80]	2009	India	NM	Hospital - CC	6 - 12 years	Both	NM	HPLC	5
Garg et al [81]	2013	India	Urban	Community - CS	Mean age 14 years	Both	NM	RIA	1
Khadilkar et al [82]	2012	India	NM	Community - CS	8 - 12 years	Girls	Lower	RIA	2
Patel et al [83]	2015	India	NM	Community - CS	10 - 14 years	Both	Both	CMIA	1
Marwaha et al [84]	2017	India	NM	Community - CS	6 - 18 years	Girls	NM	CLIA	8

Table (Continued): Characteristics of selected study articles

Authors	Year	Country	Study Area (Urban / Rural)	Study design	Age	Gender	Socio Economic status	Vitamin D estimation method	Sam Size (N)
Holland et al [32]	2007	Afghanistan	NM	Community - CS	0.5 - 5 years	Both	NM	HPLC	107
Marasinghe et al [85]	2015	Sri Lanka	Urban	Community - CS	2 - 5 years	Both	NM	CLIA	340
Hettiarachchi et al [86]	2010	Sri Lanka	NM	Hospital - CS	3 - 5 years	Both	NM	IRMA	248
Hettiarachchi et al [87]	2011	Sri Lanka	NM	Hospital - CS	3 - 5 years	Both	NM	IRMA	105
Haugen et al [88]	2016	Nepal	Urban	Community - CS	1 - 12 months	Both	NM	LCMS	466
Avagyan et al [89]	2015	Nepal	Rural	Community - CS	1 year - 5 years	Both	NM	LCMS	280
Ahmed et al [90]	2015	Bangladesh	Urban	Community - CS	0.5 - 2 years	Both	Both	EIA	913

Anwar et al[33]	2015	Pakistan	Both	Community - CS	NM	Both	Lower	CLIA	227
Karim et al [55]	2010	Pakistan	NM	Hospital - CS	NM	Both	Both	NM	50
Prasad et al[91]	2016	India	NM	Hospital - CC	< 3 years	Both	NM	ELISA	61
Agarwal et al[92]	2012	India	NM	Hospital - CS	Not mention	Both	NM	RIA	336
Basu et al [71]	2014	India	Both	Hospital - CS	1 - 16 years	Both	Lower	CLIA	156
Wayse et al[93]	2003	India	NM	Hospital - CC	2 month - 5 years	Both	Middle	RIA	70
Filteau et al [94]	2015	India	NM	Community - CS	Mean age 5 years	Both	Lower	RIA	902
Taru et al [61]	2015	India	NM	Hospital - CC	NM	Both	NM	NM	50
Sreedharan et al [95]	2018	India	NM	Hospital - CC	2 - 13 years	Both	NM	ELISA	109
Agarwal et al [96]	2010	India	Urban	Hospital - CS	10 weeks	Both	Lower	RIA	97
Mathur et al [97]	2016	India	NM	Hospital - RCT	Not mention	Both	NM	ECLIA	50
Kumar et al [98]	2011	India	NM	Hospital - RCT	6 months	Both	NM	RIA	237
Marwaha et al[67]	2011	India	NM	Hospital - CS	6 weeks	Both	Lower	RIA	342
Agrawal et al[99]	2019	India	Both	Hospital -CC	3 days - 21 days	Both	NM	CLIA	50
Shukla et al[31]	2016	India	NM	Hospital - CS	Less than 20 years	Both	NM	ECLIA	73
Meyer et al [37]	2007	Sri Lanka	Urban	Community - CS	30 - 60 years	Both	NM	RIA	196
Haugen et al[88]	2016	Nepal	Urban	Community - CS	17 - 44 years	Female	NM	LCMS	500
Sherchand et al[100]	2018	Nepal	NM	Hospital – CS	18 years or above	Both	NM	CLIA	300
Mahmood et al[34]	2017	Bangladesh	Both	Community - CC	20 - 40 years	Female	Lower	CMIA	80
Islam et al[101]	2007	Bangladesh	Urban	Community - CS	18 - 36 years	Female	Lower	EIA	200
Islam et al[102]	2006	Bangladesh	Urban	Community - CS	18 - 60 years	Female	NM	RIA	66
Islam et al[103]	2002	Bangladesh	Both	Community - CS	16 - 40 years	Female	Both	RIA	189
Acherjya et al[104]	2019	Bangladesh	Both	Hospital – CS	10 - 70 years	Both	NM	RAIA	160
Mubashir et al[105]	2017	Pakistan	NM	Hospital – CC	20 - 70 years	Both	NM	AMK	345
Junaid et al[106]	2016	Pakistan	NM	Hospital – CC	15 - 56 years	Both	Both	ELISA	112
Roomi et al[107]	2015	Pakistan	NM	Hospital – CS	18 - 40 years	Both	Both	EIA	88
Junaid et al[108]	2015	Pakistan	NM	Community - CS	15 - 50 years	Female	Both	EIA	215
Sheikh et al[109]	2012	Pakistan	Urban	Community - CS	30 - 80 years	Both	Both	RIA	300
Mehboobali et al[110]	2015	Pakistan	NM	Community - CS	18 - 60 years	Both	Lower	ECLIA	858
Mansoor et al[111]	2010	Pakistan	Urban	Hospital – CS	20 - 75 years	Both	NM	RIA	123
Mustafa et al[112]	2018	Pakistan	Both	Hospital – CS	18 - 37 years	Female	Both	CMIA	67
Rehman et al[113]	2018	Pakistan	NM	Hospital – CS	25 - 55 years	Male	NM	NM	313

Table (Continued): Characteristics of selected study articles

Authors	Year	Country	Study Area (Urban / Rural)	Study design	Age	Gender	Socio Economic status	Vitamin D estimation method	San Size (N)
Khan et al[114]	2019	Pakistan	Urban	Hospital – CS	Median age 20 years	Both	NM	CLIA	167
Nadeem et al[38]	2018	Pakistan	NM	Community - CS	19 - 25 years	Both	NM	NM	221
Iqbal et al[115]	2019	Pakistan	NM	Hospital – CS	19 - 69 years	Both	Both	CK	226
Mahmood et al[116]	2009	Pakistan	NM	Hospital – CS	16 - 62 years	Both	NM	ECLIA	244
Afsar et al[117]	2014	Pakistan	NM	Hospital – CS	16 - 80 years	Both	NM	NM	376
Kumar et al[118]	2016	Pakistan	NM	Hospital – CS	Mean age 40.2 years	Both	NM	NM	160
Sharif et al[119]	2013	Pakistan	NM	Hospital – CC	20 - 40 years	Female	Both	ELISA	60
Khan et al[120]	2012	Pakistan	Both	Community - CS	18 years or above	Female	Both	ECLIA	305
Dar et al[121]	2012	Pakistan	Urban	Community - CS	18 - 48 years	Female	NM	ECLIA	174
Arya et al[18]	2003	India	Urban	Hospital – CS	24 - 53 years	Both	NM	RIA	92
Malhotra et al[122]	2009	India	NM	Hospital - RCT	18 years or above	Female	NM	RIA	100
Harinarayan et al[123]	2011	India	Urban	Hospital – CS	Mean age 38 years	Female	NM	RIA	55
Agrawal et al[124]	2013	India	NM	Hospital – CS	50 years or above	Male	NM	RIA	200
Vupputuri et al[125]	2006	India	Urban	Community - CS	Mean age 43.3 years	Both	Middle	RIA	105
Suryanarayana et al [126]	2018	India	Urban	Community - CS	60 years or above	Both	Both	RIA	298
Shivane et al[127]	2011	India	Urban	Community - CS	25 - 35 years	Both	NM	RIA	113
Harinarayan et al[128]	2006	India	Both	Community - CS	Mean age 44.5 years	Both	Both	RIA	114
Shukla et al[31]	2016	India	NM	Hospital – CS	More than 20 years	Both	NM	ECLIA	262
Sanket et al[129]	2016	India	NM	Hospital – CC	18 - 65 years	Both	NM	CLIA	81
Karoli et al[130]	2014	India	Both	Hospital – CS	18 - 60 years	Both	Lower	ECLIA	100
Laway et al[131]	2014	India	NM	Hospital – CC	More than 25 years	Both	NM	RIA	102

Gupta et al[132]	2014	India	NM	Hospital – CC	35 years or more	Both	NM	CLIA	70
Bhatt et al[133]	2014	India	Urban	Community - CS	18 - 60 years	Both	Both	RIA	137
Marwaha et al[134]	2011	India	Urban	Community - CS	More than 50 years	Both	NM	RIA	134
Goswami et al[17]	2009	India	NM	Community - CS	15 - 60 years	Both	NM	RIA	642
Zargar et al[135]	2007	India	Both	Community - CS	18 - 40 years	Both	NM	RIA	92
Harinarayan et al[16]	2004	India	Both	Community - CS	Mean age 45 years	Both	NM	RIA	316
Sofi et al[136]	2017	India	Both	Hospital – CS	20 - 49 years	Female	Both	CLIA	224
Beloyartseva et al[137]	2012	India	Urban	Community - CS	Mean age 42.71 years	Both	NM	RIA	211
Singh et al[138]	2018	India	Both	Hospital – CS	20 - 50 years	Female	NM	CLIA	72
Shetty et al[139]	2014	India	Urban	Community - CS	50 years or above	Male	NM	CLIA	252
Kajale et al[140]	2015	India	Urban	Hospital – CS	Mean age 27.7 years	Female	Both	ELISA	300
Goswami et al[141]	2008	India	Rural	Community - CS	Mean age 42.8 years	Both	NM	RIA	57
Kiran et al[142]	2014	India	Rural	Community - CS	20 - 72 years	Both	Both	CMIA	81
Kumar et al[143]	2017	India	NM	Hospital – CC	Mean age 48.26 years	Both	NM	CLIA	150
Goswami et al[144]	2016	India	Urban	Community - CS	Mean age 25 - 32 years	Male	NM	CLIA	194
Meena et al[145]	2016	India	Urban	Hospital – CS	Not mention	Female	Lower	RIA	100
Singh et al[146]	2011	India	NM	Hospital – CS	Mean age 28 years	Male	NM	RIA	80
Garg et al[81]	2013	India	Urban	Community - CS	50 years or above	Both	NM	RIA	134
Harinarayan et al[123]	2011	India	Urban	Hospital – CS	Mean age 53 years	Female	NM	RIA	136

Table (Continued): Characteristics of selected study articles:

Authors	**Year**	**Country**	**Study Area (Urban / Rural)**	**Study design**	**Age**	**Gender**	**Socio Economic status**	**Vitamin D estimation method**	**San Size (N)**
Paul et al[147]	2008	India	Urban	Community - CS	50 years or above	Female	NM	RIA	150
Srimani et al[148]	2017	India	Rural	Community - CS	45 - 70 years	Female	NM	EIA	222
Harinarayan et al[149]	2004	India	NM	Community - CS	Mean age 54 years	Female	NM	RIA	164
Agarwal et al[150]	2013	India	Urban	Hospital - RCT	40 - 73 years	Female	High	RIA	92
Mitra et al[151]	2016	India	NM	Hospital – CS	45 - 52 years	Female	NM	CLIA	64
Agarwal et al[152]	2014	India	NM	Hospital – CS	Mean age 56.3 years	Female	NM	CK	71
Dixit et al[153]	2018	India	NM	Hospital – CS	Mean age 56.41 years	Female	NM	RIA	334
Kadam et al[154]	2010	India	Urban	Hospital – CS	40 - 75 years	Female	Both	RIA	172

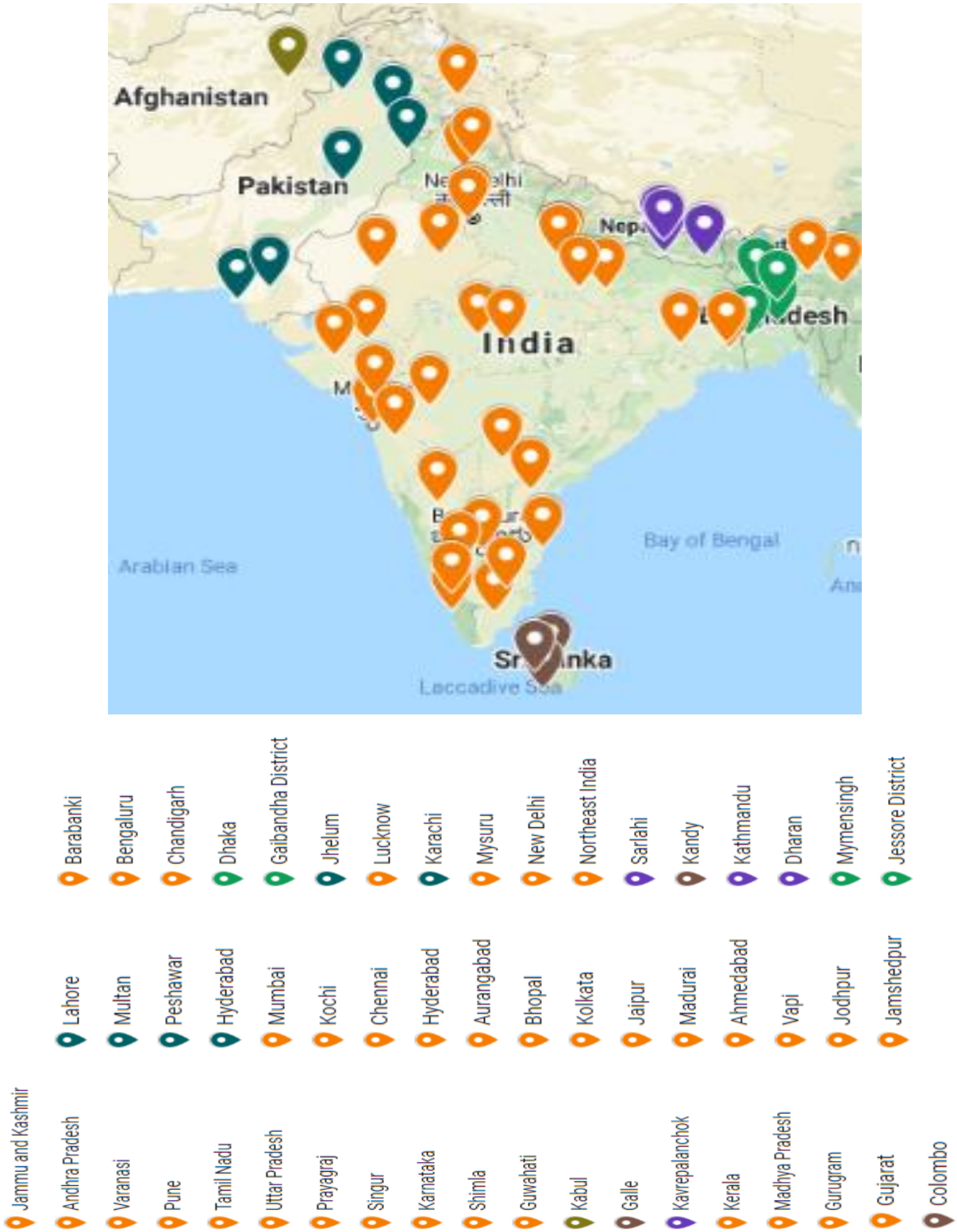

Figure 4: Country Wise location for our selected studies via google map

The study selected in this systematic review consisted of 70751 participants. Participants belonged to all kinds of age groups, ranging from 0-80 years and included all groups of population such as pregnant women, children and adults. Prevalence of vitamin D deficiency and average level of vitamin D was mentioned in all studies. To show the complete picture of Vitamin D deficiency among the South Asian population, we segregate our overall findings into three sections. These are pregnant women, Children and adults. For each section we also show gender wise, age wise and country wise analysis if necessary.

