


# Association Between Vitamin D Deficiency and Tuberculosis among HIV-Negative Individuals: A Systematic Review & Meta-Analysis



Ahmed Oubaasri<sup>1,\*</sup> , Fatima Zahra El Mskini<sup>1</sup>, Asmae Labyad<sup>1</sup>, Aicha Madkour<sup>1</sup>, Slimane Mehdad<sup>1</sup> and Souad Benaich<sup>1</sup>

<sup>1</sup>Physiology and Physiopathology Team, Faculty of Sciences, Mohammed V University in Rabat, Morocco

## Abstract:

**Background and Objective:** Tuberculosis is an infectious disease mainly caused by *Mycobacterium tuberculosis* (MTB). It is associated with several factors, with vitamin D deficiency being a focus of current research. This systematic review aims to compare plasma vitamin D levels between TB cases and controls and examine the association between vitamin D deficiency and TB risk in HIV-negative participants through meta-analysis.

**Methods:** This study, registered with PROSPERO (CRD42024518012) and conducted per PRISMA guidelines, analyzed the association between vitamin D deficiency and tuberculosis. Searches were conducted in PubMed/Medline, Scopus, ScienceDirect, and Web of Science for studies up to March 8, 2024. Two independent reviewers screened articles, extracted data, and assessed bias. A random-effects model and R software were used for statistical analyses, with significance set at  $P < 0.05$ .

**Results:** We identified 2168 articles, and only 9 articles meeting the inclusion criteria were retained for our systematic review and meta-analysis. Sample sizes ranged from 33 to 520 participants. We found a mean difference of -6.58 ng/ml in 25(OH)D levels, indicating consistently lower levels in TB patients compared to controls ( $p < 0.0001$ ) and an increased risk of TB associated with VDD with a pooled OR of 2.11 (95% CI: 1.50 to 2.98),  $p = 0.09$ .

**Conclusion:** This study highlights lower 25(OH)D levels in TB patients and the association between vitamin D deficiency and increased TB risk, emphasizing the need for further research, standardized clinical trials, and preventive supplementation protocols.

**PROSPERO Registration Number:** CRD42024518012

**Keywords:** 25(OH)D, Tuberculosis, Vitamin D, Systematic review, Vitamin D deficiency, Meta-analysis, PRISMA.

© 2025 The Author(s). Published by Bentham Open.

This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International Public License (CC-BY 4.0), a copy of which is available at: <https://creativecommons.org/licenses/by/4.0/legalcode>. This license permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

\*Address correspondence to this author at the Physiology and Physiopathology Team, Faculty of Sciences, Mohammed V University in Rabat, Morocco; E-mail: [ahmedoubaasri2013@gmail.com](mailto:ahmedoubaasri2013@gmail.com)

Cite as: Oubaasri A, Zahra El Mskini F, Labyad A, Madkour A, Mehdad S, Benaich S. Association Between Vitamin D Deficiency and Tuberculosis among HIV-Negative Individuals: A Systematic Review & Meta-Analysis. Open Public Health J, 2025; 18: e18749445386757. <http://dx.doi.org/10.2174/0118749445386757250328080921>



CrossMark

Received: January 28, 2025

Revised: March 09, 2025

Accepted: March 19, 2025

Published: April 10, 2025



Send Orders for Reprints to  
[reprints@benthamscience.net](mailto:reprints@benthamscience.net)

## 1. INTRODUCTION

Tuberculosis (TB) is an infectious disease caused mainly by *Mycobacterium tuberculosis* (MTB) [1]. The disease is commonly spread through the air when individuals with active TB cough or sneeze, dispersing droplets that carry the MTB [2, 3]. While pulmonary

tuberculosis (PTB), which affects the lungs, is the most prevalent form, TB can also impact other organs, resulting in extrapulmonary tuberculosis (ETB) [1]. Currently, TB remains the second leading cause of death from infectious diseases worldwide after COVID-19 (surpassing HIV/AIDS) [1]. In 2022, 10.6 million people in the world contracted TB, and 1.3 million died from it [1]. The WHO Southeast

Asia Region, the African Region, and the Western Pacific Region had the highest incidences, with 46%, 23%, and 18%, respectively [4]. Several factors associated with tuberculosis have been identified, including HIV infection, smoking [1], comorbidities [5], alcohol abuse, and poor socio-economic conditions, such as low income, lack of education, malnutrition, unsuitable housing, and other social determinants of TB [6]. Additionally, current studies are exploring potential contributing factors, particularly vitamin D deficiency (VDD) [7-10]. Vitamin D or 25-hydroxyvitamin D (25[OH]D) is defined as a fat-soluble prohormone steroid known to be involved in phosphocalcic metabolism [11], the immune response against microbial pathogens and many other metabolic disorders [12-14]. It is mainly synthesized by the skin's exposure to ultraviolet sunlight but can also be provided by diet and supplements [13-17]. Several definitions are used to assess plasma levels of 25-hydroxyvitamin D (25(OH)D), and recommendations differ regarding the threshold for defining vitamin D deficiency [15]. According to Giustina *et al.*, vitamin D deficiency is defined as levels below 12 ng/mL (30 nmol/L) [15], whereas other studies define it as a 25(OH)D level below 20 ng/mL (50 nmol/L) [16, 18]. Currently, vitamin D deficiency is a major public health problem in many countries and even continents. A recent meta-analysis of 7.9 million participants estimated that 15.7% of participants had serum 25-hydroxyvitamin D levels below 30 nmol/L, and 47.9% had levels below 50 nmol/L [19]. The same study highlighted that vitamin D deficiency could contribute to an increased global burden of disease. This situation creates the conditions for contracting tuberculosis, which in turn worsens the nutritional status, leading to a vicious cycle [20]. Several observational studies have reported significantly lower vitamin D levels in TB patients compared to their controls [7, 8, 21-23] and demonstrated an association between vitamin D deficiency (VDD) and tuberculosis [11, 24-26]. However, other observational studies have reported contrasting results or inconclusive results, with no significant association between VDD and TB [27, 28]. Even recent meta-analyses have yielded inconsistent results. Cao *et al.* found no association between serum vitamin D levels and the incidence of LTBI, nor did they find that higher serum vitamin D levels conferred protection against LTBI [29]. In contrast, Acen *et al.* demonstrated that pulmonary tuberculosis is significantly associated with hypovitaminosis D [30]. In view of the contrasting and inconclusive results concerning the association between VDD and TB, it is evident that, although some studies suggest a possible association between these two factors, the number of studies providing conclusive evidence remains limited. Furthermore, many existing studies fail to address methodological biases that could affect their results, such as omitting HIV status, which is often not verified or reported in studies exploring this association. This systematic review aims to compare plasma vitamin D levels between TB cases and controls and to establish the association between vitamin D deficiency and the risk of developing TB by evaluating primary studies that exclusively included HIV-negative

participants and applying quantitative analysis through meta-analysis.

