A review article

Vitamin D deficiency is less prevalent among children with common medical illnesses than apparently healthy children in sub-Saharan Africa: A systematic review and meta-analysis

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Background: Studies shows that 25(OH)D status appears to have some beneficial influence on the incidence and severity of some types of infections. However, studies with vitamin D supplementation on young children produced conflicting results. Method: A systematic review of PubMed, CINAHL, Web of science, global health and Google scholar electronic databases was conducted. STATA Version 14 was used for analysis. Heterogeneity of studies was assessed using I^2 test. A random-effects model was used to estimate the pooled prevalence among both healthy and sick children. Result: A total of 1212 articles were retrieved from data bases of which 13 papers were included. The pooled prevalence of vitamin D deficiency among healthy children was 50.06% with mean serum vitamin D level of 41.06 nm/L. The pooled prevalence among the sick children was 39.36% with 66.96nm/L of mean concentration. The pooled prevalence among healthy children was significantly higher compared to those who have common medical illnesses and the pooled mean concentration among the sick was also much higher than the mean concentration among healthy children. Conclusion**:** The pooled prevalence among both group of population was significantly of public health concern and the prevalence among healthy children was much higher among sick children.

Key words: Vitamin D; under five; healthy; sick; sub-Saharan

1. Introduction

Micronutrients deficiencies in children can have multi-dimensional health impact on growth, immune system, cognitive development and physical growth and development[1]. Its deficiencies are also widely found in low income countries where micronutrient deficiencies account for approximately 7 percent of the global disease burden[2].

Globally, an estimated two billion people suffer from a chronic deficiency of essential vitamins and minerals (micronutrients), a condition known as hidden hunger[2] with Vitamin

D deficiency being among the common micronutrient deficiencies worldwide[3]. According to the recent estimates, greater than 50% population is at risk in the globe[4].

As general consensus, serum 25-hydroxyvitamin D (25(OH)D) level below 50 nmol/L considered as a cutoff point for vitamin D deficiency and if its serum level is less than 25 nmol/L, severe deficiency is diagnosed[3]. Vitamin D deficiency is associated with infection and increased autoimmunity[5]. Different studies among under five children shows that decreased level of 25(OH)D were more prevalent among under five children with RTIs and its deficiency was   associated with increased risk of RTIs. Furthermore, studies also shows that, normal to high serum 25(OH)D status appears to have some beneficial influence on the incidence and severity of some, though not all, types of infections. However, studies with vitamin D supplementation on

young children produced conflicting results, and it still remains unclear whether supplementation may be of benefit and at what doses[6].

An observational study conducted to assess the serum concentration of 25(OH)D among children with active TB using non-TB pneumonia and healthy controls revealed that larger number of vitamin D deficient children were from active TB group[7]. Similarly, many studies conducted elsewhere[8–12] delineated similar findings including Dabla's study conducted among pediatric osteoarticular tuberculosis patients which revealed that 56% of active TB cases were vitamin D deficient and had lower levels of serum 25(OH)D compared to healthy controls[9]. However, significant number of studies found no significant difference in vitamin D deficiency status TB patients and healthy children[13–15].

For growing children, deficiency of Vitamin D is among the issues of significant concern while there are limited information on its association with malnutrition[16,17]. Studies shows that, linear growth could be affected by vitamin D status of children even in the absence of rickets clinical signs[18]. From the evidences currently available in literature world, a strong evidence base of the contributions of vitamin D deficiency for malnutrition, both regionally and globally, has been lacking. Even though the role of macronutrients in physical growth is well known, the roles of micronutrients including vitamin D in physical growth is not well

established. Particularly, evidences with respect to the role of vitamin D on stunting among children are not conclusive, and sometimes conflicting [16–21].

Hence, these review was done to avail better data on the relation between common medical illnesses and micronutrient deficiency particularly vitamin D, to guide intervention programs and to prioritize global focus on addressing vitamin D deficiency.

2. Materials and Methods

Study design and search strategy

A systematic review and meta-analysis study was conducted to determine and compare the pooled prevalence of vitamin D deficiency among apparently healthy and sick under five children in sub-Saharan Africa. The major databases of PubMed, Cochrane library, CINAHL and Google scholar were used for systematic search of literatures with Boolean operators like "AND", "NOT" and "OR". Using the Boolean operator we searched as: ((vitamin d"[MeSH Terms] OR "ergocalciferols"[MeSH Terms] OR vitamin D [Text Word])) AND ("child"[MeSH Terms] OR CHILDREN[Text Word])) AND "Africa South of the Sahara"[Mesh])). A search output from different data bases were shown below (Table 1).

Table 1: Summary of search results for the PubMed, Google Scholar and other databases to assess the prevalence of vitamin D deficiency among under five children in Sub-Saharan Africa.

Databases	Searching terms	Number of studies
Google scholar	All in title: vitamin D OR ergocalciferols AND Children	852
PubMed	Search (((("vitamin d"[MeSH Terms] OR "ergocalciferols"[MeSH Terms] OR vitamin D[Text Word])) AND ("child"[MeSH Terms] OR CHILDREN[Text Word])) AND "Africa South of the Sahara"[Mesh]	331
Web of science, CINAHL and global health	"prevalence" or "magnitude" and "Vitamin D" and "Deficiency" or "level" and "children" or "Child" or "ergocalceferols" and "sub-Saharan Africa"	29

Total retrieved articles		1212
Full text available papers appropriate to our review		9

Selection of study and eligibility criteria

All studies that were conducted on vitamin D deficiency among under five children and those fulfilled the inclusion criteria according to the interest of the study were included. All types of article types published in English were included. Initially, availability of full text titles, and abstracts of the articles were assessed. Then the full papers of relevant articles were reviewed. We excluded articles with inaccessible full paper.

Inclusion criteria

Study area: studies conducted in Sub-Saharan Africa only.

Study design: observational studies (cross-sectional, case-control and cohort studies)

Outcome measures: Studies that measured 25(OH)D in blood

Language: studies published/written in the English language only were included

Population: studies conducted among under five children.