Pregnant women:

Out of 126 studies, 20 studies were conducted on pregnant women. Prevalence of Vitamin D deficiency ranged from 9% to 97% and average vitamin D level was ranged from 9 ng/ml to 24.86 ng/ml. The overall pooled prevalence of vitamin D deficiency was 65% [95% CI: 0.51 to 0.78] and the weighted mean level of Vitamin D status was 16.36978 ng/ml (SD 7.1256 ng/ml). There was a large amount of heterogeneity in the prevalence of vitamin D deficiency ($I2$ = 99.37%; p = 0.00). This group covers four out of eight south Asian countries which are Bangladesh, India, Pakistan and Nepal. Since all of the study participants were pregnant women in this section we prefer only country wise analysis.

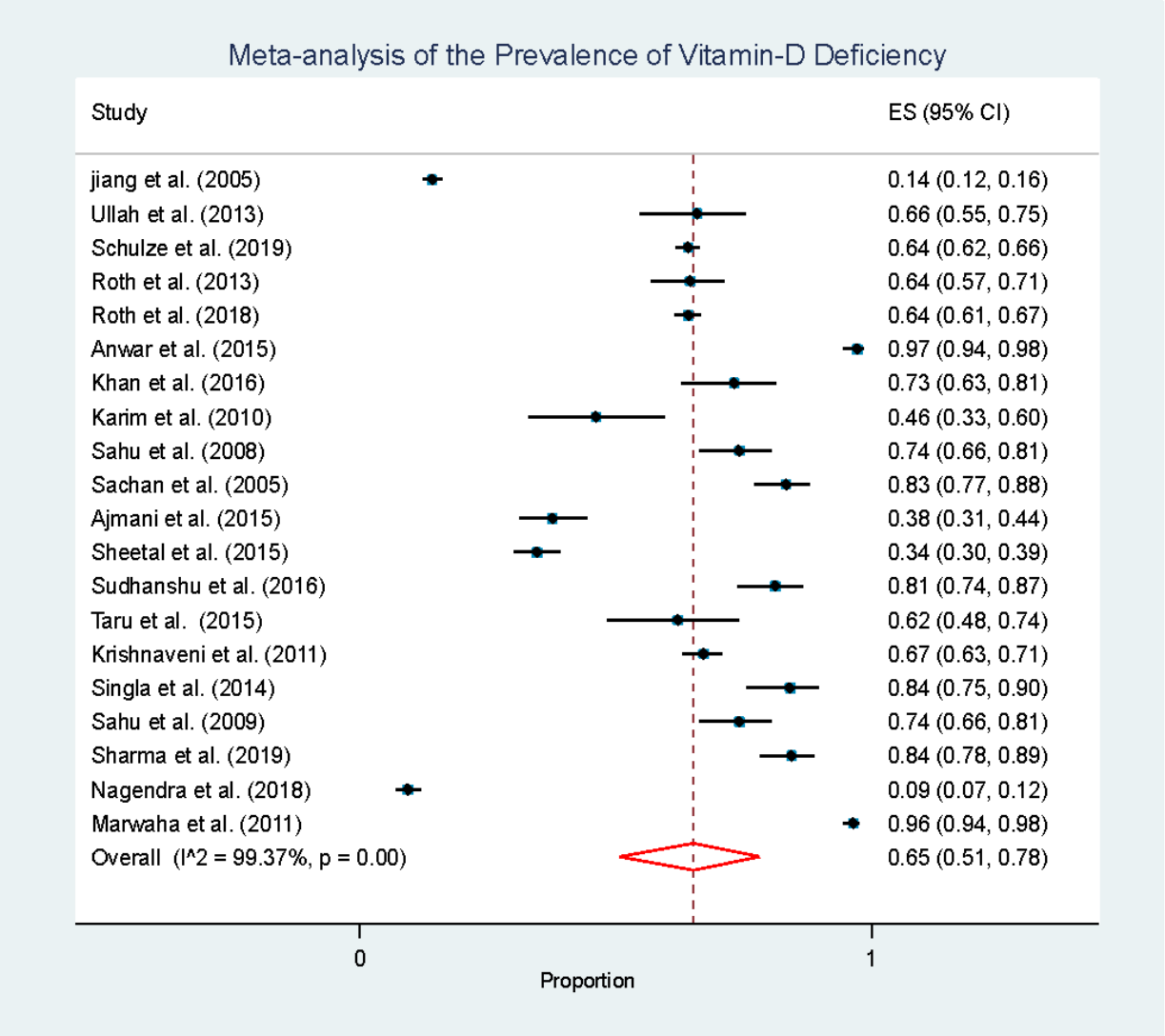

Figure 5: Forest plot represent overall pooled prevalence of Vitamin D deficiency among South Asian Pregnant women

Effect of geographical location on Prevalence of Vitamin D deficiency among South Asian pregnant women:

Google map displays country wise locations for our selected studies. (Supplementary file: Figure-1). Forest plot shows country wise prevalence of Vitamin D deficiency (Figure-3)

Nepal:

We found only one study in Nepal and it was a community based randomized control trial and conducted among one thousand one hundred sixty three rural pregnant women. Socio economic

status was not mentioned. Study reports showed that 14% of study participants were vitamin D deficient with an average of 20.44 ng/ml vitamin D level.

Bangladesh:

We found four studies from Bangladesh which consisted of 3055 participants. Study design was Hospital based case control, Community based randomized control trial and hospital based randomized control trial. Out of four studies, two studies were conducted among urban populations, one in rural population and one study did not mention demographic areas for study population. Out of four studies 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 level of Vitamin D for study participants was 15.55 ng/ml (Weighted S.D 5.290625 ng/ml) [Supplementary file: Figure-3] and Random effect meta-analysis showed that the weighted pooled prevalence of vitamin D deficiency was 64% [95% CI: 0.62 to 0.66]. No heterogeneity was observed ($I2 = 0\%$; $p = 0.99$).

Pakistan:

We found three studies from Pakistan which consisted of 404 participants. Study design was Hospital based cross sectional, Community based cross sectional and Community based randomized control trial. Out of three studies, one study was conducted among both rural and urban populations, the other two studies did not mention demographic areas for study. Socio economic status for study participants was not mentioned in one study, one study conducted on a lower socioeconomic group of population and another one on both lower and upper socioeconomic class. The weighted mean level of Vitamin D for study participants was 11.27 ng/ml (Weighted S.D 6.2838 ng/ml) [Supplementary file: Figure-3] and Random effect meta-analysis showed that the weighted pooled prevalence of vitamin D deficiency was 76% [95% CI: 0.39 to 0.99].

India:

We found twelve studies from India which consisted of 3182 participants. Study design was Community based cross sectional and Hospital based case control, cross sectional and randomized control trial. Out of twelve studies, half of the studies 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, rest of studies include either both socioeconomic groups (upper and lower) of populations or only lower economic groups of populations. The weighted mean level of Vitamin D for study participants was 16.3148 ng/ml (Weighted S.D 7.9054 ng/ml) [Supplementary file: Figure-3] and Random effect meta-analysis shows that the weighted pooled prevalence of vitamin D deficiency is 67% [95% CI: 0.46 to 0.85]. Large amount of heterogeneity was present among these studies (I2 = 99.30%; p = 0.00)

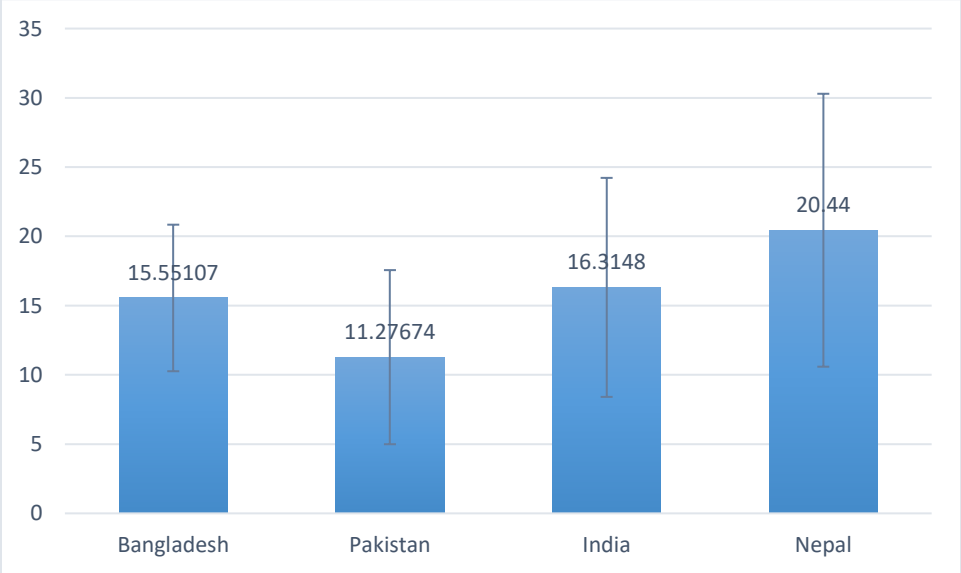

Figure 6: Bar diagram for mean (SD) level of Vitamin D (ng/ml) among South Asian pregnant women

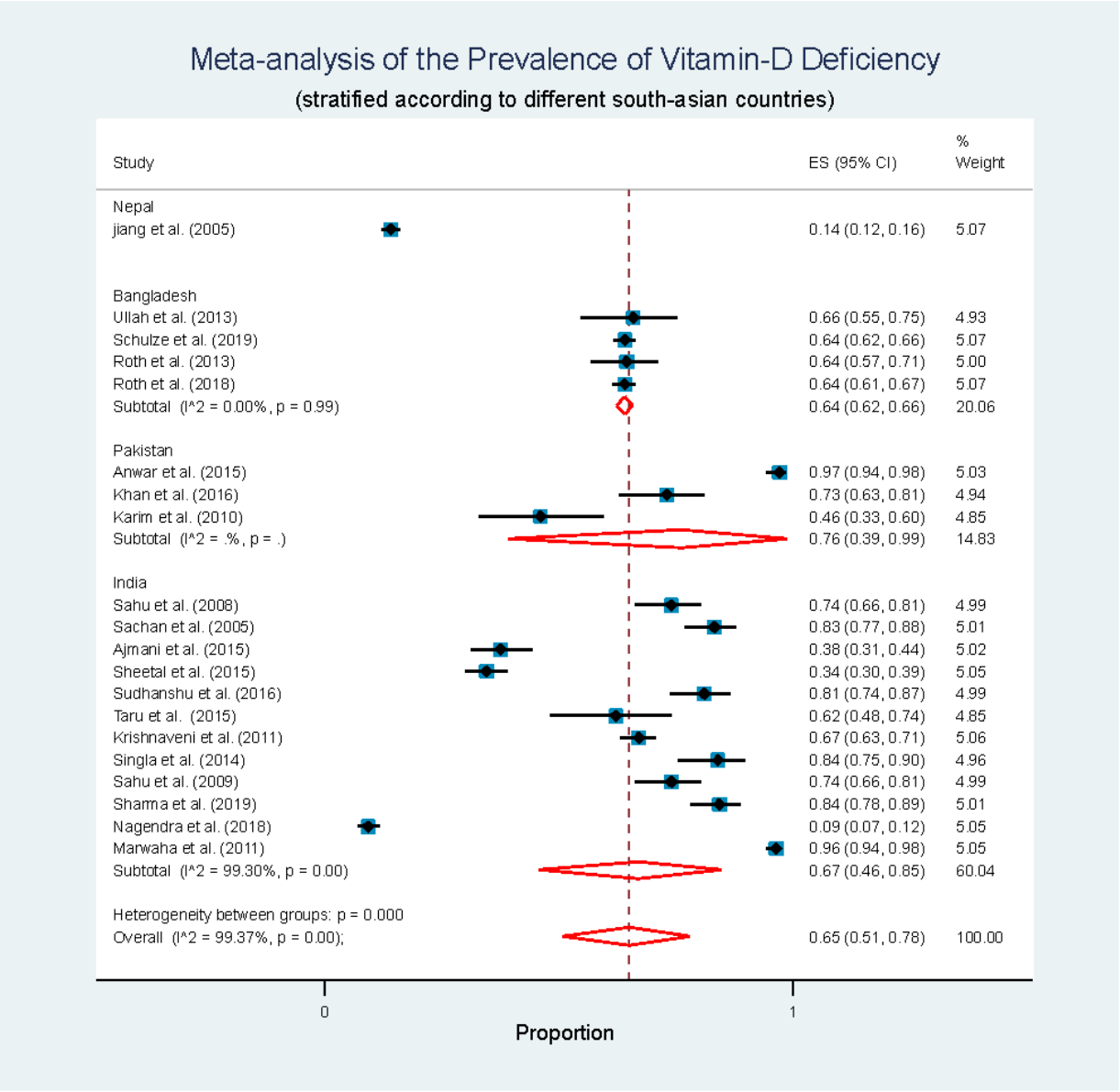

Figure 7: Forest plot shows country wise prevalence of Vitamin D deficiency among South Asian Pregnant women

Children:

In this section we found 41 studies which were conducted on children who are 0-18 years of age. Prevalence of vitamin D deficiency ranged from 8% to 96% and average vitamin D level was ranged from 5 ng/ml to 30.01 ng/ml. The overall pooled prevalence of vitamin D deficiency was 61% [95% CI: 0.46 to 0.71] and the weighted mean level of Vitamin D status was 15.4868 (Weighted SD 7.49) ng/ml. There was a large amount of heterogeneity in the prevalence of vitamin D deficiency (I2 = 99.72%; p = 0.00 ;). This group covers all south Asian countries

except Maldives and Bhutan. All of the study participants belong to both gender with different age groups such as neonates, infants, preschool children, school children and all of them represents different south Asian countries, that's why we prefer country wise gender wise and age wise analysis for this section.