## 2. METHODS

This study was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [31] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under number CRD420245 18012 (supplementary data).

### 2.1. Data Sources and Inclusion Criteria

The following databases were searched: PubMed/Medline, Scopus, ScienceDirect, and Web of Science for published studies testing the association between Vitamin D Deficiency and tuberculosis from inception to 8 March 2024. The search strategy utilized a combination of medical subject headings (MeSH) terms and keywords to ensure a thorough and broad search. The key terms included "vitamin D," "vitamin D deficiency," "25-hydroxyvitamin D", "1,25-dihydroxy vitamin D", "25(OH)D", and "tuberculosis," both as MeSH terms and keywords. The detailed search strategy is provided in the supplementary data. All observational studies (cross-sectional, cohort, and case-control studies) of tuberculosis patients examining the association between VDD and TB, regardless of sample size or age, published in English or French, were included. Case series, case reports, studies without a comparison group, studies with unavailable data, studies that did not mention HIV status, clinical trials, systematic reviews, meta-analyses, and studies involving participants diagnosed with conditions known to affect Vitamin D levels, as well as those with human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS) were excluded.

### 2.2. Data Extraction

The data was compiled, and duplicates were removed. Two independent reviewers (AO and SB) selected articles based on predetermined criteria. The reviewers assessed titles, abstracts, and full-text articles for inclusion. Disagreements regarding inclusion are addressed and resolved through consultation with a third reviewer. The following data were extracted from the articles: author, year, country, type of study, target population, the method used to assess serum 25(OH)D levels and the cut-off value for vitamin D deficiency and the association of vitamin D, including epidemiological measures such as relative risk, odds ratio, and their respective 95% confidence intervals.

### 2.3. Quality Assessment

The two reviewers (AO and SB) independently assessed the risk of bias for each included study using the Newcastle-Ottawa quality assessment Scale [32]. This scale evaluates studies based on three domains: (1) selection of subjects, (2) comparability of groups, and (3) assessment of outcomes or exposures. Each study was assigned a score ranging from 0 to 9, with quality categorized as low (0-3), moderate (4-6), or high (7-9) [29-33]. A third examiner resolved potential disagreements.

## 2.4. Definition of Outcomes

In this study, vitamin D deficiency was defined as serum 25-OH-D below 20 ng/mL (50 nmol/L). This threshold is based on widely accepted clinical guidelines [15, 16]. To convert 25-OH-D concentration values from the conventional system (ng/mL) to the international system of units (nmol / L), we multiplied by the factor 2.496 [34].

## 2.5. Statistical Analysis

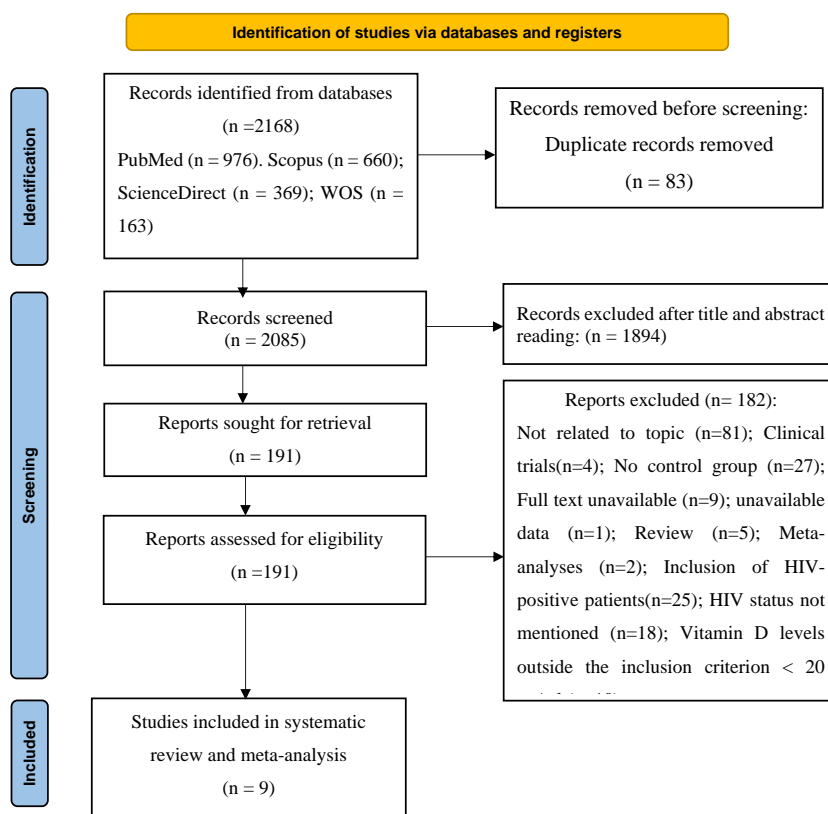
We performed a meta-analysis of the mean difference (MD) between patient and control groups. For studies that presented results as medians and ranges, these data were converted to means and standard deviations using the Hozo method [35]. In our study, vitamin D deficiency was defined as a concentration below 20 ng/ml [15]. Analyses were performed using a random-effects model to account for heterogeneity between studies. For odds ratios (ORs), we also employed a random-effects model to obtain an overall estimate of the association between vitamin D deficiency and tuberculosis. ORs and RRs were treated as ORs, and all data from the included studies were converted to log (OR) and standard error (SE). Heterogeneity was assessed using Cochran's Q statistic and the  $I^2$  statistic. An  $I^2$  value greater than 50% was considered indicative of substantial heterogeneity. The Tau<sup>2</sup> statistic was used to estimate the variance between studies in the random-effects model. Publication bias was

examined visually using funnel plots and statistically using the Egger test. An asymmetrical funnel plot and a p-value < 0.05 for the Egger test were considered indicative of potential publication bias. All statistical analyses were performed using the R software, specifically the “meta” and “metafor” packages. Statistical significance was set at  $P < 0.05$ .