Publication issue: both published and unpublished articles were searched
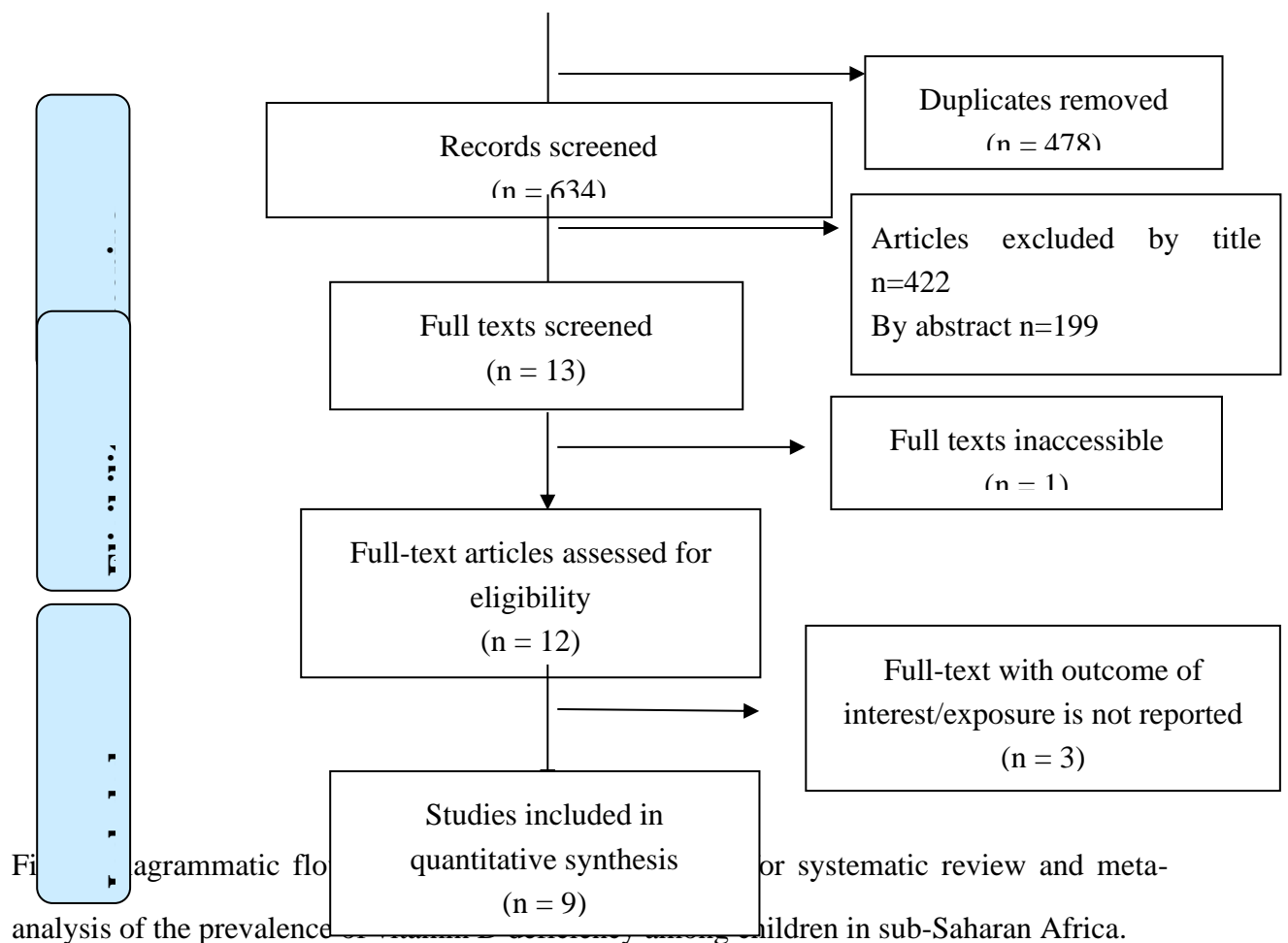
Study period: 2010-2020

General characteristics of studies

In the first step screening, we got a total number of 1212 papers and 478 papers were excluded due to repetition. According to the titles and abstract 621 papers were excluded. Thirteen papers were found to be suitable. But the full text of 1 paper was inaccessible and after assessing the full text 3 papers were excluded due to failure to report outcome of interest/exposure and 9 papers were finally included in the study (Fig.1). After identification of the available papers, the papers were categorized in to two (healthy and sick) based on the type of population used to study. If the individual study used both types of population we used the included population of each population to do the pooled measurement for the current study.
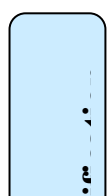
1112 Records identified through database searching
pubmed (n = 331), Google scholar (n=852)
CINAHL (n=8) Global health (n=12), web of

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                                          ┌─────────────────────────┐
                                          │  Duplicates removed      │
            ┌─────────────────────────┐   │  (n = 478)               │
            │   Records screened       │──▶└─────────────────────────┘
            │   (n = 634)              │   ┌─────────────────────────┐
            └─────────────────────────┘──▶│ Articles excluded by title│
                                          │ n=422                     │
            ┌─────────────────────────┐   │ By abstract n=199         │
            │   Full texts screened    │   └─────────────────────────┘
            │   (n = 13)               │   ┌─────────────────────────┐
            └─────────────────────────┘──▶│ Full texts inaccessible   │
                                          │ (n = 1)                   │
            ┌─────────────────────────┐   └─────────────────────────┘
            │ Full-text articles       │
            │ assessed for eligibility │   ┌─────────────────────────┐
            │ (n = 12)                 │──▶│ Full-text with outcome of │
            └─────────────────────────┘   │ interest/exposure is not  │
                                          │ reported (n = 3)          │
            ┌─────────────────────────┐   └─────────────────────────┘
            │ Studies included in      │
            │ quantitative synthesis   │
            │ (n = 9)                  │
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Figure. Diagrammatic flow for systematic review and meta-analysis of the prevalence of vitamin D deficiency among children in sub-Saharan Africa.

Data extraction

Data extraction for all the necessary data was done by RH and MF independently using a standardized data extraction format prepared in Microsoft Excel. Any disagreements between the authors during data extractions was discussed and reached on consensus. The data extraction format includes first author, publication year, name of country, sample size, included and number of event and prevalence with 95% CI. The main outcome of interest for this study is prevalence of vitamin D deficiency among healthy and sick children in sub-Saharan Africa. The main types of illnesses used in this study were TB, malnutrition and HIV/AIDS.

Risk of bias

The two authors (RH and MF) independently assessed the risk of bias for each article using the Newcastle-Ottawa Scale quality assessment tool[22]. The tool has indicators consisting

of three main parts in which, the first part has five components and it assesses the methodological quality of each study. The second part of the assessment tool examines the comparability of the studies. The last part of the tool measures the quality of the original articles with respect to their statistical analysis. Using an assessment tool as a guideline, two authors independently evaluated the qualities of the original articles. Quality of each study was evaluated using these parameters; those with medium (fulfilling 50% of quality assessment criteria) and high quality (>= 6 out of 10 scales) were included for analysis. Disagreements between assessors were solved by taking the mean score of their assessment results.