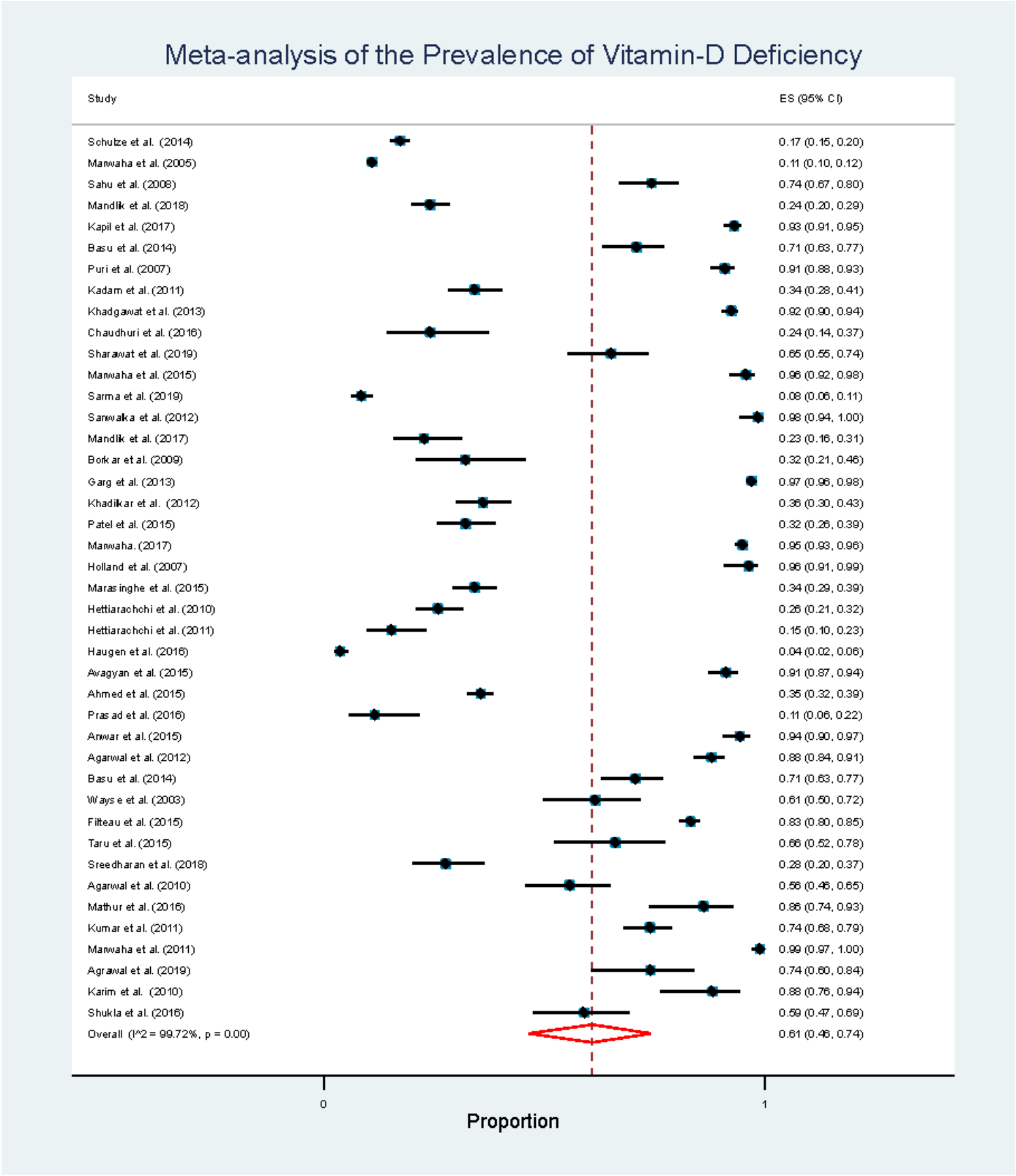

Figure 8: Forest plot shows overall prevalence of Vitamin D deficiency among South Asian children.

Effect of geographical location on prevalence of Vitamin D deficiency among south Asian children:

Google map showed country wise position for our selected studies (Supplementary file: Figure-1). Forest plot showed country wise prevalence of Vitamin D deficiency (Figure-3)

Nepal:

We found three studies from Nepal which consisted of 1746 participants. Study design was Community based cross sectional and Community based randomized control trial. Out of three studies, two studies were conducted among rural populations and one in urban population. No study mentioned socioeconomic status for study participants. No study participants were above eight years. The weighted mean level of Vitamin D for study participants was 25.9638 ng/ml (weighted S.D 7.2926 ng/ml) [Supplementary file: Figure-3] and Random effect meta-analysis showed that the weighted pooled prevalence of vitamin D deficiency was 35% [95% CI: 0.01 to 0.83.]

India:

We found thirty two studies from India which comprised 14497 participants. Study design was community based cross sectional for fifteen studies, Hospital based case control for seven studies, Hospital based cross sectional for eight studies and two studies were hospital based randomized control trials. Out of thirty two studies, most of the studies (21 studies) did not mention demographic areas for study populations, three studies were conducted among urban populations, four in rural populations and four in both rural and urban populations. Most of the studies did not mention socio economic status for study participants (19 study), eight studies conducted on lower economic groups of population, four studies conducted on both lower and upper economic groups of population and one study on middle income populations. Almost all

study participants belonged to eighteen years or less, only two studies showed that participants belonged to twenty years or less [31,56]. The weighted mean level of Vitamin D for study participants was 13.40 ng/ml (weighted S.D 6.61322 ng/ml) [Supplementary file: Figure-3] and Random effect meta-analysis showed that the weighted pooled prevalence of vitamin D deficiency is 64% [95% CI: 0.46 to 0.79]. There was presence of large amount of heterogeneity (I2 = 99.75%; p = 0.00)

Afghanistan:

We found only one study from Afghanistan which was a community based cross sectional study and conducted among boys and girls who belong 6 month to 5 years of age. Demographic areas and socioeconomic status were not mentioned. There were 107 participants and study showed that 96.2% of them were vitamin D deficiency with mean vitamin D level 5 ng/ml.

Sri Lanka:

We found three studies from Sri Lanka which comprised 693 participants. Study design was Community based cross sectional and Hospital based cross sectional. Out of three studies, two studies did not mention demographic areas for study populations and one in urban population. No study mentioned socioeconomic status for study participants. No study participants were above five years. The weighted mean level of Vitamin D for study participants was 27.3473 ng/ml (weighted S.D 9.5467 ng/ml) [Supplementary file: Figure-3] and Random effect meta-analysis shows that the weighted pooled prevalence of vitamin D deficiency is 25% [95% CI: 0.16 to 0.36].

Bangladesh:

We found only one study from Bangladesh which was a community based cross sectional study and conducted among urban boys and girls who belong 6 month to 2 years of age. Study participants represent both upper and lower socioeconomic status. There were 913 participants and studies showed that 35.48% of them were vitamin D deficient with mean vitamin D level 21.86 ng/ml.

Pakistan:

We found two studies from Pakistan which together consisted of 277 Participants. One study was community based cross sectional and the other study was hospital based cross sectional. Both studies were conducted on neonates. Random effect meta-analysis showed that 94% of participants were Vitamin D deficient [95% CI: 0.90 to 0.96] with 11.78 ng/ml weighted mean level of Vitamin D (weighted S.D 7.99 ng/ml) [Supplementary file: Figure-3]. Socio economically study participants represent both upper and lower socio economic class. Demographic area for study participants was not mentioned in these studies.

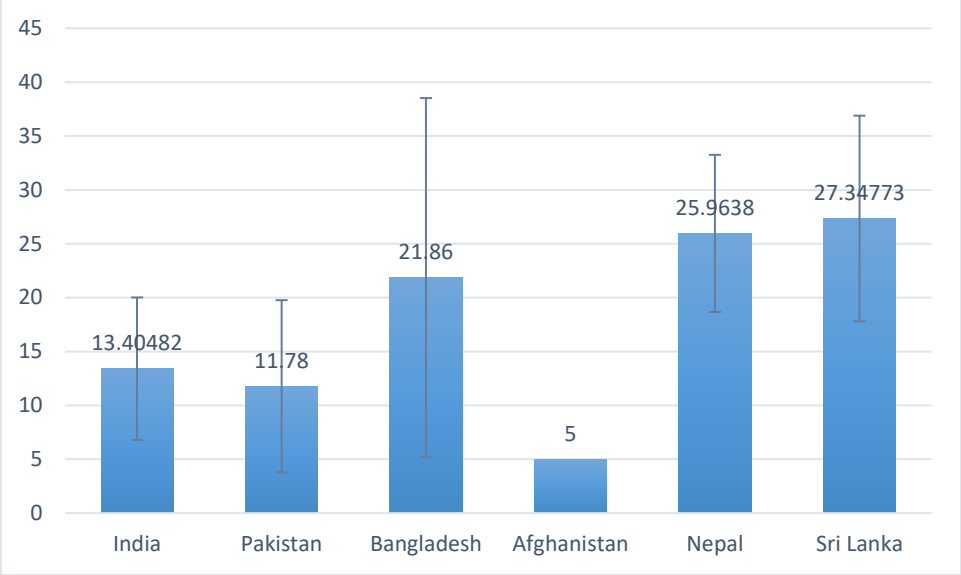

Figure 9: Bar diagram for mean (SD) level of Vitamin D (ng/ml) among South Asian Children

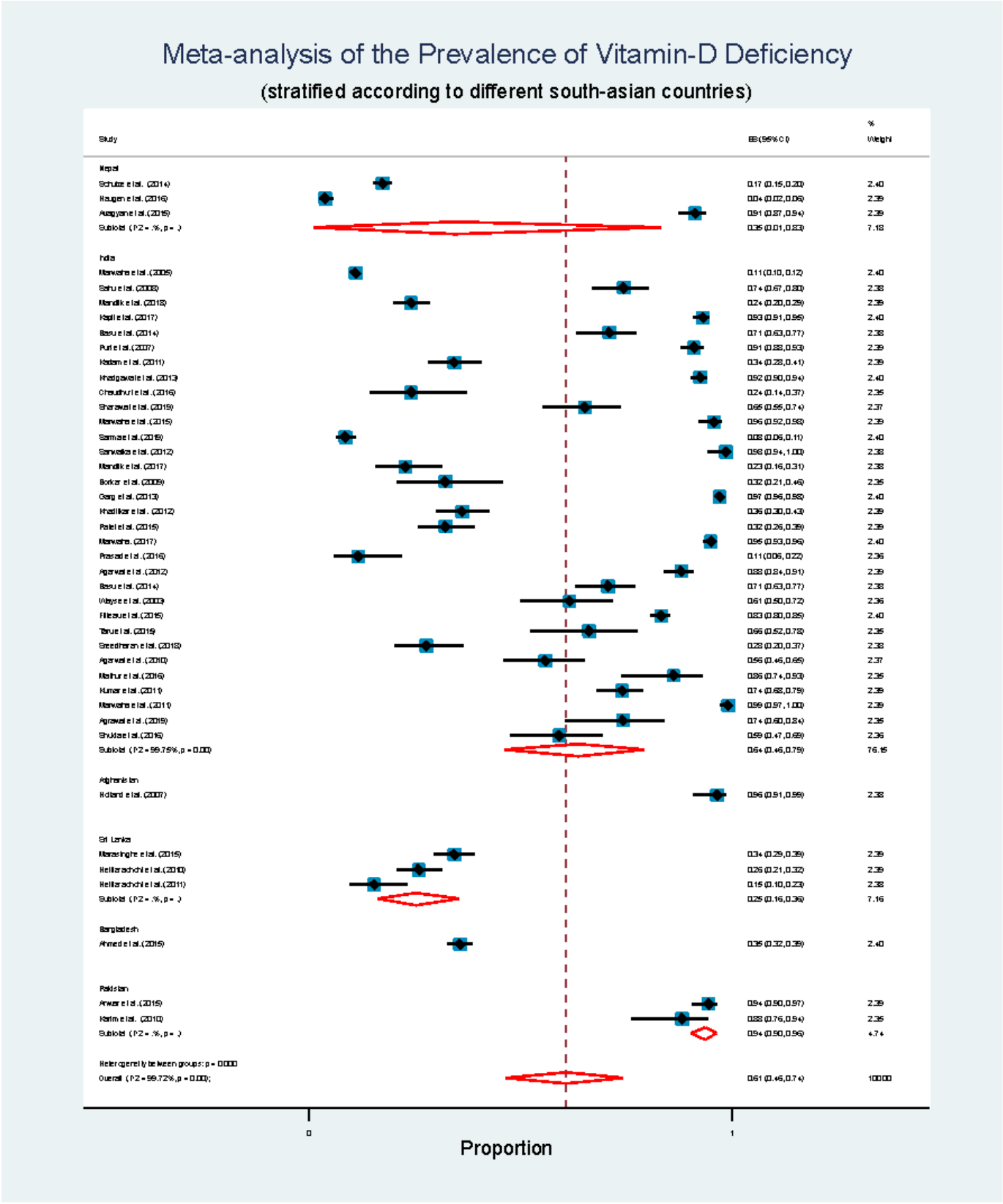

Figure 10: Forest plot displays country wise prevalence of Vitamin D deficiency among South Asian children.

Effect of gender on prevalence of Vitamin D deficiency among south Asian Children:

We did not find a single study which was conducted on only male pediatrics. All of the studies we found were conducted either on both gender or only among female children. [Gender wise forest plot available in supplementary file: Figure-4]

Studies included participants from both gender:

We found 37 out of 42 studies which included participants from both gender and among these studies, 27 studies conducted on Indian Pediatrics, 2 studies on Pakistani pediatrics, 3 studies on Nepali pediatrics, 3 studies on Sri Lankan pediatrics and single study from Bangladeshi, and Afghanistan pediatrics children. These studies in together comprised of 16434 participants and random effect meta-analysis showed that 58% [95% CI: 0.43 to 0.73] of study participants were Vitamin D deficient with high number of heterogeneity ($I2 = 98.72\%$; $p = 0.00$) Average Vitamin D level of study participants ranged from 5 to 34 ng/ml.

Studies included only female participants:

We found 5 studies which conducted on only female pediatrics children and all of these studies were conducted in India.These studies in together comprised of 1799 participants and random effect meta-analysis showed that 76% [95% CI: 0.46 to 0.96] of study participants were Vitamin D deficient with high number of heterogeneity ($I2 = 99.37\%$; $p = 0.00$). Average Vitamin D level of study participants ranged from 9 to 24 ng/ml.