## 3. RESULTS

### 3.1. Results of Study Search

A bibliographic search was carried out in several electronic databases, including PubMed, Scopus, ScienceDirect, and Web of Science, identifying a total of 2168 articles published from the inception of the database until March 8, 2024. An Excel spreadsheet was used to detect duplicates, leading to the removal of 83 articles, leaving 2085 records to be examined. After the evaluation of titles and abstracts, 1894 articles were excluded. The remaining 191 articles were reviewed in full text, of which 182 were excluded for the following reasons: not related to topic (n = 81), clinical trials (n = 4), no control group (n = 27), full text unavailable (n = 9), unavailable data (n=1), review (n = 5), meta-analysis (n = 2), inclusion of HIV-positive patients (n = 25), HIV status not mentioned (n = 18), and vitamin D levels not meeting inclusion criteria of less than 20 ng/ml (n = 10). Finally, 9 articles meeting the inclusion criteria were retained for our systematic review and meta-analysis (Fig. 1).



**Fig. (1).** PRISMA chart: flow diagram of the process of selection of articles.

### 3.2. Characteristics of the Studies

Table 1 presents the characteristics of the nine included studies [7, 8, 21-25, 36, 37]. These studies come from various geographical regions, with the majority based in Asia (India, China, South Korea, Pakistan), two from Europe (Spain, Russia), one from Africa (Ethiopia), and one from South America (Chile). Among the included studies, four are cross-sectional studies [8, 21, 23, 36], four are case-control studies [7, 22, 24, 25], and one is a cohort study [37]. Sample sizes ranged from 33 to 520 participants, with the largest sample size observed in a Spanish cohort study [37]. The average age of participants varied considerably between studies. On average, the age of cases is around 36.28 years, while that of controls is 36.6 years, with a mean age variation of 0.32 years between the two groups. Some studies provide medians instead of means [22, 23, 36], with median values ranging from 22.9 years [36] to 48 years [22]. It should be noted that in one study, age data were not provided [7]. Regarding vitamin D measurement methods, nine studies used four main techniques to measure vitamin D levels. Of these, enzyme-linked immunosorbent assay (ELISA) was used in three studies [21, 36, 24], while liquid chromatography with tandem mass spectrometry (LC-MS/MS) was utilized in two studies [22, 23]. The radio immunoassay (RIA) [8, 25] and electro chemiluminescence immunoassay (ECLIA) techniques were each used in two studies [7, 37]. Vitamin D levels in cases ranged from 6.50 to 30.1 ng/ml, while in controls, they ranged from 16.03 to 43.3 ng/ml. Three studies [7, 22, 25] provided medians (range) for vitamin D levels, whereas the remaining studies presented means  $\pm$  standard deviation [8, 21, 23, 24, 36, 37]. All studies reported a significant association between vitamin D deficiency and tuberculosis, with vitamin D levels consistently lower in tuberculosis patients compared with healthy controls. Six studies reported a significant difference in mean vitamin D levels between the two groups [7, 8, 21-23, 36], while two case-control studies reported a significant association between vitamin D deficiency and active tuberculosis [24, 25].

Additionally, one cohort study identified an inverse association between Vitamin D status and tuberculosis incidence [37]. The quality assessment of the included studies was classified as high, with a score between 8 and 9 on the Newcastle-ottawa scale (supplementary data).

### 3.3. Meta-analysis

The meta-analysis, performed using a random effects model, revealed significant differences in 25(OH)D levels between tuberculosis (TB) patients and controls. In all the included studies (Fig. 2), TB patients had an average reduction in 25(OH)D levels of -9.61 ng/ml (95% CI: -11.87 to -7.35), with considerable heterogeneity ( $I^2=99\%$ ,  $p<0.01$ ), suggesting a substantial variation between studies. To mitigate this heterogeneity, a sub-group analysis of four studies was carried out (Fig. 3), showing a mean difference in 25(OH)D levels of -6.58 ng/ml (95% CI: -7.71 to -5.44) with moderate heterogeneity ( $I^2=29\%$ ,  $p=0.24$ ). This sub-analysis confirms that 25(OH)D levels were systematically lower in patients with tuberculosis. Meanwhile, examination of the association between VDD and TB risk, expressed as odds ratio (OR), shows a significant association, with a pooled OR of 2.11 (95% CI: 1.50 to 2.98,  $Z = 4.26$ ,  $p < 0.001$ ;  $I^2=59\%$ ,  $p=0.09$ ) (Fig. 4). These results highlight the association between VDD and an increased risk of developing tuberculosis.

### 3.4. Publication Bias

Funnel plots and Egger tests were used to assess publication bias. The funnel plots were examined visually for any asymmetries, and statistical tests were performed to assess the presence of bias. The results of the Egger tests showed p-values of 0.2908, 0.0612, and 0.5980, indicating varying levels of evidence of asymmetry. Specifically, the first and third tests revealed no significant asymmetry, suggesting that publication bias is unlikely. The second test indicated a slight tendency towards asymmetry, but this was not statistically significant. Overall, these findings confirm that publication bias does not affect the results of this meta-analysis (supplementary data).