Data processing and analysis

After extraction, the data were imported to STATA Version 14.0 statistical software for analysis. The standard error for each original study was calculated using the binomial distribution formula. Heterogeneity among reported prevalence was assessed by computing p-value I^2 test static[23]. As the test statistic showed there is significant heterogeneity among the studies ($I^2 = 98.3\%$, p=0.000) and as a result a random effect meta-analysis model was used to estimate the pooled effect. To reduce the random effect variations between the point estimates of the primary studies, a subgroup analysis was done based on sample size. Funnel plot and Egger's test at 5% significance level was used to asses the publication bias. From the result, the articles were symmetrically distributed and Egger's test at 5% significant level was not significant for the publication bias. Pooled prevalence with 95% confidence intervals was presented in the forest plot format for both healthy and sick children. For reporting the finding 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)' protocol was used

3. Results

Prevalence of vitamin D deficiency among healthy children

The finding from the studies included for assessment of the pooled prevalence of vitamin D deficiency among healthy children revealed that, the prevalence was 50.06% (CI ranges from 33.46% to 66.67%) (Fig. 2). On the other hand, sub-group analysis was done using sample size of the included studies as unit of sub-grouping. Accordingly, the pulled prevalence was

52.18% with CI of 32.78% to 71.57% among those having less than 100 sample size and 46.51% with CI of 4.44 to 97.31 among those having less than 100 sample size (Fig. 4). The pooled mean serum vitamin D level among the healthy children was 41.06 nm/L with CI of 23.82nm/L to 58.31nm/L (Fig. 4).

Study ID		ES (95% CI)
RWEBEMBERA et al (2013)		34.55 (27.81, 41.29)
sudfeld et al (2014)		60.97 (57.86, 64.08)
ludmir et al (2016)		17.00 (5.50, 28.50)
sudfeld et al (2017)		76.40 (72.95, 79.85)
Hassam et al (2019)		31.90 (18.57, 45.23)
Bellows et al (2017)		36.40 (33.13, 39.67)
Bodin et al (2019)		90.00 (83.97, 96.03)
Overall (I-squared = 98.8%, p = 0.000)		50.06 (33.46, 66.67)
NOTE: Weights are from random effects analysis		
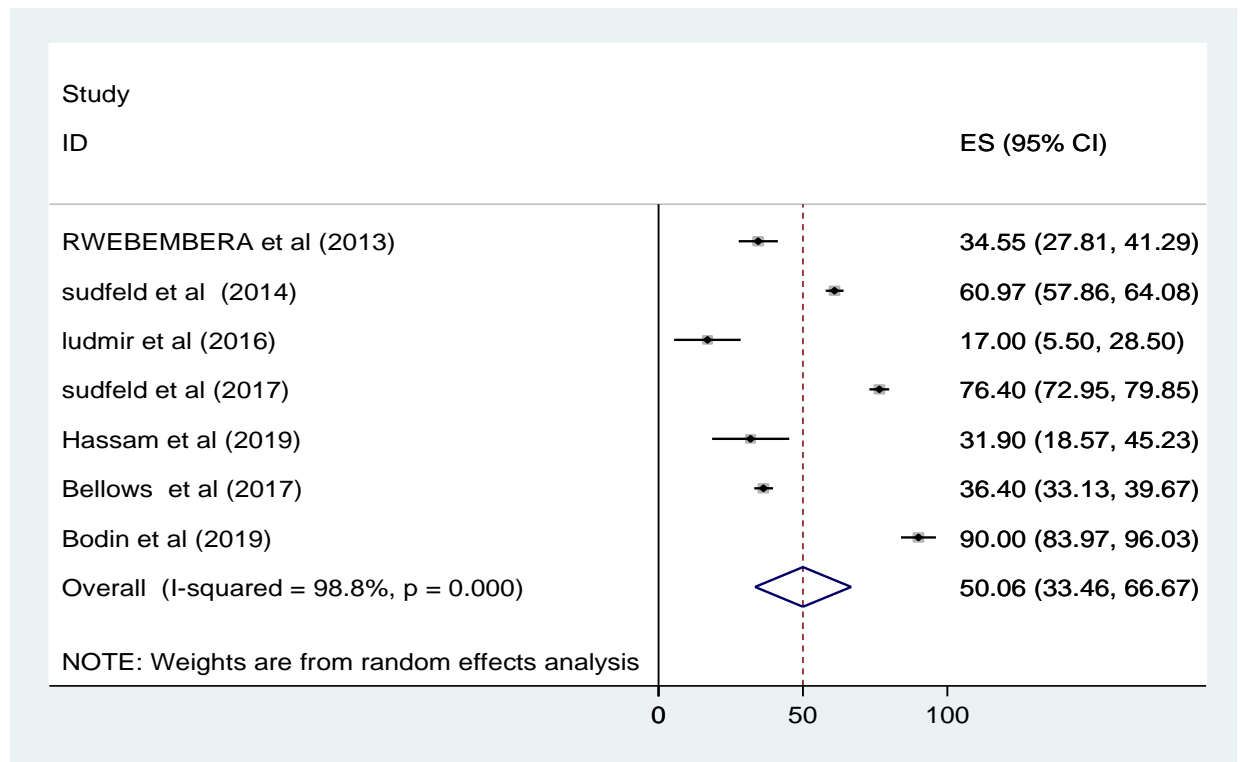
Figure: 2 Pooled prevalence of vitamin D deficiency among healthy children in sub-Saharan Africa