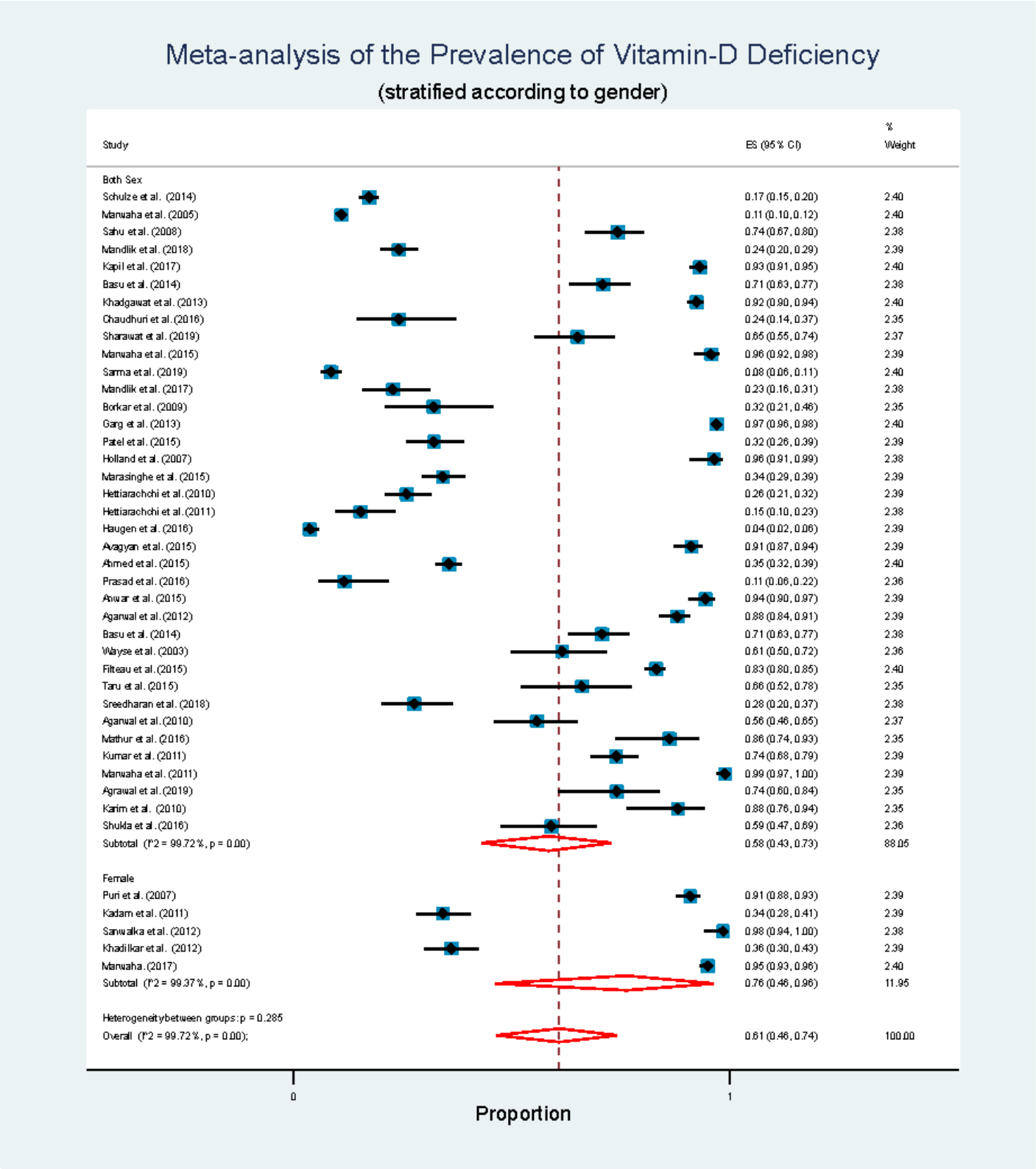

Figure 11: Forest plot in accordance with gender for prevalence of Vitamin D deficiency among South Asian children

Effect of age on prevalence of Vitamin D deficiency among south Asian Children:

In this section we categorized study participants into four groups according to their age and these are 6 to 18 years (School children), 1 month to 5 years (Preschool children), 1 month (Infants) and others**.** Forest plot available in [Supplementary file: Figure-5]

School Children (6-18 years):

We found 18 studies which were conducted on participants belonging to the 6 to 18 years age group and among these studies only a single study conducted on Nepali children and rest of them conducted on Indian children. These studies together consisted of 12709 participants and random effect meta-analysis showed that 57% [95% CI: 0.33 to 0.80] of study participants were Vitamin D deficient with high number of heterogeneity (I2 = 99.85%). Average Vitamin D level of study participants ranged from 6.3 to 26.52 ng/ml.

Infants and Preschool Children (1 month - 5 years):

We found 13 studies which conducted on participants who belonged to 1 month to 5 years age group and among these studies 7 studies were conducted on Indian children, 3 studies on Sri Lankan children, 2 studies on Nepali children and only single study conducted on Bangladeshi and Afghanistan children. These studies together consisted of 4324 participants and random effect meta-analysis showed that 55% [95% CI: 0.35 to 0.75] of study participants were Vitamin D deficient with high number of heterogeneity (I2 = 99.47%; p = 0.00). Average Vitamin D level of study participants ranged from 5 to 33.71 ng/ml.

Neonates (1 month):

We found 6 studies which were conducted on participants who are up to 1 month of age and among these studies 4 studies were conducted on Indian children, and 2 studies on Pakistani children. These studies together consisted of 763 participants and random effect meta-analysis showed that 85% [95% CI: 0.76 to 0.91] of study participants were Vitamin D deficient with high number of heterogeneity (I2 = 84.82%; p = 0.00). Average Vitamin D level of study participants ranged from 6 to 20 ng/ml.

Others:

In this group participants' age range were 2 years to 20 years and that's why they named it others. In total we found 4 studies in this section and all were Indian children. These studies together consisted of 437 participants and random effect meta-analysis showed that 57% [95% CI: 0.35 to 0.77] of study participants were Vitamin D deficient with high number of heterogeneity (I2 = 95.20%; p = 0.00). Average Vitamin D level of study participants ranged from 14 to 30 ng/ml.

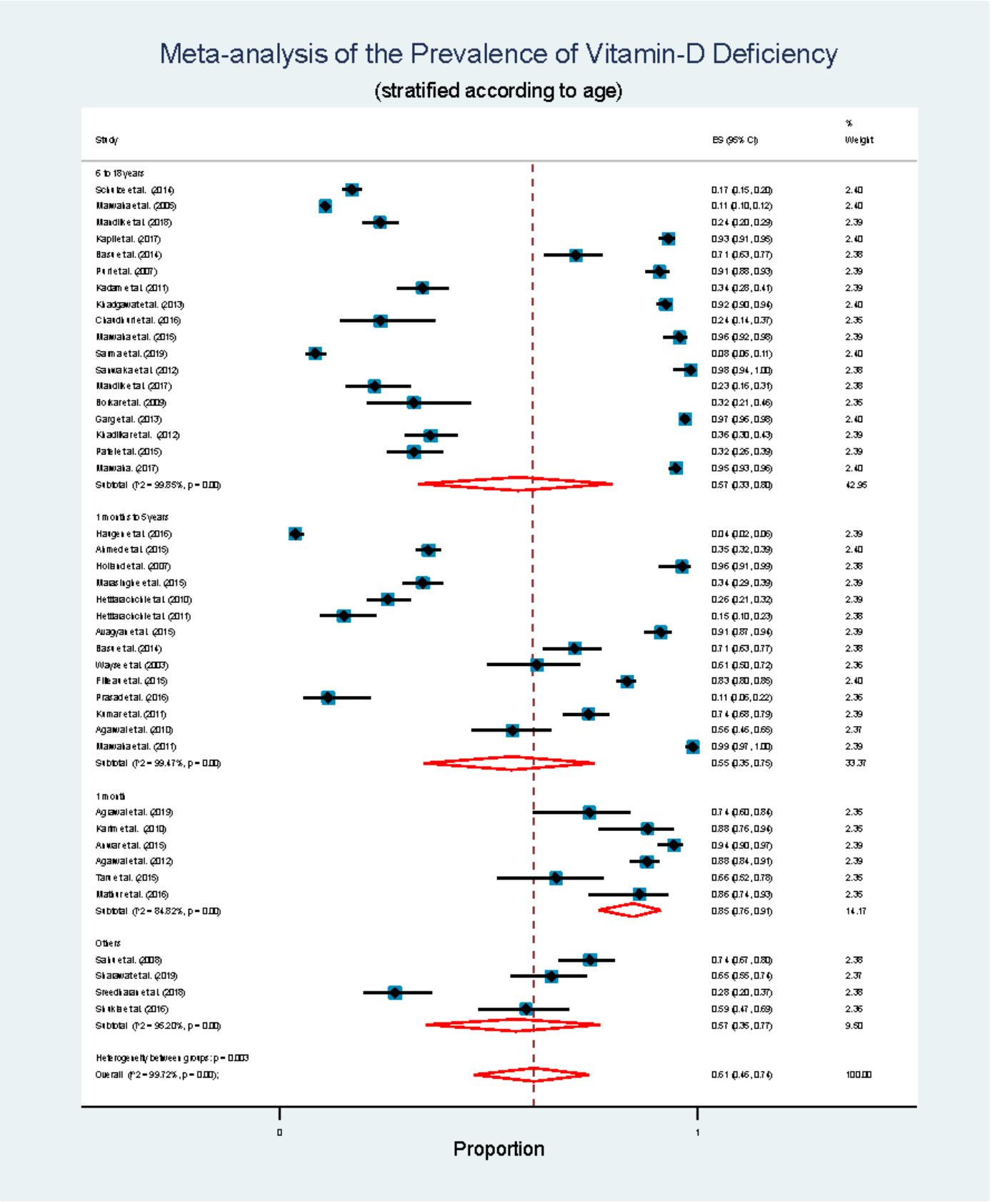

Figure 12: Forest plot in accordance with age for prevalence of Vitamin D deficiency among South Asian children

Adults:

This group consisted of participants who are 18 years or above. Out 126 studies, 65 studies conducted on adult. Prevalence of Vitamin D deficiency ranged from 17% to 99% and average vitamin D level was ranged from 4.7 ng/ml to 32 ng/ml. The overall pooled prevalence of vitamin D deficiency was 68% [95% CI: 0.64 to 0.72] and the weighted mean level of Vitamin D was 19.15 ng/ml (Weighted SD 11.59 ng/ml). There was a significant amount of heterogeneity in the prevalence of vitamin D deficiency ($I2 = 98.46\%$; $p = 0.00$). Overall forest plot shows prevalence of Vitamin D deficiency (Figure-2). This section included participants from all south Asian countries except Afghanistan, Bhutan and Maldives. Participants belonged to both gender and all of them were adults. So in this section we prefer country wise and gender wise analysis.

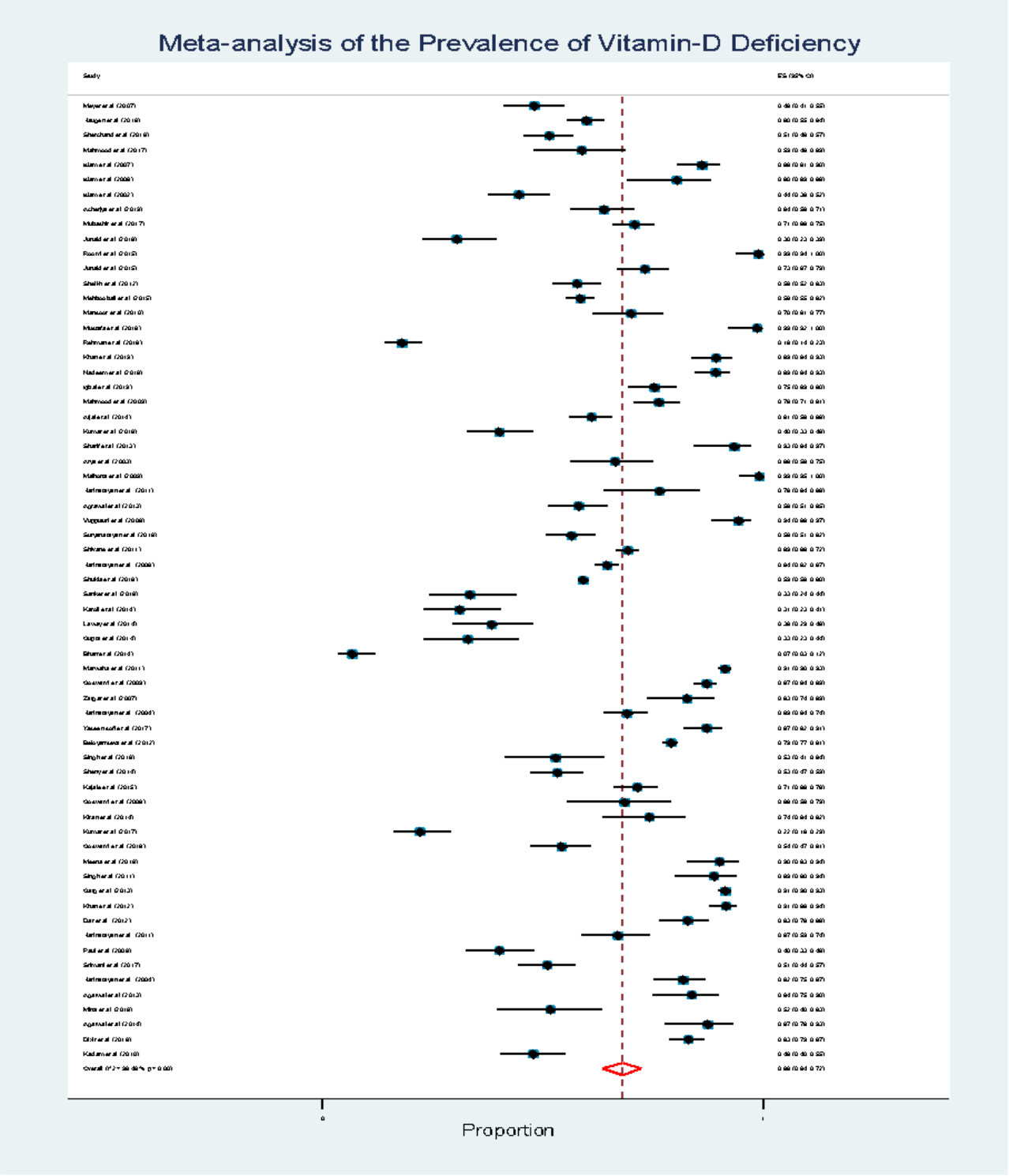

Figure 13: Forest plot represent overall pooled prevalence of Vitamin D deficiency among South Asian adult

Effect of geographical location on prevalence of Vitamin D deficiency among south Asian adults:

Country wise locations for our selected studies were available in google map (Supplementary file: Figure-1). Forest plot displays country wise prevalence of Vitamin D deficiency (Figure-3).

Sri Lanka:

We found only one study from Sri Lanka which was a community based cross sectional study and included urban adult participants from both genders. Socioeconomic status was not mentioned. There were 196 participants and study showed that 47.95% of them were vitamin D deficiency with mean vitamin D level 21.68 ng/ml.

Nepal:

We found two studies from Nepal and these occupied 800 participants together. One study was community based cross sectional which was conducted on adult females and another study was hospital based cross sectional which included adult male and female. Random effect meta-analysis showed that 57% of participants were Vitamin D deficient [95% CI: 0.53 to 0.60] with mean Vitamin D level 19 ng/ml. Out of two studies one study mentioned demographic area for study population but socioeconomic status was not mentioned in both studies.