**Table 1. Characteristics of the included studies.**

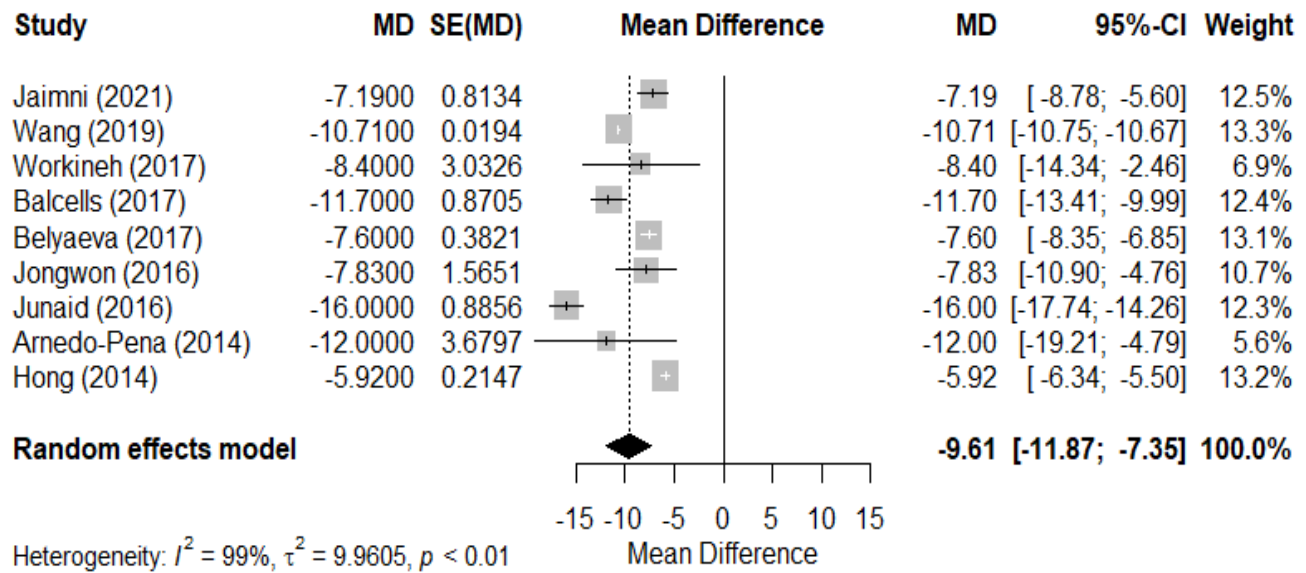
Author (Ref.)	Country	Study Design	Study Population	Population		Age, Years Mean $\pm$ SD/ Median (Range)		Method of Measuring Vitamin D	Vit. D ng/ml (25OH D)		Association TB & VDD
				Case	Control	Case	Control		Case	Control	
Jaimni (2021) [7]	India	Case-control	PTB patients/ healthy controls	50	50	NA	NA	ECLIA	19(7.75-27.25)	25(19.75, 32)	Yes
Wang (2019) [8]	China	Cross-sectional	PTB patients/ healthy controls	299	91	45.14 $\pm$ 16.45	47.45 $\pm$ 9.24	RIA	6.50 $\pm$ 0.22	17.21 $\pm$ 0.14	Yes
Workineh (2017) [21]	Ethiopia	Cross-sectional	TB patients/ HHC/Controls	126	70	29.8 $\pm$ 11.9	27.3 $\pm$ 7.6	ELISA	30.1 $\pm$ 19.3	38.5 $\pm$ 20.9	Yes
Balcells (2017)	Chile	Cross-sectional	PTB patients/ HHC/controls	107	31	37(29-53)	32 (26-48)	LC-MS/MS	11.7	23.4	Yes
Belyaeva (2017) [23]	Russia	Cross-sectional	PTB patients / healthy donors	33	41	22.9(17-33)	31.5(17-56)	ELISA	11.7 $\pm$ 1.8	19.3 $\pm$ 1.4	Yes
Jongwon (2016) [22]	South Korea	Case-control	TB patients/ controls	152	137	48(18-80)	45 (21-80)	LC-MS/MS	10.6(0.49-52.3)	19.3(6.2-60.5)	Yes



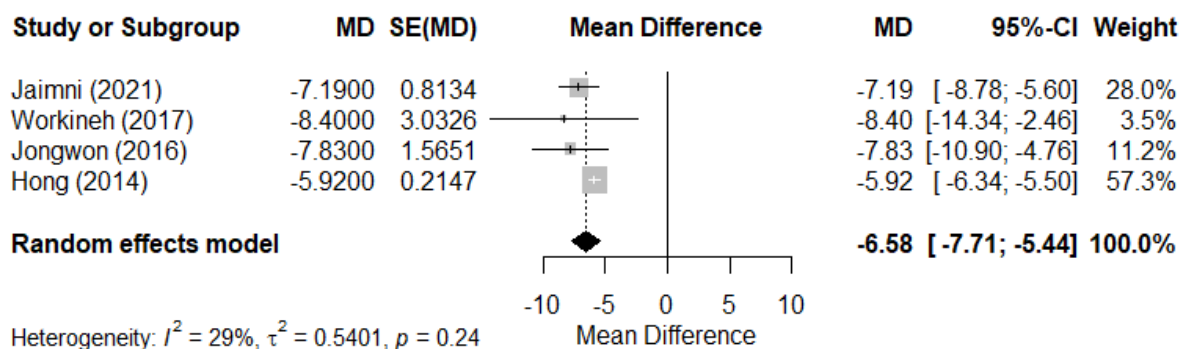
(Table 3) contd....

Author (Ref.)	Country	Study Design	Study Population	Population		Age, Years Mean $\pm$ SD/ Median (Range)		Method of Measuring Vitamin D	Vit. D ng/ml (25OH D)		Association TB & VDD
				Case	Control	Case	Control		Case	Control	
Junaid (2016) [24]	Pakistan	Case-control	PTB patients/controls	260	112	31.6 $\pm$ 10.5	30.6 $\pm$ 9.3	ELISA	27.3	43.3	OR = 1.87 (1.15 - 3.04)
Arnedo-Pena (2014) [37]	Spain	Cohort	Contacts of PTB patients	3	520	42.3 $\pm$ 24	38.0 $\pm$ 14.0	ECLIA	13.7 $\pm$ 6.3	25.7 $\pm$ 12.7	HR = 0.89 (0.80-0.99)
Hong (2014) [25]	South Korea	Case-control	TB patients/controls	94	282	35.4 $\pm$ 15.5	35.4 $\pm$ 15.2	RIA	9.86 (7.19-14.15)	16.03(12.38-20.30)	OR = 2.64 (1.33-5.22)

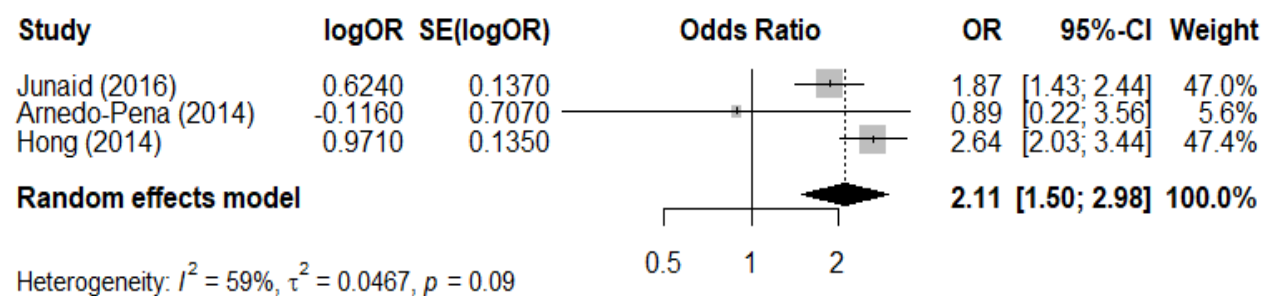
NA=not available, TB=tuberculosis, PTB= pulmonary tuberculosis, HHC=household contacts VDD=vitamin D deficiency, ECLIA=Electrochemiluminescence Immunoassay, RIA=Radioimmunoassay, ELISA=Enzyme-Linked Immunosorbent Assay, LC-MS/MS=Liquid Chromatography with Tandem Mass Spectrometry, OR=Odds Ratio, HR=Hazard Ratio.