Publication bias using funnel plot for prevalence among healthy children

Funnel plot and Egger's test were used to test Publication bias. From the result the articles were symmetrically distributed (Fig. 3) and Egger's test result for small study effects revealed that publication bias in estimating vitamin D deficiency was not statistically significant.
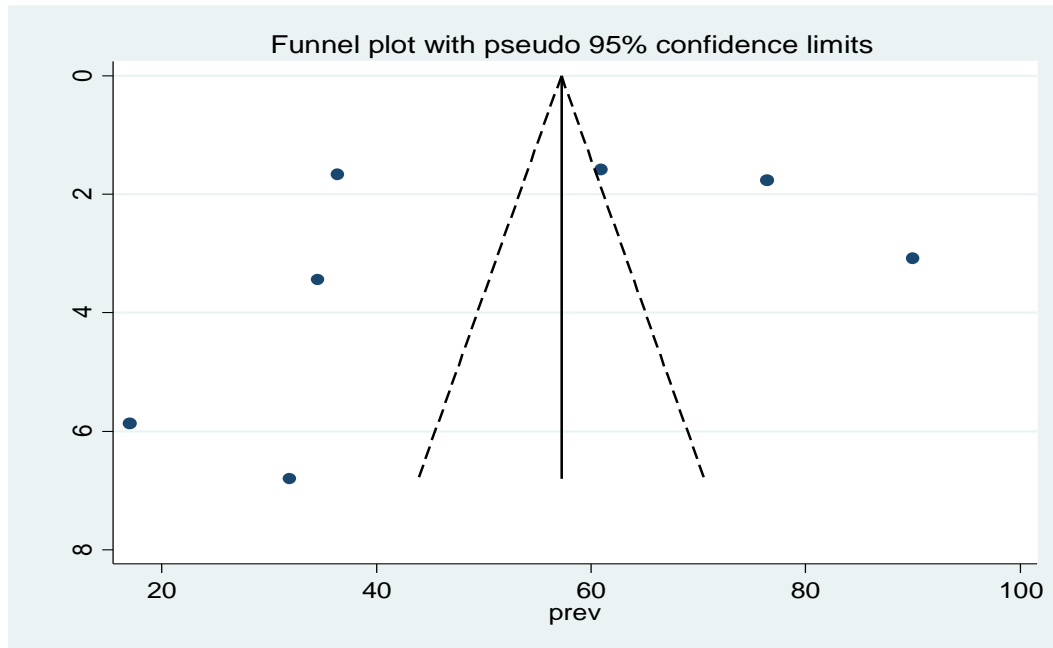
Figure 3: Funnel plot with 95% confidence interval of the pooled prevalence of vitamin D deficiency among healthy under five children in sub-Saharan Africa, 2020
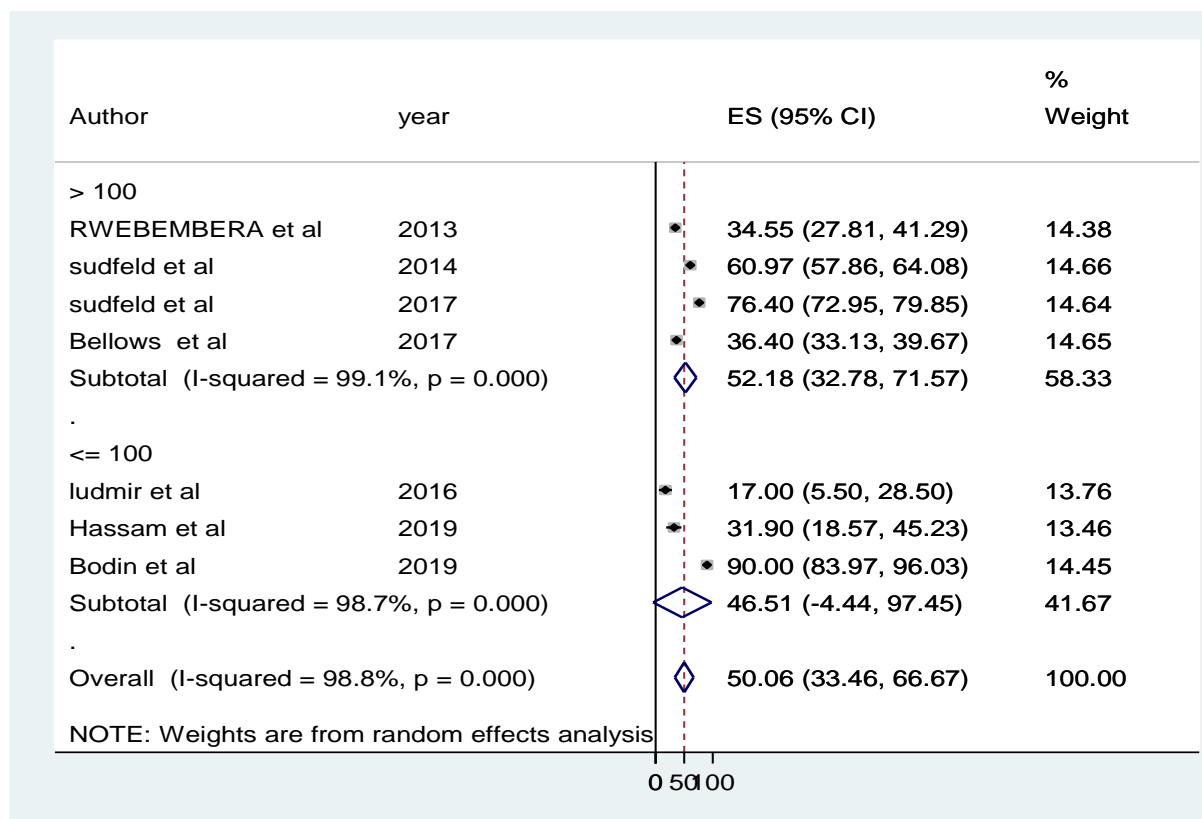