Bangladesh:

We found five studies from Bangladesh which consisted of 695 participants. Study design was Hospital based cross sectional and Community based cross sectional and case control. Out of five studies, two studies were conducted among urban populations and the other three studies on both rural and urban populations in Bangladesh. Socio economically most of the study

participants belong to the lower class. Out of five studies, three study participants were eighteen years or above and two studies show that participant's age range started from 16 years and 10 years. The weighted mean level of Vitamin D for study participants was 16.14296 ng/ml (SD--4.83 ng/ml) {Supplementary file: Figure-3} [Mean Vitamin D level ranged from 12.3 ng/ml to 18.6 ng/ml] and Random effect meta-analysis shows that the weighted pooled prevalence of vitamin D deficiency is 67% [95% CI: 0.50 to 0.83]. Large amount of heterogeneity was present (I2 = 95.53%; p =0.00)

Pakistan:

We found eighteen studies from Pakistan which consisted of 4354 participants. Study design was Hospital based and Community based cross sectional for most of the studies. Only three studies were hospital based case control. Most of the studies did not mention demographic areas (urban/rural) for study population, four studies were conducted among urban populations and two studies included both rural and urban populations. Socio economic status for study participants was not mentioned in most of the studies, eight studies conducted on both lower and upper socio economic groups of population and only one study conducted on lower class population. Most study participants were eighteen years or above, only two studies mention that age range started from fifteen years for study participants. The weighted mean level of Vitamin D for study participants was 17.929 ng/ml (SD--8.24 ng/ml) {Supplementary file: Figure-3} [Mean Vitamin D level ranged from 8.44 ng/ml to 32ng/ml] and random effect meta-analysis showed that the weighted pooled prevalence of vitamin D deficiency was 73% [95% CI: 0.63 to 0.83]. There is large amount of heterogeneity (I2 = 98.20%; p =0.00)

India:

We found thirty nine studies from India which consisted of 38672 participants. Study design consists of hospital based and community based cross sectional for most of the studies. Only three studies were hospital based case control and one hospital based randomized control trial. Out of thirty nine studies, seventeen studies were conducted among urban populations, three studies in rural population and six studies conducted on both rural and urban population. Other thirteen studies did not mention demographic areas for the study population. Most of the study did not mention demographic areas for the study population, seven studies include both urban and rural population, two studies on lower economic groups and one study on higher and middle economic groups of population. All the study participants were eighteen years or above. The weighted mean level of Vitamin D for study participants was 19.342 ng/ml (SD--12.08 ng/ml) {Supplementary file: Figure-3} [Mean Vitamin D level ranged from 4.7 ng/ml to 30.6 ng/ml] and random effect meta-analysis showed that the weighted pooled prevalence of vitamin D deficiency is 67% [95% CI: 0.61 to 0.73]. There is large amount of heterogeneity ($I2 = 98.76\%$; $p = 0.00$)

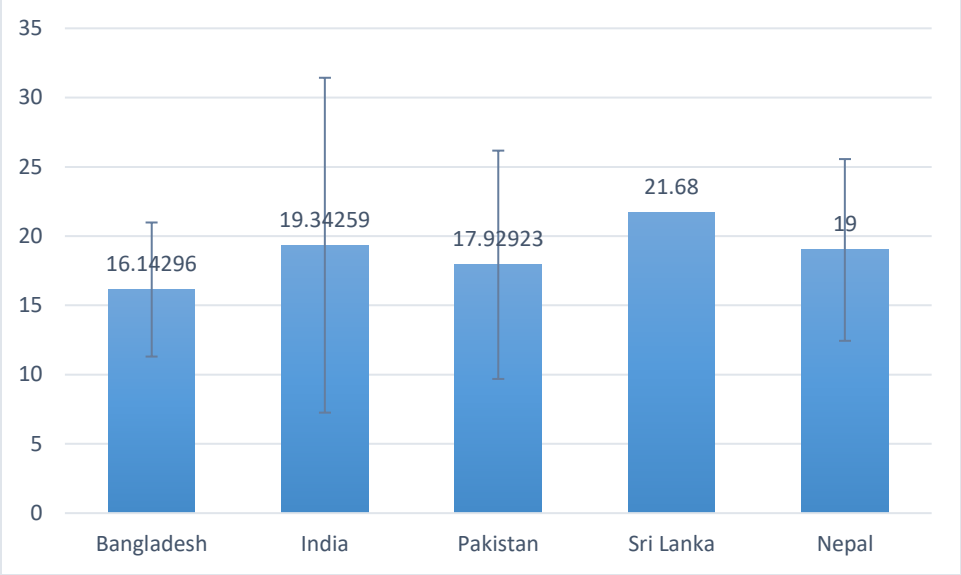

Figure 14: Bar diagram for mean (SD) level of Vitamin D (ng/ml) among south Asian adult populations

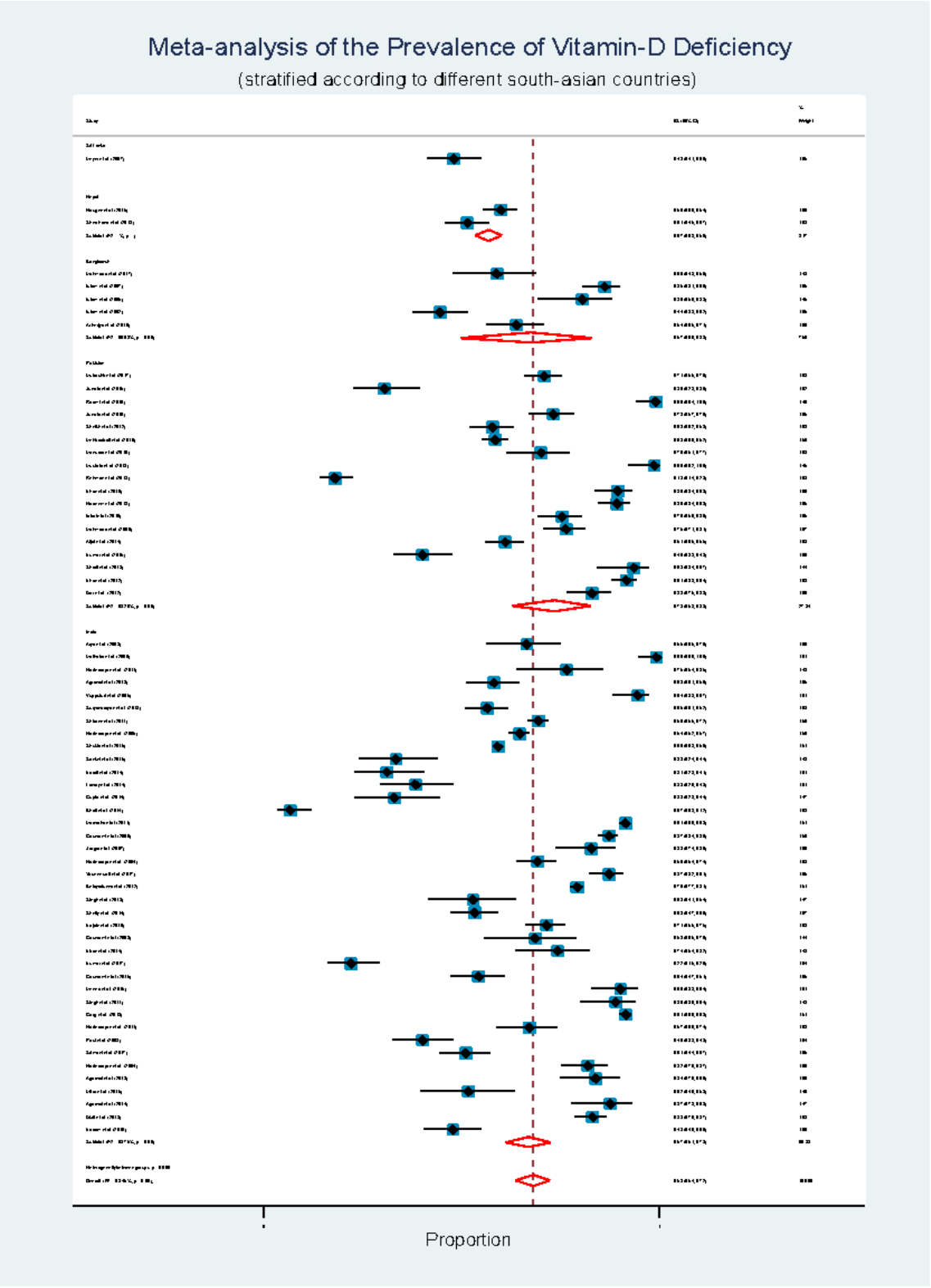

Figure 15: Forest plot shows country wise prevalence of Vitamin D deficiency among South Asian adult.

Effect of gender on prevalence of Vitamin D deficiency among south Asian adults:

Out of sixty five studies, 25 studies conducted on adult females and 6 studies conducted on adult male, the rest of the studies included both male and female adults. [Gender wise forest plot available in Supplementary file: Figure-5].

Studies included participants from both gender:

We found 35 studies which included participants from both gender and among these studies, 20 studies conducted on Indian adults, 12 studies on Pakistani adults and a single study from Bangladeshi, Nepali and Sri Lankan adults. These studies in together comprised of 39566 participants and random effect meta-analysis showed that 65% [95% CI: 0.59 to 0.71] of study participants were Vitamin D deficient with high number of heterogeneity (I2 = 98.89%; p = 0.00). Average Vitamin D level of study participants ranged from 7 to 32 ng/ml [Weighted mean 19.54 ng/ml (SD- 12.06 ng/ml].

Studies included only female adult:

We find 25 studies which included only female adults as participants and among these studies 15 studies conducted on Indian female adults, 5 studies on Pakistani adult females, and 4 studies from Bangladeshi adult females and single study on Nepali adult females. These studies together consisted of 4112 participants and random effect meta-analysis showed that 76% [95% CI: 0.68 to 0.82] of study participants were Vitamin D deficient with high number of heterogeneity (I2 = 96.20%; p = 0.00). Weighted mean Vitamin D level of study participants was 14.68ng/ml (SD- 7.86 ng/ml). [Supplementary file – figure 4]

Studies included only male adult:

We found 5 studies which included only adult male as participants and all of these studies were conducted on Indian adult male. These studies together consisted of 1039 participants and random effect meta-analysis showed that 51% [95% CI: 0.33 to 0.71] of study participants were Vitamin D deficient with high number of heterogeneity ($I^2 = 97.68\%$; $p = 0.00$). Weighted mean Vitamin D level of study participants was 22.13 ng/ml (SD- 7.39 ng/ml). [Supplementary file – figure 4]

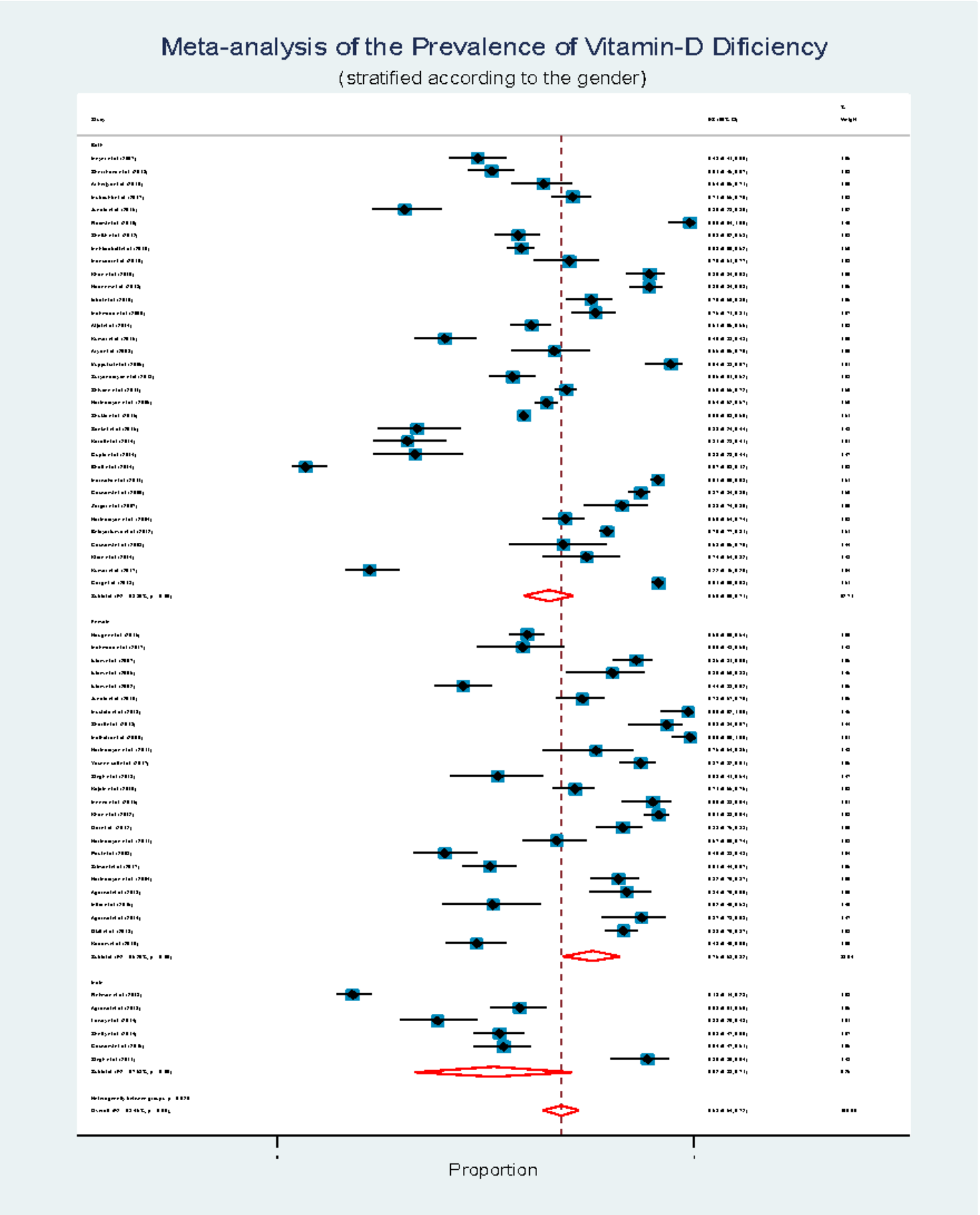

Figure 16: Gender wise forest plot for prevalence of Vitamin D deficiency among South Asian adult population

Quality assessment:

According to hoy et al checklist studies which score 0-3 will be considered low risk, 4-6 moderate risk and studies with score 7-9 will be considered as high risk of bias. Table of RoB (Risk of Bias) assessment for selected studies were available in [Figure:]. Among these 65 studies no study was found with high risk of bias, more than half of these studies (71 studies) with moderate risk of bias and rest of them (55 studies) showed low risk of bias.

Out of 10 parameters, 2 parameters showed no risk of bias in all of the selected studies which included (a) chance of non-response bias and (b) data collection. In Moderate risk of studies, high risk of bias mostly showed in 4 out of 10 parameters which include (a) representation of target population (b) sampling frame (c) as well as selection of responders (d) and appropriate shortest length of prevalence period. Few studies also showed high risk of bias in parameters like numerator(s) and denominator(s) for appropriate parameters of interest and also in case definition of studies. On the other hand, low risk of studies showed high risk of bias mostly in 2 out of 10 parameters which include (a) representation of target population and also in (b) shortest length of prevalence period.