**Fig. (2).** Forest plot of mean differences in vitamin D levels between tuberculosis (TB) patients and control groups. The plot displays the mean differences and 95% confidence intervals for each study, along with the pooled estimate under the random-effects model. Diamonds represent the overall mean difference estimate and its confidence interval.



**Fig. (3).** Forest plot of subgroup analysis of mean differences in vitamin D levels between TB patients and control groups. The plot displays the mean differences and 95% confidence intervals for each study, as well as the pooled estimate under the random-effects model. Diamonds represent the overall mean difference estimate and its confidence interval.



**Fig. (4).** Forest plot of pooled odds ratios for the association between vitamin D deficiency and tuberculosis (TB), using a random-effects model. The diamonds represent the pooled effect estimate.

4. DISCUSSION

In this meta-analysis, we included studies that involved HIV-negative participants to explore the association between vitamin D deficiency (< 20 ng/mL) [18] and tuberculosis. our finding revealed significant differences in 25(OH)D levels between the TB group and controls, with vitamin D concentrations being notably lower on average in the TB group. Vitamin D deficiency was observed in four [8, 25, 36, 22] of the nine studies included in the control group and seven of the nine [7, 8, 22, 23, 25, 36, 37] studies included in the TB group, indicating a significantly higher prevalence of VDD in TB patients compared with controls. All studies [7, 8, 21-25, 36, 37] reported negative mean differences (MD) between the groups, with an overall MD of -9.6097 ng/ml (95% CI: -11.87 to -7.35). A sub-group analysis showed a mean difference in 25(OH)D levels of -6.58 ng/ml (95% CI: -7.71 to -5.44) with moderate heterogeneity ( $I^2=29\%$ ,  $p=0.24$ ), consistently indicating lower 25(OH)D levels in TB patients ( $p<0.0001$ ). Acen *et al.* also reported similar results, finding that TB patients had significantly lower vitamin D levels than those without TB ( $p < 0.01$ ). Their meta-analysis estimated the standardized mean difference (SMD) in vitamin D levels, revealing an overall pooled effect of SMD -0.625 (95% CI [-0.784, -0.466], ( $p < 0.001$ ) [30]. Similarly, Huang *et al.* conducted a meta-analysis of 25 studies involving 3599 TB cases and 3063 controls, revealing significantly lower 25(OH)D levels in TB patients than in controls (MD = -13.05; 95% CI [-19.02, -7.08];  $p < 0.0001$ ) [38]. Several other recent studies, including both reviews and primary research, have yielded similar results [39-41, 9]. This consistent observation across studies underscores the main role of vitamin D in the immune response against microbial pathogens, particularly those caused by *Mycobacterium tuberculosis* [13, 14, 42]. Furthermore, in the presence of vitamin D, monocytes and macrophages produce antimicrobial peptides, such as cathelicidin, which enhances their ability to eliminate bacteria more effectively. In addition, vitamin D regulates the response of type 1 T helper lymphocytes (Th1), crucial for the production of interferon-gamma (IFN- $\gamma$ ), a key cytokine in TB control [13, 14, 43-45]. Moreover, our findings highlight the significant association between VDD

and an increased risk of developing tuberculosis with a pooled OR of 2.11 (95% CI: 1.50 to 2.98,  $Z = 4.26$ ,  $p < 0.001$ ;  $I^2=59\%$ ,  $p=0.09$ ). Various studies have suggested an association between VDD and tuberculosis. Davies *et al.* were the first to establish this link in 1985 [46]. Over the years, several studies have identified a significant association between VDD and tuberculosis [9, 10, 26, 39, 47]. A recent meta-analysis by Kafle *et al.* [40] and Huang *et al.* [48] reported similar results with (OR=3.23, 95% CI = [1.91-5.45],  $p < 0.0001$ ) and (OR = 4.26; 95% CI =[2.48, 7.30],  $p < 0.00001$ ) respectively. Even in children, Gou *et al.* reported a significant association between VDD and TB with a pooled OR of 1.78 (95% CI: 1.30-2.44,  $p < 0.05$ ) and between latent tuberculosis infection (LTBI) and VDD with a pooled OR of 1.54 (95% CI: 1.12-2.10,  $p < 0.05$ ) [49]. Although these studies established a relationship between tuberculosis and serum 25(OH)D levels, it remains uncertain whether VDD status increases the risk of developing tuberculosis or if tuberculosis leads to VDD. Recently, a prospective study conducted by Hsu *et al.* reported that vitamin D deficiency is an independent risk factor for incident active tuberculosis [10]. Huang *et al.* suggested that VDD is more probably a cause of TB rather than a result of it [48]. In their review, Junaid *et al.* concluded that VDD is a risk factor for tuberculosis due to vitamin D's well-documented role in the innate immunity pathway [13]. Moreover, Aibana *et al.* found in their meta-analysis that low serum 25-(OH)D levels increased the risk of progressing to tuberculosis in a dose-dependent manner [50]. Another piece of evidence supporting the association between VDD and TB is the presence of vitamin D receptor (VDR) gene polymorphisms [51-54]. Sutaria *et al.* found in their pooled analysis of seven studies that only BsmI and FokI VDR polymorphisms significantly affect TB risk. Specifically, both the heterozygous and recessive forms of BsmI, as well as the recessive form of FokI, are associated with an increased risk of TB compared to the wild-type (ORs of 1.70, 1.55, and 1.93, respectively,  $p < 0.05$ ) [41]. In their meta-analysis, Huang *et al.* demonstrate that the VDR FokI polymorphism plays a role in increasing the risk of TB [55]. The positive effects of vitamin D have long been recognized, whether through the administration of cod liver oil, exposure to sunlight, or