Figure 4: Subgroup analysis (using sample size) of pooled prevalence of vitamin D deficiency among healthy children in sub-Saharan Africa
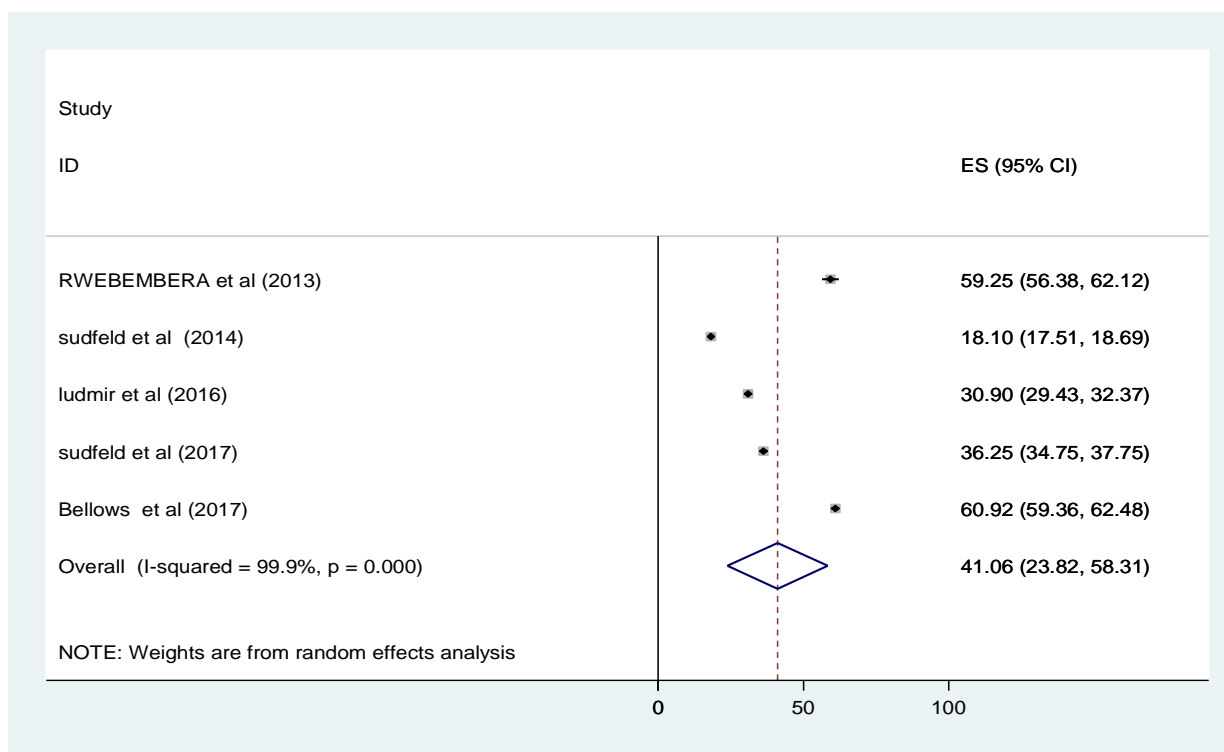
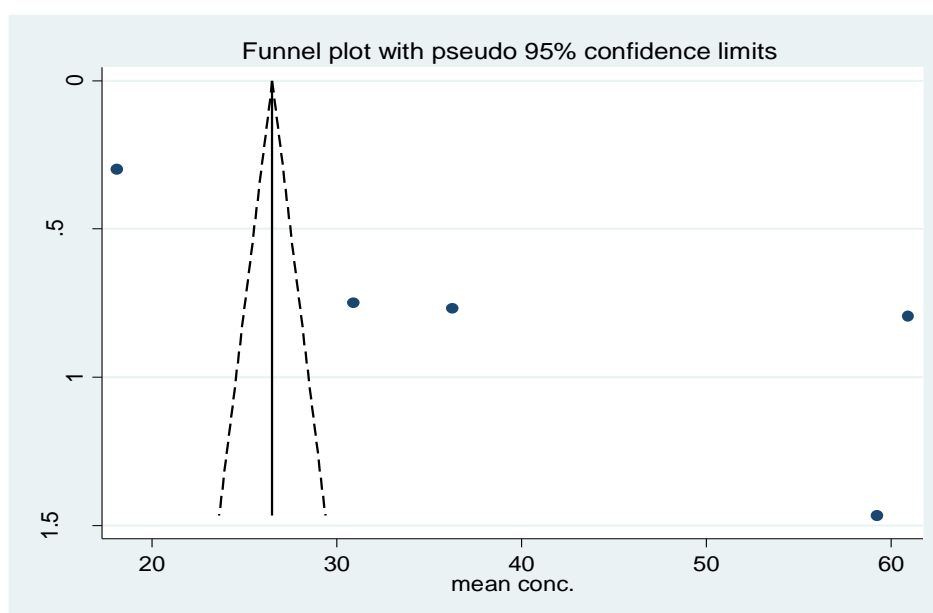Figure 5: Mean serum vitamin D level among healthy children in sub-Saharan Africa,

Figure 6: Publication bias for mean concentration of serum vitamin D among health children in sub-Saharan Africa

Pooled prevalence of vitamin D deficiency among sick children in sub-Saharan Africa

Analysis was done to assess the pooled prevalence of vitamin D deficiency among sick children (children having certain medical conditions). The analysis result revealed that, the

pooled prevalence of vitamin D deficiency among the sick children was 39.36% with CI of 20.57 to 57.96% (Fig. 7). The pooled mean serum vitamin D level among the sick children was 66.96nm/L with 95% CI of 54.81nm/L to 79.11nm/L (Fig. 8). Publication bias was assessed using funnel plot and the diagram shows that, there is symmetrical distribution of articles showing no significant publication bias (Fig. 9).
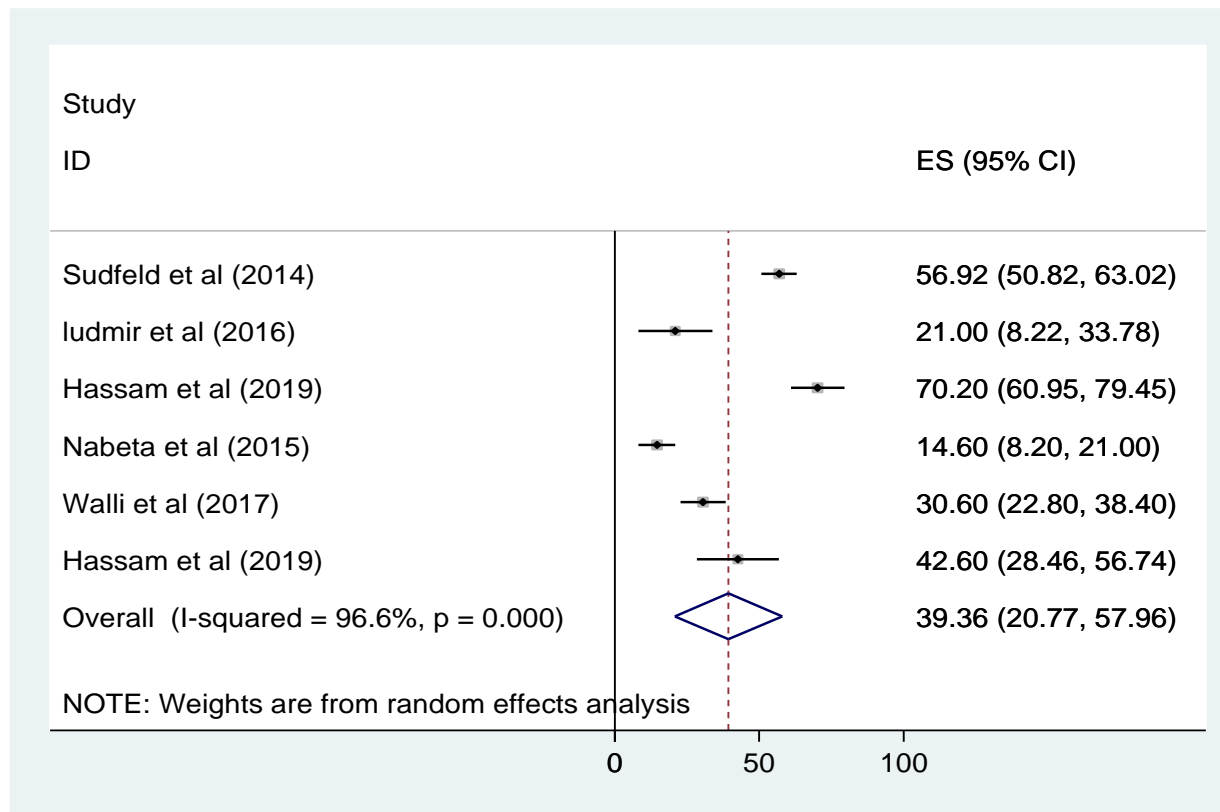