Table 3: Quality assessment of selected studies using hoy et al check list

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total score	Quality
Jiang et al [50]	0	0	0	0	0	0	0	0	1	1	2	Low
Ullah et al [51]	0	1	1	0	0	0	0	0	1	1	4	Moderate
Schulze et al [52]	0	0	0	0	0	0	0	0	1	0	1	Low
Roth et al [53]	1	1	0	0	0	0	0	0	1	1	4	Moderate
Roth et al [39]	1	1	1	0	0	0	1	0	1	1	6	Moderate
Anwar et al [33]	0	0	0	0	0	0	0	0	1	0	1	Low
Khan et al [54]	1	0	0	0	0	0	0	0	1	0	2	Low
Karim et al [55]	1	1	1	0	0	0	1	0	1	0	5	Moderate
Sahu et al [56]	0	1	1	0	0	0	0	0	0	0	2	Low
Sachan et al [57]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Ajmani et al [58]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Sheetal et al [59]	1	1	1	0	0	0	0	0	1	1	5	Moderate
Sudhanshu et al [60]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Taru et al [61]	0	1	1	0	0	0	1	0	1	1	5	Moderate
Krishnaveni et al [62]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Singla et al [63]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Sahu et al [64]	1	0	0	0	0	0	0	0	1	0	2	Low
Sharma et al [65]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Nagendra et al [66]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Marwaha et al [67]	1	0	0	0	0	0	0	0	0	0	1	Low
Schulze et al [40]	0	0	0	0	0	0	0	0	1	0	1	Low
Marwaha et al [68]	0	0	0	0	0	0	0	0	1	0	1	Low
Sahu et al [56]	1	0	0	0	0	1	0	0	0	0	2	Low
Mandlik et al [69]	1	0	0	0	0	0	0	0	1	0	2	Low
Kapil et al [70]	0	0	0	0	0	0	0	0	1	0	1	Low
Basu et al [71]*	1	1	1	0	0	0	0	0	0	0	3	Low
Puri et al [72]	0	0	0	0	0	0	0	0	1	0	1	Low
Kadam et al [73]	1	1	0	0	0	0	0	0	1	0	3	Low
Khadgawat et al [41]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Chaudhuri et al [74]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Sharawat et al [75]	1	0	0	0	0	0	0	0	1	0	2	Low
Marwaha et al [76]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Sarma et al [77]	1	1	0	0	0	0	0	0	1	0	3	Low
Sanwalka et al [78]	0	0	0	0	0	0	0	0	1	0	1	Low
Mandlik et al [79]	1	0	0	0	0	0	0	0	1	0	2	Low
Borker et al [80]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Garg et al [81]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Khadilkar et al [82]	1	0	0	0	0	0	0	0	1	0	2	Low
Patel et al [83]	0	0	0	0	0	0	0	0	1	0	1	Low
Marwaha et al [84]	0	0	0	0	0	0	0	0	1	0	1	Low
Holland et al [32]	0	0	0	0	0	0	0	0	1	1	2	Low
Marasinghe et al [85]	0	0	0	0	0	0	0	0	1	0	1	Low
Hettiarachchi et al [86]	0	0	0	0	0	0	0	0	1	1	2	Low
Hettiarachchi et al [87]	1	1	0	0	0	0	0	0	1	1	4	Moderate
Haugen et al [88]	0	0	0	0	0	0	0	0	1	1	2	Low

Avagyan et al [89]	1	0	0	0	0	0	0	0	1	0	2	Low
Ahmed et al [90]	1	0	0	0	0	0	0	0	0	0	1	Low
Anwar et al[33]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Karim et al [55]	0	0	0	0	0	0	0	0	1	0	1	Low
Prasad et al[91]	1	1	1	0	0	0	0	0	1	1	5	Moderate
Agarwal et al[92]	1	1	1	0	0	0	0	0	0	0	3	Low
Basu et al [71]	1	1	1	0	0	0	0	0	1	0	4	Moderate

Table 2 (Continued): Quality assessment of selected studies using hoy et al check list

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total score	Quality
Wayse et al[93]	1	1	1	0	0	0	0	0	0	0	3	Low
Filteau et al [94]	0	1	1	0	0	0	1	0	1	1	5	Moderate
Taru et al [61]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Sreedharan et al [95]	1	1	1	0	0	0	0	0	1	1	5	Moderate
Agarwal et al [96]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Mathur et al [97]	1	0	0	0	0	0	0	0	0	0	1	Low
Kumar et al [98]	1	0	0	0	0	0	0	0	0	0	1	Low
Marwaha et al[67]	1	1	1	0	0	0	1	0	1	1	6	Moderate
Agrawal et al[99]	1	1	1	0	0	0	0	0	1	1	5	Moderate
Shukla et al[31]	0	1	1	0	0	0	1	0	0	0	3	Low
Meyer et al [37]	1	0	0	0	0	0	0	0	1	1	3	Low
Haugen et al[88]	1	0	0	0	0	1	0	0	1	1	4	Moderate
Sherchand et al[100]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Mahmood et al[34]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Islam et al[101]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Islam et al[102]	0	0	0	0	0	0	0	0	1	1	2	Low
Islam et al[103]	1	0	0	0	0	1	0	0	1	1	4	Moderate
Acherjya et al[104]	0	1	1	0	0	1	0	0	1	0	4	Moderate
Mubashir et al[105]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Junaid et al[106]	1	1	1	0	0	1	0	0	1	1	6	Moderate
Roomi et al[107]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Junaid et al[108]	0	0	0	0	0	1	0	0	0	0	1	Low
Sheikh et al[109]	0	0	0	0	0	0	0	0	1	0	1	Low
Mehboobali et al[110]	1	0	0	0	0	0	0	0	1	0	2	Low
Mansoor et al[111]	1	1	1	0	0	0	0	0	0	0	3	Low
Mustafa et al[112]	1	1	1	0	0	0	0	0	1	1	5	Moderate
Rehman et al[113]	1	1	1	0	0	0	1	0	1	1	6	Moderate
Khan et al[114]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Nadeem et al[38]	1	1	1	0	0	0	1	0	1	0	5	Moderate
Iqbal et al[115]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Mahmood et al[116]	0	1	1	0	0	1	0	0	1	0	4	Moderate
Afsar et al[117]	1	1	1	0	0	1	1	0	1	0	6	Moderate
Kumar et al[118]	1	1	1	0	0	0	0	0	1	1	5	Moderate
Sharif et al[119]	1	1	1	0	0	0	0	0	1	1	5	Moderate
Khan et al[120]	1	1	1	0	0	0	0	0	1	1	5	Moderate
Dar et al[121]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Arya et al[18]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Malhotra et al[122]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Harinarayan et al[123]	0	1	0	0	0	0	0	0	1	0	2	Low
Agrawal et al[124]	0	0	0	0	0	0	0	0	1	0	1	Low

Table 2 (Continued): Quality assessment of selected studies using hoy et al check list

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total score	Quality
Vupputuri et al[125]	1	0	0	0	0	0	0	0	1	0	2	Low
Suryanarayana et al [126]	1	0	0	0	0	0	0	0	1	0	2	Low
Shivane et al[127]	0	1	1	0	0	0	0	0	0	0	2	Low
Harinarayan et al[128]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Shukla et al[31]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Sanket et al[129]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Karoli et al[130]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Laway et al[131]	1	1	0	0	0	0	0	0	1	1	4	Moderate
Gupta et al[132]	1	1	0	0	0	0	0	0	1	0	3	Low
Bhatt et al[133]	0	0	0	0	0	1	0	0	1	1	3	Low
Marwaha et al[134]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Goswami et al[17]	0	0	0	0	0	0	0	0	1	1	2	Low
Zargar et al[135]	1	1	1	0	0	0	0	1	0	0	4	Moderate
Harinarayan et al[16]	1	0	0	0	0	0	0	1	0	0	2	Low
Sofi et al[136]	1	1	1	0	0	0	0	1	0	0	4	Moderate
Beloyartseva et al[137]	1	0	0	0	0	0	0	1	0	0	2	Low
Singh et al[138]	0	1	1	0	0	0	0	1	0	0	3	Low
Shetty et al[139]	1	0	0	0	0	0	0	1	0	0	2	Low
Kajale et al[140]	1	1	1	0	0	0	0	1	0	0	4	Moderate
Goswami et al[141]	1	1	1	0	0	0	0	1	0	0	4	Moderate
Kiran et al[142]	1	1	1	0	0	0	0	1	0	0	4	Moderate
Kumar et al[143]	1	1	1	0	0	0	0	1	0	0	4	Moderate
Goswami et al[144]	1	1	1	0	0	0	0	1	1	0	5	Moderate
Meena et al[145]	1	1	1	0	0	0	0	1	0	0	4	Moderate
Singh et al[146]	1	0	0	0	0	0	0	0	1	0	2	Low
Garg et al[81]	1	0	0	0	0	0	0	0	1	0	2	Low
Harinarayan et al[123]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Paul et al[147]	1	1	0	0	0	0	0	0	1	1	4	Moderate
Srimani et al[148]	1	0	0	0	0	0	0	0	1	0	2	Low
Harinarayan et al[149]	0	1	0	0	0	0	0	0	1	1	3	Low
Agarwal et al[150]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Mitra et al[151]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Agarwal et al[152]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Dixit et al[153]	1	1	1	0	0	0	0	0	1	0	4	Moderate
Kadam et al[154]	1	1	1	0	0	0	0	0	1	1	5	Moderate

Discussion:

In this section, our overall result points out that 65% pregnant women, 61% children and 68% adults who lived in south Asia were affected with Vitamin D deficiency. This means more than six out of ten people lived in south Asia were affected with Vitamin D deficiency. Beside this, we also found large amounts of heterogeneity for all three groups [I^2 = 98% (adult), 99% (pregnant women and children)]. Geographical location, gender and age might act as a factor for such a high percentage of heterogeneity.

Country wise analysis suggested that Pakistan had the highest percentage of prevalence for all three groups [pregnant women, children and adults]. In Pakistan 76% pregnant women, 94% children and 73% adults were affected with Vitamin D deficiency. On the other hand Sri Lanka had the lowest percentage of prevalence for two (children and adults) out of three groups. In Sri Lanka 25% of children and 48% of adults were affected with Vitamin D deficiency [In Sri Lanka we did find a single study which was conducted on pregnant women]. So geographical location might act as a factor for such a high percentage of prevalence among Pakistani population and low percentage of prevalence among the Sri Lankan population. Because People living in tropical regions get more sunlight throughout the year than those who are living in subtropical regions. From our review of literature we all know that Vitamin D is synthesized naturally in the human body when UVB from sunlight penetrates our skin and undergoes some physiological process. So, sunlight availability and exposure is necessary for the production of Vitamin D in our body [5]. Pakistan is located in a sub-tropical region where sunlight availability is low. So might be because of this that children, adult and pregnant women lived in Pakistan had the highest percentage of prevalence in comparison with other south Asian countries. On the other

hand Sri Lanka is located in a tropical region where sunlight availability is high throughout the year and that's why children and adults living in Sri Lanka showed lowest prevalence in comparison to other south Asian countries [155].

Gender wise analysis showed that prevalence of Vitamin D deficiency is high among South Asian females in comparison to male. In south Asia 76% of adult female and young girls (children) were affected with Vitamin D deficiency whereas in the case of male it was 52% for adults [we did find a single study which was conducted only on boys (children)]. So females are more affected with Vitamin D deficiency than male in south Asia. This might be because most of the south Asian women spend their life in household work. A recent report from the World Bank points out that the female labor force participation rate is near about 24% whereas male labor force participation rate is 80%[156]. UNICEF reported that women make up less than 5% in the police force and less than 10% of judges in this region [157]. As women in this region spend more time in household work, they did not get much time to expose themselves in sunlight. Besides this, clothing practice of women in this region may be also influenced by such a high percentage of Vitamin-D deficiency. News reports suggested that the use of burqas and hijabs increased exponentially in this region in the past three decades [158]. As women cover their arms and feet when going outside, opportunity for sunlight exposure is reduced. As a result they are affected more than male with Vitamin D deficiency. Apart from the custom of clothing, early marriage, poor education, and insufficient decision-making ability may also serve as a cause for such a high prevalence of vitamin D deficiency among South Asian girls. According to UNICEF in South Asia social norms prioritize boys receiving higher education, and so the girls lose their continuing education. Additionally, 1 in 2 girls in this region get married before the age of 18. More than 20-40% adolescent's girls in this region receive their recommended dietary intake.

These all factors could influence such a high percentage of Vitamin D deficiency among females in this region.

Age wise analysis points out that prevalence of Vitamin D deficiency is highest among neonates (85%) than followed by adults (68%), preschool (55%) and school children (57%). This may be because of the high prevalence of vitamin D deficiency among south Asian pregnant women. Moreover 38% (64 million) of under 5 year's children in South Asia are stunned. They suffer from lack of essential nutrients at an early age [159]. This poor diet may also act as a factor for such a high prevalence of Vitamin D deficiency among neonates in this region.

In south Asia most of the studies (92%) conducted among Indian, Pakistani and Bangladeshi population and very few amounts of studies from Nepalese and Sri Lankan (7%) population. Bar diagram showed that average level of Vitamin D status was less than 20 ng/ml among all groups (Pregnant women, children and adult) of population lived in India, Pakistan and Bangladesh. For Nepalese and Sri Lankan Population average level of Vitamin D status was less than 30 ng/ml. We found only a single study from Afghanistan and did not find a single study from Bhutan and Maldives. So our findings do not demonstrate a complete picture of Vitamin D status in the South Asian population but point out that it is in an alarming state.

In South Asia various types of communicable and non-communicable diseases are rising. The main communicable and non-communicable diseases in South Asia are diabetes, cardiovascular disease, cancer, tuberculosis, chronic respiratory disease. Besides those communicable and non-communicable diseases obesity, rickets, osteomalacia and several kinds of other bone related diseases are also rising in south Asia [160,161,162,163]. According to the World Bank in the year 2017, the number of maternal deaths in South Asian countries is more than fifty seven thousands.

Among eight south Asian countries, India reported the highest number (35000) of maternal death and then followed by Pakistan (8300), Afghanistan (7700) and Bangladesh (5100) in that year [164]. Study reports indicated that infections (sepsis), hypertension (pre-eclampsia and eclampsia), and complications during delivery is the major cause of maternal death in India, Bangladesh and Pakistan [165–167]. This high prevalence of deficiency of vitamin D and low status of vitamin D may serve as a factor in the growth of these communicable, non-communicable, bone related diseases and pregnancy related complications in this region. In the future, this high prevalence of vitamin D deficiency and low Vitamin D status may cause severe health effects and may also increase mortality rates in this region among all groups of population.

We did not find any national level policy from any one of eight south Asian countries to overcome this scenario and improve vitamin-D status. Policy makers need to address this thing with serious concern. We should recommend, increase of study numbers is essential among countries where limited number of studies or no study is conducted regarding Vitamin D status. Moreover, because of lack of data our findings does not point out anything on the effect of demographic area and socio economic status on such a high prevalence of Vitamin D deficiency in this region. So future systematic review should be focused on these two points. Beside this, our overall findings are based on published literature. A molecular level analysis is necessary by including sufficient people from all south Asian countries to show is there any association with genetic factors for such a high prevalence of Vitamin D deficiency in this region.

However, the government of every south Asian country should include the importance of Vitamin D in their national health policy and develop their nutritional guidelines. Besides improving policy, south Asian governments should also aware mass communication by electronic, print and social media about the negative impact of Vitamin D deficiency on our

health, encourage people to take sunlight exposure and eat Vitamin D containing food such as egg yolk, cod liver oil, beef lever, salmon, and tuna fish. To improve Vitamin D status, south Asian governments might also develop a food fortification program and fortified milk, orange juice, yogurt with Vitamin D [5]

Chapter 2:

To evaluate Knowledge, Attitude and Practice regarding Vitamin D and Sunlight: A KAP study among Bangladeshi Doctors and students from College, University and Medical College

From the previous section, it is clear that Vitamin D deficiency is highly prevalent among the south Asian population, especially in this subcontinent (Bangladesh, India and Pakistan) it was in an alarming state. To identify the main reason behind this in this section we performed two KAP (Knowledge, Attitude and Practice) study. A KAP study evaluates knowledge, attitude and practice of a community. It measures change of knowledge, attitude and practice pattern of a

community and acts as an educational diagnosis of a community. In this section we perform KAP study only among Bangladeshi students and doctors [168].

In this section our aim is to evaluate the knowledge, attitude and practice regarding Vitamin-D and sunlight from Bangladeshi general students (college level and university level), medical students (M.B.B.S and B.D.S) and doctors (Registered and Intern doctor) who are either studied in different colleges and universities or working in different medical institution. We assume that our findings will identify the most significant reason behind Vitamin D deficiency and suggest appropriate intervention to overcome this problem.