with proper nutrition and fresh air [13]. In vitro studies demonstrated that vitamin D has the ability to restore impaired immune responses in macrophages exposed to *Mycobacterium tuberculosis* [56], and the administration of 1,25-dihydroxyvitamin D<sub>3</sub> reduced the proliferation of *Mycobacterium tuberculosis* bacilli inside macrophages [14, 57, 58]. Additionally, low serum levels of 25(OH)D were found to correlate with an increased incidence of upper respiratory tract infections, chronic and acute airway diseases [59, 60], mortality in adult patients with sepsis [61], and many other diseases [62]. Several research into vitamin D as an adjunct treatment for tuberculosis have produced conflicting results in the various clinical trials. Some Randomized Controlled Trials (RCT) studies have confirmed that vitamin D supplementation has positive effects on tuberculosis, including improved therapeutic outcomes [63], accelerated sputum conversion [64], and alleviation of clinical signs of TB [64-66]. In contrast, other studies have reported no effect of vitamin D on reducing the risk of infection, mortality, or acute respiratory infection [67, 68]. A recent review of clinical trials by Santos-Mena *et al.* highlights that factors such as genetic variations, geographical differences, variable dosages, duration of treatment, tuberculosis status, and the different forms of vitamin D used contribute to the variability observed in results [56].

#### 4.1. Limitations of the Study

Our study is subject to a few limitations. Firstly, we only had access to four electronic databases (PubMed, Scopus, ScienceDirect, and Web of Science), which may have led to publication bias by restricting the diversity of included studies. Secondly, the limited number of studies and small sample sizes may have reduced the reliability of our findings. Thirdly, variations in analytical methods, such as RIA, ELISA, LC-MS/MS, and ECLIA, could have influenced the comparability and accuracy of the findings. Nonetheless, despite the inclusion of various study designs (case-control, cross-sectional, and cohort), Egger's test did not indicate any significant heterogeneity. Additionally, while we focused solely on HIV-negative patients to reduce a key confounding factor, other potential confounders such as socioeconomic status, nutritional factors, and comorbid conditions were not systematically addressed. Given the multifactorial nature of TB risk, future studies should incorporate a more comprehensive adjustment for these factors. Despite these limitations, our study demonstrates a link between vitamin D deficiency (VDD) and tuberculosis by consistently defining VDD as 20 ng/mL, which helped maintain uniformity in the findings. Furthermore, our results highlight the need for standardized methodologies and diagnostic criteria in future research to enhance comparability and reliability.

#### CONCLUSION

Our meta-analysis revealed that tuberculosis patients have significantly lower 25(OH)D levels than controls. Vitamin D deficiency is also significantly associated with an increased risk of TB. These findings highlight the

potential role of vitamin D in TB risk and underscore the need for further investigation into its implications for tuberculosis prevention and management. Future research should prioritize standardized vitamin D supplementation trials to assess its effectiveness in TB prevention and treatment. Additionally, developing targeted screening strategies for at-risk populations, such as individuals with chronic vitamin D deficiency or those in high-burden TB areas, could help identify vulnerable groups and guide preventive interventions. Integrating vitamin D assessment into TB management protocols may also provide valuable insights into its role in disease progression and treatment outcomes. While further evidence is necessary before establishing clinical guidelines, these considerations could contribute to a more comprehensive approach to TB control and prevention. Moreover, the standardization of clinical trial protocols on vitamin D supplementation is essential to minimize confounding factors and ensure more conclusive and reproducible results.

#### AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: conceptualization, methodology, software, investigation, writing - original draft, writing - review: AO; data collection: FZEM; data analysis or interpretation: AL; methodology: AM; methodology, validation, writing - review & editing: SM; conceptualization, methodology, supervision, project administration, writing - review & editing: SB. All authors reviewed the results and approved the final version of the manuscript.

#### LIST OF ABBREVIATIONS

AIDS	= Acquired immunodeficiency syndrome
ECLIA	= Electrochemiluminescence immunoassay
ELISA	= Enzyme-linked Immunosorbent assay
HHC	= Household contacts
HIV	= Human immunodeficiency virus
LCMS/MS	= Liquid chromatography tandem mass spectrometry
LTBI	= Latent tuberculosis infection
MD	= Mean difference
MTB	= <i>Mycobacterium tuberculosis</i>
ORs	= Odds ratios
PRISMA	= Preferred reporting items for systematic reviews and meta-analyses
PTB	= Pulmonary tuberculosis
RIA	= Radioimmunoassay
RR	= Relative risk
SMD	= Standardized mean difference
TB	= Tuberculosis
Th1	= T-helper type 1

VDD = Vitamin D deficiency  
 VDR = Vitamin D receptor  
 25[OH]D = 25-Hydroxyvitamin D

## CONSENT FOR PUBLICATION

Not applicable.

## STANDARDS OF REPORTING

PRISMA and methodological guidelines were followed.

## AVAILABILITY OF DATA AND MATERIAL

The data supporting the findings of the article is available in the Zenodo repository at <https://zenodo.org/records/15192275>, reference number 15192275.

## FUNDING

None.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

## ACKNOWLEDGEMENTS

I would like to thank all the authors who contributed to this article.

## SUPPLEMENTARY MATERIAL

PRISMA checklist is available as supplementary material on the publisher's website along with the published article.