Figure 7: Pooled prevalence of vitamin D deficiency among sick children in sub-Saharan Africa
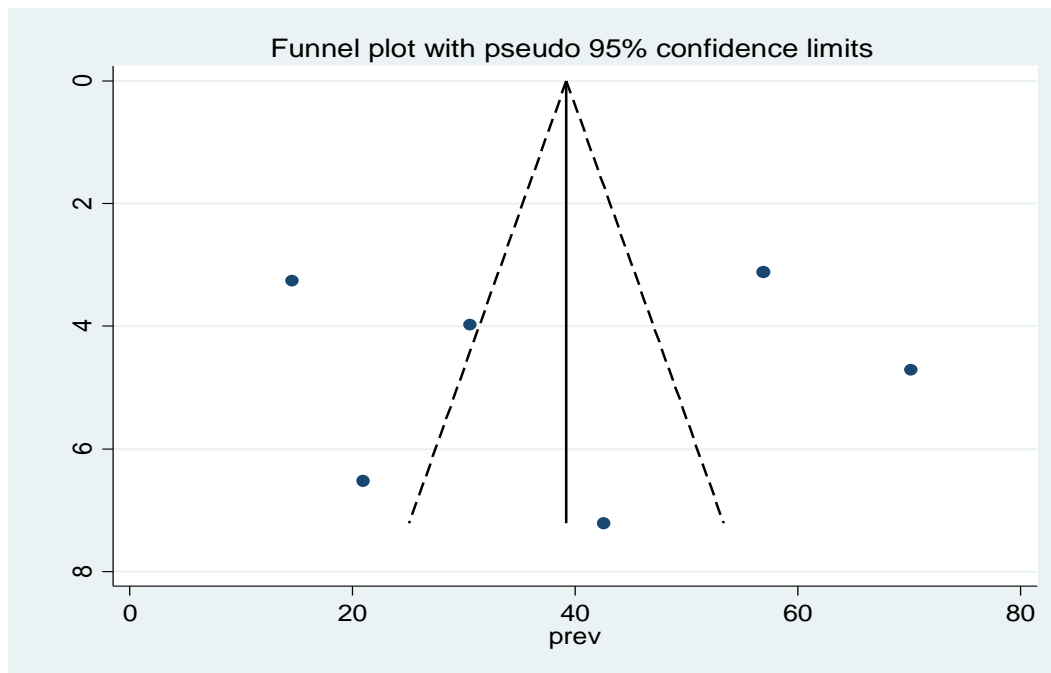
Figure 8: Funnel plot with 95% confidence interval for publication bias of prevalence of vitamin D deficiency among sick under five children in sub-Saharan Africa, 2020
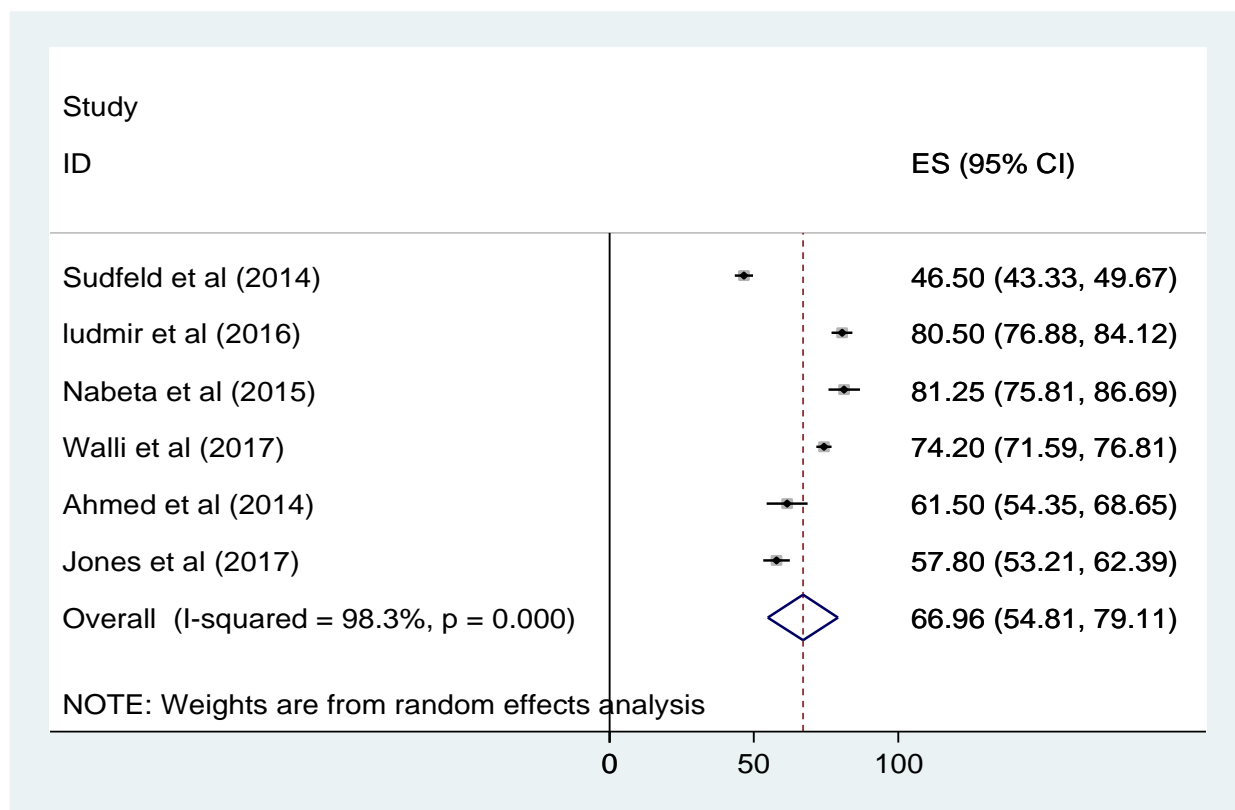