Methods:

Study design:

Two descriptive cross sectional studies were conducted. Firstly, among Bangladeshi students who studied in college level (higher secondary) or university level (graduation or post-graduation) and pursuing their relative course of interest. After this another study was conducted among Bangladeshi doctors (registered doctors and intern doctors) and medical students (4^{th} or

5th year M.B.B.S students and B.D.S students) who were either studying or working in different medical institutions. Study was conducted after getting ethical permission from Bangladesh biomedical research foundation and BRAC University ethical committee.

Sampling:

According to Bangladesh Bureau of Educational Information and Statistics (banbeis) there are currently a total of 4700 recognized colleges and universities in Bangladesh, where over 50 lakhs students take their higher secondary, graduate and postgraduate courses [169,170]. Furthermore, at present there are in total 128 recognized medical and dental colleges in Bangladesh and every year more than 11000 thousands students get admitted in these institutions to fulfill their M.B.B.S and B.D.S degree [171,172]. Beside this, there are about 1 lakhs Doctors and Dentists registered with the Bangladesh Medical and Dental Council (BM & DC), the regulatory body for doctors, and medical education [173].

To obtain an accuracy level of 95% (assuming prevalence 50%) with ± 2.5% margin of error, the calculated sample size was 1537 for both of our study community[174]. We randomly selected 35 institutions (20 colleges and universities and 15 medical institutions) from the databases of Bangladesh Bureau of Educational Information and Statistics (banbeis) and Directorate General of Health Services (DGHS) [169,170]. These two studies were carried out from August 2019 to February 2020.

Instrument:

Two self-administered questionnaires were developed by two researchers based on previously published KAPs study, conducted in other countries [175–177]. The questionnaire consisted of both open ended and closed ended questions. The questionnaire was prepared both in Bengali and English version and supplied as per participants preference. We did not take any kind of personal information (name, age, socio economic status etc.) through questions from our study participants.

Procedure of Data collections:

After choosing our target institutions, we approach the respected institutional authority and ask for their permission to do this study by sending a formal letter from our institution. We set a date after getting their permission and scheduled a season with the participants. Two investigators and a group of pre-trained volunteers gathered data from various institutions. Participants were not previously informed about the study and there was no mention of the word "Vitamin D and Sunlight" during the invitation. Instead, a general announcement was made that there would be a health awareness based survey, with the participation of interested participants. Once we gave the questionnaires to participants we told them about the answering method such as giving a tick mark whatever you think is correct from the multiple options present in each question. Then we provide them with a questionnaire to answer in the presence of the institutions' represented authority. During answering question, all kinds of discussion between students or using a mobile phone were avoided. After completing their answers, we collected questionnaires from participants and store them in an envelope for analysis.

Data Analysis:

Data analysis was done by using RED Cap which is an online web platform for storing and analyzing data from survey based study

Result:

We divided our result into two parts where we show our KAP study result separately for (1) College and University Students and for (2) Medical students and Doctors.

(1) College and University students:

Overall 2912 students from twenty different Universities and colleges participated in this study. Among them, 136 participants were rejected because of not mentioning their gender and approaching illegal ways (using mobile phones or plagiarism) while answering the questionnaires. Finally, 2776 participants were eligible for this analysis. Among them over half of our participants (56.8%) were female and rest of them were male. More than half of our study participants (64.5%) studied at either under graduate or post graduate level and the rest of them were from higher secondary level. In case of undergraduate and postgraduate participants, 33.3% studied biological sciences (Zoology, Botany, Biotechnology and Microbiology), 26.3% was belonged to the physical sciences and engineering (Electronics and Electrical Engineering, Computer Science and Engineering and Architect), 21.3%

were from social sciences (Political science, Sociology, English, Bangla and Law) and the rest of 19.1% were from business studies (Finance, Management, Accounting and Marketing). On the other hand, in higher secondary level, most of our study participants (42%) was from the group of humanities, one fourth of them (25%) were from science and rest of them was from the group of business studies.

Participant's attitude regarding UV radiation, sunlight and using sunscreen:

Over half of our study participants (60 %) claimed that the amount of ultraviolet radiation (UV) in sunlight of Bangladesh was either at a very high or moderate level. Highest number of our study participants (77%) thought that sometimes people should go to get direct sunlight exposure, whereas 10% of our study participants claimed that direct sunlight exposure should be

totally avoided and only very few of our study participants (3%) thought that people should go always to get direct sunlight exposure. Over half of our study participants (52%) thought that daily sunlight exposure could have a harmful or relatively harmful impact on our health and almost one-third of our study participants (32%) thought it could have a relatively good or very good health effect. More than half of our study participants (60%) thought reducing skin brightness was the potential harmful effects and almost one-third of our study participants (30%) thought skin burning could be the potential harmful effects if Bangladeshi people regularly spend half an hour in direct sunlight.

Table 4: Detail answers of participant's attitude regarding UV radiation, sunlight and using sunscreen

Questions	Answers	Male (n=1200)	Female (n=1576)	Overall (n=2776)
In general, what is the level of ultraviolet (UV) radiation in sunlight in Bangladesh?	Very High	19%	31%	26%
	Moderate	36.4%	35%	36%
	Very Low	19%	10%	14%
	Almost absent	3%	1.5%	2%
	Do not Know	23%	22%	22%
What is your opinion about getting direct exposure to sunlight?	Should be totally avoided	8%	10.5%	10%
	Should go sometimes	78.6%	76%	77%
	Should go always	3.4%	3%	3%
	Not sure	10%	10.5%	10%
In your opinion, what can be the potential effects of regular sunlight exposure on our health?	Very harmful	14%	20.1%	17.5%
	Fairly harmful	35%	33.6%	34.4%
	Fairly good	25%	23%	23.4%
	Very good	8%	9.5%	9%
	There is no relationship	4.5%	2%	3.4%
	Not sure	13%	12%	13%
If Bangladeshi people spend half an hour daily in direct sunlight, what could be the possible harmful effects (can choose multiple answers)?	Skin burn	28%	32%	30%
	Reduce brightness of the skin	59%	61%	60%
	Increasing risk of cancer	12%	13%	12.6%
	Dehydration	32%	31.6%	32%
	Heat stroke	17%	18.6%	18%
	Not sure	16%	13%	14%
If you think it is harmful to get exposed to sunlight regularly, which of the following options played an important role in creating your perception?	Advertisement of fairness creams	11.6%	9%	10%
	Doctor's advice	27.6%	31.5%	30%
	Newspaper articles	4.4%	3.4%	4%

	Family	10%	8%	9%
	Textbook	9%	9%	9%
	Others	12.5%	15%	14%
	Do not think it is harmful	25%	24%	24%
Do you think it is necessary for Bangladeshi people to use sunscreen regularly to stay protected from the negative effects of direct sunlight?	Yes	39%	53%	46%
	No	38%	25%	31%
	Not sure	23%	22%	23%

More than three-fourth of our participants (76%) thought it unhealthy to get regularly exposed to sunlight and almost one-third of our study participants (30%) answered that advice from doctors plays an important role in building their understanding of this.

Nearly half of our study participants (46%) thought it was necessary for Bangladeshi people to regularly use sunscreen to stay safe from the adverse impact of direct sunlight, and almost one third of our participants (31%) thought it was not necessary. There was a thorough answer to all of these questions in Table 1.

Participant's knowledge and attitude about Vitamin D and its deficiency:

Largest number of our study participants (73 %) thought that the best time to produce vitamin D in our body from direct sunlight is from sunshine to 10 a.m., while only 11% of our study participants thought that 10 a.m. to 3 p.m. would be the best time to produce vitamin D from direct sunlight. Furthermore, nearly one-third of our study participants (32.4%) thought that spending 15-30 minutes a week in direct sunlight was enough for Bangladeshis people to get enough vitamin D and almost one-fourth of our study participants (24 %) replied that they were not sure about it. Rest of them thought 5-15 minutes (16%) or 30 minutes to 1 hour (13%) or 1-3 hours (8 %) or more than 3 hours (6.6%) was the minimum time needed to get enough Vitamin D. Bone and waist pain was identified as symptoms associated with Vitamin D deficiency by nearly half of our study participants (47%) and more than one third of our study participants identified bone loss (38%) and tiredness (35%) as symptoms associated with Vitamin D deficiency. Nearly half of our study participants (47%) reported bone and waist pain as

symptoms associated with vitamin D deficiency, and over one third of our study participants reported bone loss (38%) and tiredness (35%) as symptoms associated with vitamin D deficiency. In addition, over half of our study participants (55%) listed osteoporosis as a risk factor due to deficiency in vitamin D, whereas cancer and diabetes were reported as risk factors by 8 % of our study participants. Nearly half of our study participants (47%) replied in the affirmative that they might have Vitamin D deficiency and more than one-fourth (26%) of our study participants replied that they were not sure about it. Thorough answers to all of these questions were available in table 2.

Table 5: Detail answers of participant's Knowledge and attitude about Vitamin D and its deficiency

Questions	Answers	Male (n=1200)	Female (n=1576)	Overall (n=2776)
Which is the best time to produce vitamin D in the human body from direct sunlight in Bangladesh?	From sunshine to 10a.m	71%	75%	73%
	10a.m to 3p.m	12%	9.4%	11%
	From 3p.m to sunset	4.4%	2%	3%
	Not sure	12.6%	13%	13%
What is the required minimum duration of direct sunlight exposure per week for Bangladeshi people to get enough Vitamin D?	5 -15 minutes	13%	18%	16%
	15-30 minutes	32.5%	32%	32.4%
	30 minutes – 1 hour	15.6%	11.5%	13%
	1 – 3 hour	10%	6.5%	8%
	More than 3 hour	7.6%	6%	6.6%
	Not sure	21.4%	26%	24%
Which of the following are the symptoms associated with vitamin D deficiency (can choose multiple answers)?	Bone and waist pain	44%	50.4%	47%
	Bone loss	35.5%	40.4%	38%
	Depression	14%	11%	12.4%
	Hair loss	16%	18.5%	17%
	Tiredness	35.6%	35%	35%

	Frequent illness	16%	18.5%	17%
	Not sure	15.6%	13%	14%
For which of the following diseases, deficiency of vitamin D serves as a risk factor (can choose multiple answers)?	Osteoporosis (fragile bone)	55%	55%	55%
	Autoimmune disease	16%	17%	17%
	Cancer	8%	7%	8%
	Diabetes	8%	74%	8%
	Obesity	8.4%	6%	7%
	Not sure	27%	27%	27%
If all of the symptoms mentioned above are related to vitamin D deficiency, do you think you might have vitamin D deficiency?	Yes	41%	52%	47%
	No	31.6%	22%	27%
	Not sure	27.6%	26	26%

Participants Attitude and practice regarding Vitamin D and Sunlight:

Half of our study participants (50%) thought that getting darker skin due to sunlight-exposure is a problem and one-fifth (20%) of our study participants replied no comment on this question. Rest of them replied that they did not think getting darker skin due to sunlight exposure is a problem. More than half of our study participants (58%) replied that they did not avoid direct sunlight at home or outside and nearly one-third (31%) of our study participants avoided it. Over half of our study participants (58%) used umbrella to get protected from sunlight, nearly one fourth of our study participants (24%) used scarf / hijab and nearly one fifth of our study participants (19%) use full shelve shirt or burka as a direct sunlight safety tool and nearly one sixth of our study participants (16%) used sunscreen / fairness cream to get protected from direct sunlight when they were outside. Nearly half of our study participants (47%) went outside between 10a.m to 3p.m and almost one third of our study participants (31%) went between sunshine to 10a.m to get direct sunlight. Highest number of our study participants (85%) never checked their own Vitamin D level, 8% of them not sure about it and only 7% of our study

participants checked it. Maximum number of our study participants (69%) never took Vitamin D as medicine or supplement, 11% of them were not sure about it and only one-fifth of our study participants took (20%) Vitamin D as medicine or supplement. One fifth of our study participant (20%) replied in the affirmative that they routinely take Vitamin D whereas, more than half of our study participants (60%) replied this question in the negative.

Table 6: Detail answers of participant's attitude and practice regarding Vitamin D and Sunlight

Questions	Answers	Male (n=1200)	Female (n=1576)	Overall (n=2776)
Do you think getting darker skin due to direct sunlight-exposure is a problem?	Yes	43.4%	55%	50%
	No	39%	23.5%	30%
	No comment	17.3%	21%	20%
Do you avoid direct sunlight at home or outside?	Yes	33.4%	29.4%	31%
	No	56.6%	59%	58%
	Not sure	10%	11.6%	11%
What do you use regularly to get protected from direct sunlight when you are staying outdoors (can choose multiple answers)?	Umbrella	48%	63%	56%
	Scarf/hijab	5%	39%	24%
	Full sleeve shirt/burka	13%	24%	19%
	Cap	23%	7%	14%
	Sunscreen/fairness cream	12%	18.4%	15.6%
	Nothing	35%	15%	24%

Usually, at which time of the day you go to get direct sunlight?	From sunshine to 10a.m	27%	33.5%	31%
	10a.m to 3p.m	48%	46%	47%
	From 3p.m to sunset	9%	4.4%	6%
	Not sure	11%	11%	11%
	Usually, I do not go to get direct sunlight	5%	5%	5%
Have you ever checked your own vitamin D level?	Yes	7.4%	5.4%	7%
	No	84%	87%	85%
	Not sure	8.4%	7.5%	8%
Have you ever taken vitamin D as medicine/supplement?	Yes	22.6%	19%	20%
	No	66%	71%	69%
	Not sure	11.4%	10%	11%
Do you regularly take vitamin D?	Yes	19%	20%	20%
	No	62%	59%	60%
	Not sure	19%	20.5%	20%

(2) Medical Students and Doctors:

In total 2190 doctors, medical students and dental students participated in this study. We disqualified 132 participants from this study because they addressed the questionnaires wrongly (using cell phone or plagiarism). Finally the responses were available for analysis from 2058 participants. Among them 799 were doctors (registered and intern) and 1259 were students (medical and dental). All the students who took part in this study were in 4^{th} or 5^{th} year of their academic career.

Participant's attitude regarding UV radiation, sunlight and using sunscreen:

More than one-fourth of our study participants (26.4%) claimed that very high levels of ultraviolet radiation (UV) were present in the sunlight of Bangladesh and more than half of our study participants (56%) thought that it was at a moderate level. Maximum number (68%) of our study participants thought that daily exposure to sunlight could have a harmful or relatively harmful effect on the health of Bangladeshi citizens and only 30% of our study participants thought it could have a relatively good or very good effect on our health. Over half of our study participants (58%) thought that reducing brightness of skin is the possible harmful effects and almost half of our study participants (45.5%) claimed that skin burn could be the possible harmful effects, if Bangladeshi people spend half an hour regularly on direct sunlight. Almost all of our study participants (91%) thought that Bangladeshi people either should always use sunscreen or can be used sometimes to avoid the negative effect of direct sunlight, while only 5% of our participants thought that there was no need to use sunscreen at all to avoid the negative effect of direct sunlight. Detailed answers to all of these questions were available in table 7.