## REFERENCES

- [1] Global Tuberculosis Report. 2023. Available from: <https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023>
- [2] Migliori GB, Nardell E, Yedilbayev A, *et al.* Reducing tuberculosis transmission: A consensus document from the World Health Organization Regional Office for Europe. *Eur Respir J* 2019; 53(6): 1900391. <http://dx.doi.org/10.1183/13993003.00391-2019> PMID: 31023852
- [3] Dinkele R, Gessner S, McKerry A, *et al.* Aerosolization of *Mycobacterium tuberculosis* by tidal breathing. *Am J Respir Crit Care Med* 2022; 206(2): 206-16. <http://dx.doi.org/10.1164/rccm.202110-2378OC> PMID: 35584342
- [4] Tuberculosis. 2024. Available from: <https://www.who.int/news-room/fact-sheets/detail/tuberculosis>
- [5] Oubaasri A, Labyad A, El mskini FZ, *et al.* Epidemiological, clinical and evolutive profile of tuberculosis patients: Case of the region of Guelmim in Morocco. *Clin Epidemiol Glob Health* 2024; 29: 101769. <http://dx.doi.org/10.1016/j.cegh.2024.101769>
- [6] Social determinants of health. 2024. Available from: [https://www.who.int/health-topics/social-determinants-of-health#tab=tab\\_1](https://www.who.int/health-topics/social-determinants-of-health#tab=tab_1)
- [7] Jaimni V, Shasty BA, Madhyastha SP, *et al.* Association of vitamin D deficiency and newly diagnosed pulmonary tuberculosis. *Pulm Med* 2021; 2021: 1-6. <http://dx.doi.org/10.1155/2021/5285841> PMID: 33510909
- [8] Wang Q, Ma A, Gao T, *et al.* Poor vitamin d status in active pulmonary tuberculosis patients and its correlation with leptin and tnfr-α. *J Nutr Sci Vitaminol* 2019; 65(5): 390-8. <http://dx.doi.org/10.3177/jnsv.65.390> PMID: 31666475
- [9] Thejaswi SG, Koirala P, Pradhan U, Papanai H, Bhuyan S. Severe vitamin D deficiency as a risk factor in newly diagnosed tuberculosis patients: Comparative study on inhabitants of high altitude region. *Int J Prev Med* 2023; 14: 106. [http://dx.doi.org/10.4103/ijpvm.ijpvm\\_180\\_22](http://dx.doi.org/10.4103/ijpvm.ijpvm_180_22) PMID: 37854998
- [10] Hsu MS, Chung TC, Wang PH, *et al.* Revisiting the association between vitamin D deficiency and active tuberculosis: A prospective case-control study in Taiwan. *J Microbiol Immunol Infect* 2024; 57(3): 490-7. <http://dx.doi.org/10.1016/j.jmii.2024.03.005> PMID: 38594108
- [11] El Maataoui A, Ouzzif Z, Vitamin D. Vitamin D Status in the North African Population: A Review. *Clin Rev Bone Miner Metab* 2018; 16(3): 67-73. <http://dx.doi.org/10.1007/s12018-018-9247-y>
- [12] Bleizgys A, Vitamin D. Vitamin D dosing: Basic principles and a brief algorithm (2021 Update). *Nutrients* 2021; 13(12): 4415. <http://dx.doi.org/10.3390/nu13124415> PMID: 34959969
- [13] Junaid K, Rehman A. Impact of vitamin D on infectious disease-tuberculosis-A review. *Clin Nutr Exp* 2019; 25: 1-10. <http://dx.doi.org/10.1016/j.yclnex.2019.02.003>
- [14] Papagni R, Pellegrino C, Di Gennaro F, *et al.* Impact of vitamin D in prophylaxis and treatment in tuberculosis patients. *Int J Mol Sci* 2022; 23(7): 3860. <http://dx.doi.org/10.3390/ijms23073860> PMID: 35409219
- [15] Giustina A, Adler RA, Binkley N, *et al.* Consensus statement from 2<sup>nd</sup> international conference on controversies in vitamin D. *Rev Endocr Metab Disord* 2020; 21(1): 89-116. <http://dx.doi.org/10.1007/s11154-019-09532-w> PMID: 32180081
- [16] Płudowski P. Guidelines for preventing and treating of vitamin D deficiency: An Ukrainian approach A.D. 2023. *Bol Sustavy Pozvonoch* 2023; 13(2): 58-9. <http://dx.doi.org/10.22141/pjs.13.2.2023.367>
- [17] Whiting SJ, Calvo MS. Current Understanding of Vitamin D Metabolism Nutritional Status and Role in Disease Prevention. *Nutrition in the Prevention and Treatment of Disease (Fourth Edition)*. Elsevier Inc 2012. <http://dx.doi.org/10.1016/B978-0-12-391884-0.00043-3>
- [18] Holick MF, Binkley NC, Bischoff-Ferrari HA, *et al.* Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; 96(7): 1911-30. <http://dx.doi.org/10.1210/jc.2011-0385> PMID: 21646368
- [19] Cui A, Zhang T, Xiao P, Fan Z, Hu Wang YZ. Global and regional prevalence of vitamin D deficiency in population-based studies from 2000 to 2020: A pooled analysis of million participants from 110 countries were eligible for this study. *Front Nutr* 2023; 10: 1070808. <http://dx.doi.org/10.3389/fnut.2023.1070808> PMID: 37006940
- [20] Nutritional care and support for patients with tuberculosis i Nutritional care and support for patients with tuberculosis. 2024. Available from: [www.who.int](http://www.who.int)
- [21] Workineh M, Mathewos B, Moges B, Gize A, Getie S, Stendahl O. Vitamin D deficiency among newly diagnosed tuberculosis patients and their household contacts: A comparative cross-sectional study. *Arch Public Health* 2017; 75: 25. <http://dx.doi.org/10.1186/s13690-017-0195-7> PMID: 28638616
- [22] Oh Jongwon, Choi R, Park H-D, Lee H, Jeong B-H, Park HY. Evaluation of vitamin status in patients with pulmonary tuberculosis. *J Infect* 2017; 74(3): 272-80. <http://dx.doi.org/10.1016/j.jinf.2016.10.009> PMID: 27838523
- [23] Balcells ME, García P, Tiznado C, Villarroel L, Scioscia N, Carvajal C. Association of vitamin D deficiency, season of the year, and latent tuberculosis infection among household contacts. *PLoS One* 2017; 12(4): e0175400. <http://dx.doi.org/10.1371/journal.pone.0175400> PMID: 28403225
- [24] Junaid K, Rehman A, Jolliffe DA, Saeed T, Wood K, Martineau AR. Vitamin D deficiency associates with susceptibility to tuberculosis in Pakistan, but polymorphisms in VDR, DBP and CYP2R1 do not. *BMC Pulm Med* 2016; 16(1): 73. <http://dx.doi.org/10.1186/s12890-016-0240-2> PMID: 27160686