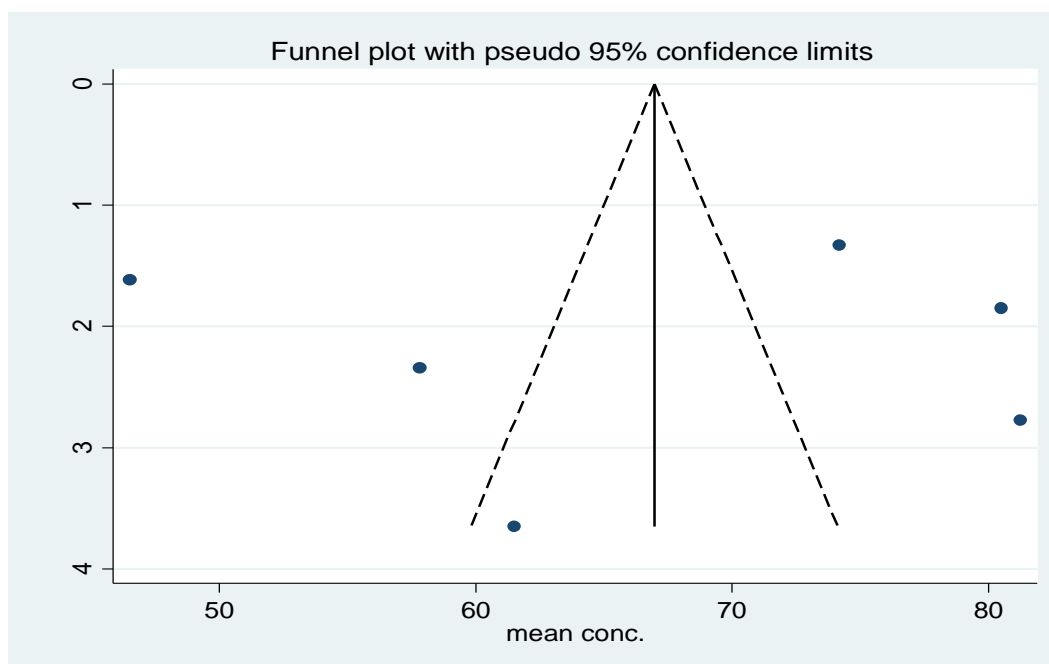Figure 9: Mean serum vitamin D level among sick children in sub-Saharan Africa

Figure 10: Publication bias for mean concentration of serum vitamin D among sick children in sub-Saharan Africa, August 2020

Subgroup analysis result among sick children using sample size as unit of subgrouping

Subgroup analysis was done to assess the prevalence of vitamin D deficiency among children using sample size as unit of subgroup analysis and the result revealed that prevalence of vitamin D deficiency was 34.07% with CI of 8.05 to 60.08 among those having greater than 100 number of participants and 44.85% with CI of 14.41 to 75.30 among those having less than 100 number of participants.
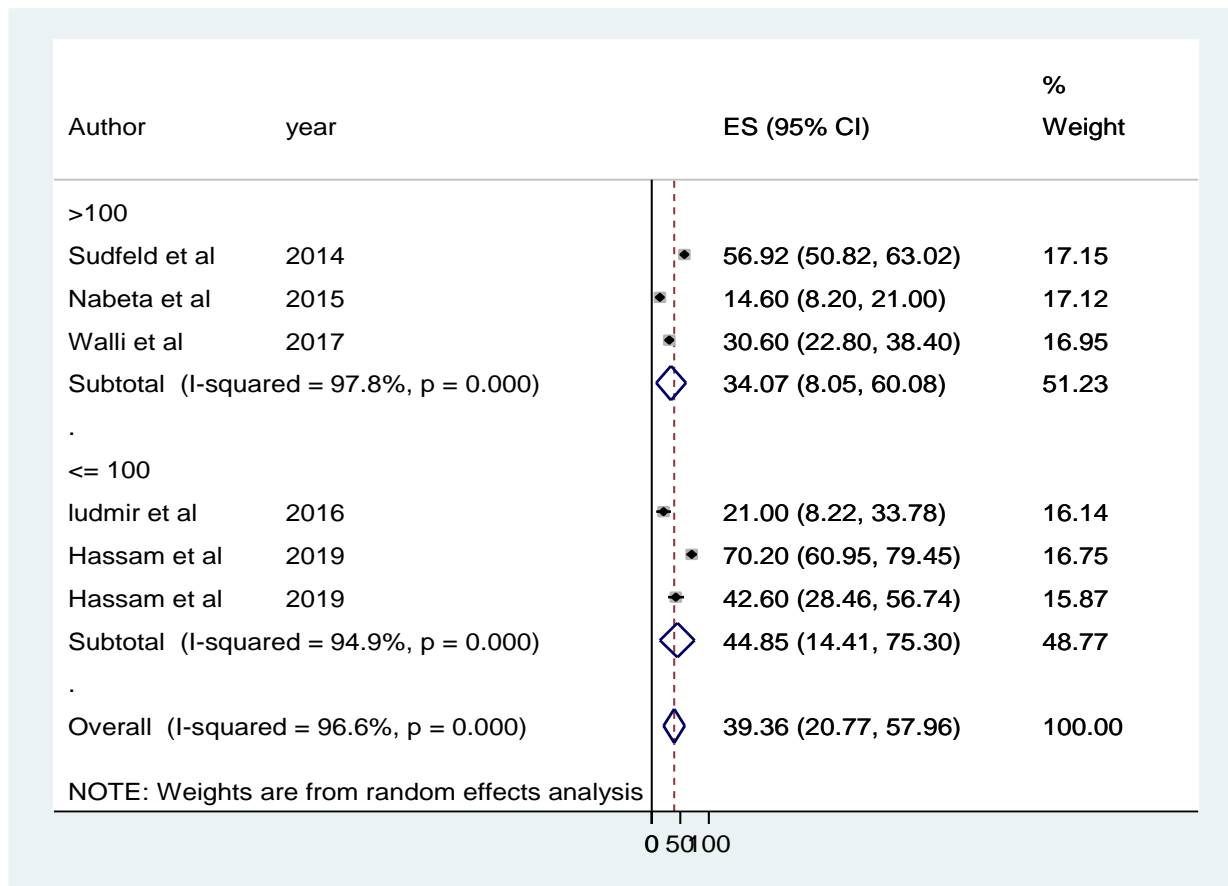
Author	year		ES (95% CI)	% Weight
>100				
Sudfeld et al	2014		56.92 (50.82, 63.02)	17.15
Nabeta et al	2015		14.60 (8.20, 21.00)	17.12
Walli et al	2017		30.60 (22.80, 38.40)	16.95
Subtotal (I-squared = 97.8%, p = 0.000)			34.07 (8.05, 60.08)	51.23
.				
<= 100				
ludmir et al	2016		21.00 (8.22, 33.78)	16.14
Hassam et al	2019		70.20 (60.95, 79.45)	16.75
Hassam et al	2019		42.60 (28.46, 56.74)	15.87
Subtotal (I-squared = 94.9%, p = 0.000)			44.85 (14.41, 75.30)	48.77
.				
Overall (I-squared = 96.6%, p = 0.000)			39.36 (20.77, 57.96)	100.00