Table 7: Detail answers of participant's attitude regarding UV radiation, sunlight and using sunscreen

Questions	Answers	Registered doctors (n = 379)	Intern doctors (n = 420)	M.B.B.S students (4^{th} / 5^{th} year) (n = 899)	B.D.S students (4^{th} / 5^{th} year) (n = 360)	Overall (n = 2058)
In general, what is the level	Very High	22.5%	37%	22%	28%	26.4%

of ultraviolet (UV) radiation in sunlight in Bangladesh?	Moderate	58%	53%	55%	60.6%	56%
	Very Low	10%	3%	6%	5.3%	6%
	Almost absent	3%	1.4%	2%	0%	2%
	Do not Know	6.4%	5.5%	14.2%	6.4%	10%
In your opinion, what can be the potential effects of regular sunlight exposure on the health of Bangladeshi people?	Very harmful	22%	28.5%	28%	34%	28%
	Fairly harmful	48%	38.3%	38%	39.6%	40%
	Fairly good	18.6%	27%	24%	17.4%	23%
	Very good	9.2%	5%	8%	6%	7%
	There is no relationship	2.4%	1%	2%	3.4%	2%
If Bangladeshi people spend half an hour daily in direct sunlight, what could be the possible harmful effects (can choose multiple answers)?	Skin burn	28%	65%	42%	50%	45.5%
	Reduce brightness of the skin	68%	54%	57%	55%	58%
	Increasing risk of cancer	16%	27%	35%	39%	30%
	Dehydration	16%	34%	26.4%	34%	27%
	Heat stroke	15.6%	19.%	20%	32%	21%
In your opinion, what is the level of necessity for Bangladeshi people to use sunscreen to avoid the negative effects of direct sunlight?	Should be used always	24%	50%	43%	61.5%	44%
	Can be used sometimes	63.6%	47%	45%	32.4%	47%
	No need to use at all	7%	1%	6%	2%	4.4%
	Not sure	5%	2.4%	6%	4.5%	5%

Participants Knowledge about Vitamin D, high risk group and insufficiency rate in Bangladeshi population:

Highest number of our study participants (69%) thought that from sunshine to 10a.m was the best time to produce Vitamin D in our body from direct sunlight, whereas only 22% of our study participants claimed that 10a.m to 3p.m was the best suitable time to produce Vitamin D from direct sunlight. Furthermore, most of them (40%) thought that spending 15-30 minutes weekly in direct sunlight was sufficient for Bangladeshi people to get enough Vitamin D, 19% of them thought time duration was 5-15 minutes, 18.4% of them thought it was 30 minutes to 1 hour, 15% of them thought it was between 1-3 hour and 7% of our study participants thought that more than 3 hour was the required minimum duration to get enough Vitamin D. The highest number of our study participants (81 %) described bone and waist pain as symptoms associated with vitamin D deficiency. Besides this, the highest number of our study participants (87.6%) reported osteoporosis and more than half of our study participants (56%) reported bone loss as a risk factor caused by deficiency of Vitamin D. Cancer was identified by 23% of our study

Table 8: Detail answers of participant's knowledge about Vitamin D, high risk group and insufficiency rate in Bangladeshi population

Questions	Answers	Registered doctors (n = 379)	Intern doctors (n = 420)	M.B.B.S students (4^{th} / 5^{th} year) (n = 899)	B.D.S students (4^{th} / 5^{th} year) (n = 360)	Overall (n = 2058)
Which is the best time to produce vitamin D in the human body from direct sunlight in Bangladesh?	From sunshine to 10a.m	73%	71%	63%	79%	69%
	10a.m to 3p.m	19%	22%	24%	16%	22%
	From 3p.m to sunset	2%	2%	8%	2%	4%
	Not sure	6%	5%	5%	3%	5%
What is the required minimum duration of direct sunlight exposure per week for Bangladeshi people to get enough vitamin D?	5 -15 minutes	17%	22%	17.6%	22%	19%
	15-30 minutes	53%	40%	37%	36.6%	40%
	30 minutes – 1 hour	14%	12%	22%	17%	19%
	1 – 3 hour	9%	19%	18%	10%	15%
	More than 3 hour	7%	7%	5.4%	14.4%	7%
Which of the following are the symptoms associated with vitamin D deficiency (can choose multiple answers)?	Bone and waist pain	84%	83.5%	79.5%	83%	81%
	Bone loss	57%	58%	55.4%	73%	59%
	Depression	14%	14%	10.5%	12.5%	12%
	Hair loss	34.5%	47%	40%	32.6%	39%
	Tiredness	27%	31%	33%	25.6%	30%
	Frequent illness	31%	15%	18%	14%	18.6%
For which of the following diseases, deficiency of vitamin D serves as a risk factor (can choose multiple answers)?	Osteoporosis	90%	90.4%	85.4%	89.6%	87.6%
	Heart disease	11%	7%	9.4%	10.4%	9%
	Autoimmune disease	14%	25%	17%	22.%	19%
	Diabetes	6%	3%	7.6%	5%	6%
	Obesity	7%	5%	7%	5%	6%
	Cancer	5%	40%	24%	21%	23%
	Anemia	12%	9.4%	7%	4%	7.6%
	Autism	7%	9%	11%	7%	9%
	Tuberculosis	1%	1%	6%	1.7%	3%
	Arthritis	54%	71%	55.4%	49%	56%
	Hypertension	3%	2%	6.5%	5%	5%
	Not sure	3.5%	2%	4%	3.6%	3.5%
In your opinion, which segment of Bangladeshi population is more likely to suffer from vitamin D deficiency (can choose multiple answers)?	New born (<2 years)	25.6%	48%	37%	44%	38%
	Children (2 – 12 years)	20%	19%	37%	45.5%	31%
	Adolescents (13 – 19 years)	11.6%	20%	17%	24%	18%
	Pregnant women	54.5%	45.4%	39%	45%	44%
	Postmenopausal women	29%	29%	41%	30%	34.4%
	Elderly men and women	54.5%	57%	52	32%	49.6%
	Corporate employee	31%	20%	21.6%	14.5%	22%
	Garments worker	23.6%	25%	24%	18.5%	23%
	Heart patients	3%	3%	4.4%	7%	4.4%
In your opinion, what percentage of Bangladeshi population may have vitamin D insufficiency?	Less than 25%	22.6%	15%	25%	24.5%	22%
	25-50%	54%	46.5%	44%	40%	45%
	50-75%	15.5%	23%	19.4%	25%	21%
	More than 75%	8%	16%	11.6%	10%	12%

participants and very few of our study participants claimed that heart disease (9%), diabetes (6%) and obesity (6%) serve as a risk factor for Vitamin D deficiency. Almost half of our study participants (49.6%) claimed that elderly men and women and nearly one-fourth our study

participants thought that corporate employees (22%) and garment workers (23%) were the high risk group of population in our country who could be affected with Vitamin D deficiency. Furthermore, approximately one-third of our study participants (30 percent) identified newborn babies (< 2 years) and children (2-12 years), and nearly half of our study participants (44 percent) identified pregnant women as a high risk group of population for vitamin D deficiency. In case of Vitamin D insufficiency, near about half of our study participants (45%) thought that 25-50% of Bangladeshi population may have vitamin D insufficiency, whereas just 12% of study participants thought that more 75% of Bangladeshi population might have Vitamin D insufficiency. Details answered to all of these questions were available in table 2.

Participants practice and attitude regarding Vitamin D and its source:

More than three-fourth of our study participants (80%) never checked their own Vitamin D level and only 12% of them checked it. Only one third of our study participants (33.4%) thought that regular sunlight exposure might be the most effective option to ensure adequate vitamin D levels for Bangladeshi population. Highest number of our study participants (62.4%) thought that taking fortified food or taking Vitamin D supplements might be the most effective options to ensure adequate vitamin D levels for our country's people. Detailed answers to all of these questions were available in table 3.

Table 9: Detail answers of participant's practice and attitude towards Vitamin D and its source

Questions	Answers	Registered doctors (n = 379)	Intern doctors (n = 420)	M.B.B.S students (4th / 5th year) (n = 899)	B.D.S students (4th / 5th year) (n = 360)	Overall (n = 2058)
Have you ever checked your own vitamin D level?	Yes	11.5%	9%	11.4%	14%	12%
	No	84.5%	81%	79.4%	82%	80%
	Not sure	4%	10%	9.2%	3.4%	8%
Considering the overall condition, which of the following options might be most effective to ensure adequate vitamin D level for Bangladeshi population?	Taking fortified food containing vitamin D	39%	31%	46%	53%	42.4%
	Taking vitamin D supplement	17%	27%	17%	20%	20%
	Regular sunlight exposure	41.4%	38.4%	33%	21%	33.4%
	Not sure	2%	3.4%	3.6%	6%	4%

Discussion:

Vitamin D plays an important role in several physiological activities such as calcium phosphorus homeostasis, stimulating insulin production, inhibiting renin production, inhibiting cellular proliferation and inducing terminal differentiation, stimulating macrophages cathelicidin production and inhibiting angiogenesis [5]. Since Vitamin D has an immense anti-inflammatory and immune modulating effects on our body, deficiency or insufficiency of Vitamin D can create a negative impact on our health. So if people are aware about the importance of Vitamin D, what will be the effect of Vitamin D deficiency in our health and how they can improve their Vitamin D status, it will be much easier to improve the Vitamin D status of many countries which have low Vitamin D status like Bangladesh.

Vitamin D deficiency is highly prevalent in south Asian countries, especially in this subcontinent which we discussed previously. In this part of our study, we focus on Knowledge, Attitude and Practice among Bangladeshi students and doctors regarding Vitamin D and Sunlight. Our study result showed that the maximum number of our study participants had lack of knowledge regarding Vitamin D and sunlight. This lack of knowledge creates a wrong attitude and this wrong attitude reflects on their practice.

Maximum number of our study participants thought that the importance of Vitamin D is only associated with bone and that's why more than half of our study participants (55%) from college and university replied that osteoporosis serves as a risk factor for development of Vitamin D deficiency. Whereas in case of medical students and doctors most of them (88%) select osteoporosis. But several epidemiological and observational studies suggested that besides osteoporosis low Vitamin D status is associated with development of many communicable and non-communicable diseases such as cancer, diabetes, heart disease, tuberculosis, obesity, influenza [6]. Very few of our study participants thought that Vitamin D deficiency can serve as a

risk factor for development of these communicable and non-communicable diseases.

Moreover, almost all of our study participants did not know about the best suitable time to produce Vitamin D in the human body from direct sunlight. Only 11% of our participants from college-university and 22% of participants from medical groups replied correctly that 10a.m to 3p.m is the best suitable time to produce Vitamin-D in humans from direct sunlight in Bangladesh [6].

Maximum number of Bangladeshis had black brown or light brown or dark skin colour. So, according to fitzpatrick skin colour almost all of the Bangladeshis belong to skin type III to VI. According to study reports, if an individual spend 5-30 minutes (depending on skin colour) between 10a.m to 3p.m twice in a week in direct sunlight, it will be enough to produce necessary Vitamin D [178]. So on basis of this theory spending 30 minutes to 1 hour in direct sunlight is enough for Bangladeshi people to produce necessary Vitamin, whereas less than 20% of study participants from both group replied this answer correctly.

Indoor workers are mostly affected with Vitamin D deficiency than outdoor workers reported in many countries including Bangladesh [34,179,180]. But only 22-23% of our study participants from the medical group replied that corporate employees and garment workers were more likely to suffer with Vitamin D deficiency. Moreover, In the previous section we showed that more than more than 6 out of 10 south Asian populations had Vitamin D deficiency (<20ng/ml). So in case of insufficiency (<30 g/ml) it is obvious that this percentage will be more. Study reports suggested that more than 75% of Bangladeshi population had Vitamin D insufficiency but only 12% of our medical participants thought like this [102,181].

In university and college three-fourth of our study participants never took Vitamin D as medicine and supplement. So, that means doctors rarely suggest Vitamin D to take as a nutrients or immunity boost up drug. Furthermore, four-fifth of our study participants from both groups never checked their own Vitamin D level. That means doctors were also not much concerned about their own Vitamin D status. These things clearly suggested that practice regarding Vitamin D is worse in our country.

Besides this, a maximum number of participants from medical groups thought that taking fortified food containing Vitamin D is the most effective option for Bangladeshi people to fulfill their Vitamin D status. But very few fortified foods contain Vitamin D and these things also differ from country to country. Moreover, taking Vitamin D from other sources except sunlight is costly for most of our population, since one out of five people lived below the poverty line in Bangladesh with a daily average wage less than 5$. Moreover, middle class Bangladeshi people were also suffering with the rising cost of living expenses [182,183]. So sunlight is the most effective source of Vitamin D for most of the people in Bangladesh.

However, less than 10% of our participants from both groups thought that regular sunlight exposure had a potentially good effect on our health. Furthermore, more than one-fourth of our study participants from both the group thought that in our country, there is a very high level of UV radiation present in sunlight.

According to WHO, UV index ranged from 8-10 defined as a very high level of UV radiation. We did not find any specific data which reflects the average UV index in Bangladesh. We assume that it might be ranged within 3-7 depending on seasonal variation. We assume this because Bangladesh has a very limited number of skin cancer patients. A recent report published from WHO, showed that in Bangladesh 320 people died because of melanoma skin cancer and

ranked 28 in the list of incidence, mortality and prevalence caused by cancer in Bangladesh. Australia and New Zealand were the top two countries that reported the highest rate of melanoma skin cancer whereas Bangladesh ranked 183 globally. Moreover UV index in Australia and New Zealand also ranged from 8-11 throughout the year that means very high to extreme level of UV index. This happens because Australia and New Zealand are located close to the equator region whereas Bangladesh is quite far away from the equator and that's why we thought UV levels in Bangladesh ranged between moderate to high [184–188].

Furthermore, our study result also showed that the maximum number of study participants from both groups were more concerned about the brightness of the skin rather than cancer if they spend half an hour daily on direct sunlight. Beside this, about 70% of our participants from college and university replied that they thought getting darker skin due to sunlight exposure is a problem. That means our study participants had a negative impression towards sunlight might be because they were more concerned about their skin colour.

Lack of knowledge regarding Vitamin D and sunlight create negative perception among our study participants and because of negative perception they had wrong practice. Almost half of our study participants from college and university went to get direct sunlight between 10a.m to 3p.m. If they were aware they can easily expose themselves regularly in direct sunlight for 10-15 minutes and this thing will improve their Vitamin D status. Moreover, if people need to spend more time in sunlight during mid-days they can follow WHO protocols for protection against sunlight.

In a disease map, diabetes, heart disease, cancer, preterm birth complication and tuberculosis were identified as the top ten causes of death in the Bangladeshi population. Together these diseases accounted for about 30 % of the overall annual death [189]. This mortality rate can be

reduced if people increase their Vitamin D status. Beside this recently a report from WHO showed that more than ten thousand people in Bangladesh died because of colon cancer and breast cancer. Study reports showed that low Vitamin D status is strongly associated with colon cancer and breast cancer. So improving Vitamin D status might act as a factor for decreasing our mortality rate and improving overall health status.

Conclusion:

Vitamin D deficiency is highly prevalent in south Asian countries, especially in India, Bangladesh and Pakistan. Moreover, our study result also showed that in Bangladesh educated individuals had lack of knowledge, negative attitude and wrong practice regarding Vitamin D and Sunlight. To overcome this scenario at first, Bangladesh as well as other south Asian countries need to address this issue as a problem and then take necessary steps to overcome this scenario. If government policy failed to address this issue, mortality and morbidity rate because of both communicable and non-communicable disease will not be decreased in this region. Moreover educated individuals in Bangladesh need to improve their knowledge regarding Vitamin D, develop a positive attitude towards sunlight and improve their practice in addition to Vitamin D and Sunlight.

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