NOTE: Weights are from random effects analysis

0 50 100

Figure 11: Subgroup analysis (using sample size) of pooled prevalence of vitamin D deficiency among healthy children in sub-Saharan Africa

4. Discussion

This study has tried to assess the pooled prevalence of vitamin D deficiency among under five children in sub-Saharan Africa. Attempts were made to see the pooled prevalence among the healthy and sick children separately. The common illness conditions considered in this review were mainly malnutrition, HIV/AIDS and tuberculosis.

From the result of analysis, the pooled prevalence among healthy children in sub-Saharan Africa was found to be 50.06% with 95% CI ranging from 33.46% to 66.67%. On the other hand the pooled prevalence among sick children was 39.36% with CI of 20.57 to 57.96%. Among the studies included for the sick children the lowest prevalence (14.6%) of vitamin D deficiency was found in Uganda among malnourished children[24] and the highest prevalence (70.2%) was from Tanzania among patients with diarrhea[25]. Regarding the healthy children the lowest prevalence (17%) was among children from Botswana[26] and the highest prevalence of 76.4% was from Tanzania[27]. In this study the pooled prevalence

of vitamin D deficiency among both healthy and sick children was found to be significantly of public health concern.

Regarding the comparison between the pooled prevalence among the sick and healthy children, the pooled prevalence among healthy children was found to be significantly higher. Correspondingly, the mean serum vitamin D level among healthy children (41.06nm/L) was found to be significantly lower than the level among sick children (66.96nm/L). The finding of the current study was in contrary to the presumed expectations and findings of other individual studies conducted elsewhere which shows vitamin D deficiency more prevalent among people with some type illnesses and health conditions[28,29]. In the current study the lesser prevalence of vitamin D among sick children than healthy children might be due to the fact that, most of the studies included for the sick children were conducted among malnourished children and tuberculosis children. Malnourished children were usually fed malnutrition treatment formula which have high vitamin D[30] and this might mask the usual vitamin deficiency among children. Similarly, as tuberculosis is a granulomatous disease and in granulomatous diseases, activated mononuclear cells (particularly macrophages) in the lung and lymph nodes produce calcitriol from calcidiol independent of PTH[31–34]. This may increase the serum level of vitamin D among children with tuberculosis. Furthermore, some studies among HIV patients show that ART treatment drugs particularly, use of ritonavir or tenofovir, was associated with higher levels of 25OHD[35] and this might also be contributed for higher vitamin D among the sick groups.

From another systematic review and meta-analysis done to assess vitamin D deficiency in critically ill children in the other study, the pooled VDD event rate was 54.8 (95% CI 45.4–63.9) and another study done in developing countries comparable to the current study also showed a higher pooled VDD rate of 64% with 95% CI 51–75%)[36] which is much higher than the finding of the current study. This might be due to the nature of the participants of the studies, where the participants of the previous studies were critically ill children in ICU while those in the current studies were not ICU patients.

Finding of systematic review and meta-analysis conducted to assess vitamin D deficiency in Africa among the healthy children found that, the pooled prevalence was 49.07 with 95% CI

of (24·88–73.49) among newborns and 22.99   (12.03–36.14) among older children [37]. The pooled prevalence from this study is much lower than the finding from the current study. This might be due to the fact that, most of the studies included in the earlier meta-analysis were relatively from well-off countries and the studies also used random effect meta-analysis to report the pooled prevalence.

This study has attempted to put the burden of vitamin D deficiency among under-five children in sub-Saharan Africa using different segment of population based on health status of children. It has tried to delineate the difference in the burden of the problem among healthy and sick children. However, there are certain important limitation to be considered while using the findings of this study.   One of the limitation of this study was that, all most all of the studies included in this review were considered different age groups of children and this resulted in difficulty of conducting subgroup analysis using the age group and other important factors.

5. Conclusion

In general, the pooled prevalence of vitamin D deficiency among under-five children in this study was found to be among the higher public health concern and there is significant variation in the prevalence from country to country. The pooled prevalence among the healthy children was found to be higher than the prevalence among the sick children. Correspondingly, the mean serum vitamin D level among the sick children was higher than among the healthy children.

Declarations:

Availability of data and materials: Data underlying the study is readily available can be obtained from the corresponding author on reasonable request.

Authors' contributions: "Conceptualization, M.F. and R.H.; methodology, M.F. and R.H.; software, M.F. and R.H.; validation, M.F. and R.H.; formal analysis, M.F., MD and R.H.; investigation, M.F., MD and R.H.; resources, M.F. and R.H.; data curation, M.F., MD and

R.H.; writing—original draft preparation, M.F., MD and R.H.; writing—review and editing, M.F., MD and R.H.; visualization, M.F., MD and R.H.; supervision, M.F., MD and R.H.; project administration, M.F., and R.H.; funding acquisition, none. All authors have read and agreed to the published version of the manuscript

Conflict of interest: Authors declare no competing interests.

Consent for publication: Not applicable

Ethical approval: The procedures used in this study respects the scientific ethical rules.

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children with tuberculosis. Pediatr Infect Dis J 2008: 27(10):941–942 n.d.

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