- [25] Hong JY, Kim SY, Chung KS, *et al.* Association between vitamin D deficiency and tuberculosis in a Korean population. *Int J Tuberc Lung Dis* 2014; 18(1): 73-8.  
<http://dx.doi.org/10.5588/ijtld.13.0536> PMID: 24365556
- [26] Sah S, Biswas SK, Biswas T, *et al.* Vitamin D status in Pulmonary Tuberculosis : A case control study. *BSMMU J* 2022; 14(3): 85-91.  
<http://dx.doi.org/10.3329/bsmmuj.v14i3.56604>
- [27] Ruiz-Tagle C, Romero F, Naves R, Balcells ME. Vitamin D and cathelicidin levels and susceptibility to *Mycobacterium tuberculosis* infection acquisition in household contacts. *Enferm Infecc Microbiol Clin* 2023; 41(8): 489-93.  
<http://dx.doi.org/10.1016/j.eimce.2022.04.013> PMID: 36707289
- [28] Yani FF, Lipoeto NI, Supriatno B, Darwin E, Basir D. Vitamin D status in under-five children with a history of close tuberculosis contact in Padang, West Sumatra. *Asia Pac J Clin Nutr* 2017; 26 (Suppl. 1): S68-72.  
<http://dx.doi.org/10.6133/apjcn.062017.s2> PMID: 28625040
- [29] Cao Y, Wang X, Liu P, Su Y, Yu H, Du J. Vitamin D and the risk of latent tuberculosis infection: A systematic review and meta-analysis. *BMC Pulm Med* 2022; 22(1): 39.  
<http://dx.doi.org/10.1186/s12890-022-01830-5> PMID: 35045861
- [30] Acen EL, Biraro IA, Worodria W, Joloba ML, Nkeeto B, Musaaizi J. Impact of vitamin D status and cathelicidin antimicrobial peptide on adults with active pulmonary TB globally: A systematic review and meta-analysis. *PLoS One* 2021; 16(6): e0252762.  
<http://dx.doi.org/10.1371/journal.pone.0252762> PMID: 34115790
- [31] Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.  
<http://dx.doi.org/10.1136/bmj.n71> PMID: 33782057
- [32] Newcastle-Ottawa Scale Assess Qual Nonrandomised Stud Meta-Analyses. 2024. Available from: [https://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)
- [33] Wells GA, Shea B, O'Connell D, Peterson J, Welch V. Priorities, programs and diseases. 2021. Available from: <https://www.ohri.ca/programs/>
- [34] Systeme International (SI) Conversion Factors for Selected Laboratory Components\*. *JAMA* 2000; 283(1): 135.
- [35] Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; 5(1): 13.  
<http://dx.doi.org/10.1186/1471-2288-5-13> PMID: 15840177
- [36] Vasilyevna Belyaeva I, Pavlovitch Churilov L, Robertovna Mikhailova L, Vladimirovitch Nikolaev A, Andreevna Starshinova A, Kazimirovitch Yablonsky P. Vitamin D, cathelicidin, prolactin, autoantibodies, and cytokines in different forms of pulmonary tuberculosis versus sarcoidosis. *Isr Med Assoc J* 2017; 19(8): 499-505.  
PMID: 28825769
- [37] Arnedo-Pena A, Juan-Cerdán JV, Romeu-García A, *et al.* Vitamin D status and incidence of tuberculosis among contacts of pulmonary tuberculosis patients. *Int J Tuberc Lung Dis* 2015; 19(1): 65-9.  
<http://dx.doi.org/10.5588/ijtld.14.0348> PMID: 25519792
- [38] Hammami F, Koubaa M, Mejdoub Y, *et al.* The association between vitamin D deficiency and extrapulmonary tuberculosis: Case-control study. *Tuberculosis* 2021; 126: 102034.  
<http://dx.doi.org/10.1016/j.tube.2020.102034> PMID: 33291025
- [39] Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: A systematic review and meta-analysis. *Int J Epidemiol* 2008; 37(1): 113-9.  
<http://dx.doi.org/10.1093/ije/dym247> PMID: 18245055
- [40] Kafle S, Basnet AK, Karki K, Thapa Magar M, Shrestha S, Yadav RS. Association of vitamin D deficiency with pulmonary tuberculosis: A systematic review and meta-analysis. *Cureus* 2021; 13(9): e17883.  
<http://dx.doi.org/10.7759/cureus.17883> PMID: 34660082
- [41] Sutaria N, Liu CT, Chen TC. Vitamin D status, receptor gene polymorphisms, and supplementation on tuberculosis: A systematic review of case-control studies and randomized controlled trials. *J Clin Transl Endocrinol* 2014; 1(4): 151-60.  
<http://dx.doi.org/10.1016/j.jcte.2014.08.001> PMID: 25599020
- [42] Oveissi M, Nikoonajad A, Allami A. Status of vitamin D, calcium and parathyroid hormone levels and hepatorenal function in untreated pulmonary tuberculosis: A matched case-control study. *J Adv Med Biomed Res* 2022; 30(139): 109-15.  
<http://dx.doi.org/10.30699/jambs.30.139.109>
- [43] Charoenngam N, Holick MF. Immunologic effects of vitamin D on human health and disease. *Nutrients* 2020; 12(7): 2097.  
<http://dx.doi.org/10.3390/nu12072097> PMID: 32679784
- [44] Brighenti S, Bergman P, Martineau AR, Brighenti AS, Karolinska MA. Vitamin D and tuberculosis: Where next? *J Intern Med* 2018; 284(2): 145-62.  
<http://dx.doi.org/10.1111/joim.12777> PMID: 29804293
- [45] Selvaraj P, Afsal K, Harishankar M. Vitamin D and macrophage functions in tuberculosis. *Macrophage* 2015; 1-9.  
<http://dx.doi.org/10.14800/macrophage.756>
- [46] Davies PD, Brown RC, Woodhead JS. Serum concentrations of vitamin D metabolites in untreated tuberculosis. *Thorax* 1985; 40(3): 187-90.  
<http://dx.doi.org/10.1136/thx.40.3.187> PMID: 3872485
- [47] Ageeru K, Mendu SB, Avinash S, Kalyani S, Kotha R Sr. Serum vitamin D levels in pediatric tuberculosis patients in a tertiary care center in India: A case-control study. *Cureus* 2023; 15(6): e39937.  
<http://dx.doi.org/10.7759/cureus.39937> PMID: 37409212
- [48] Huang SJ, Wang X, Liu ZD, *et al.* Vitamin D deficiency and the risk of tuberculosis: A meta-analysis. *Drug Des Devel Ther* 2016; 11: 91-102.  
<http://dx.doi.org/10.2147/DDDT.S79870> PMID: 28096657
- [49] Gou X, Pan L, Tang F, Gao H, Xiao D. The association between vitamin D status and tuberculosis in children. *Medicine* 2018; 97(35): e12179.  
<http://dx.doi.org/10.1097/MD.00000000000012179> PMID: 30170465
- [50] Aibana O, Huang CC, Aboud S, *et al.* Vitamin D status and risk of incident tuberculosis disease: A nested case-control study, systematic review, and individual-participant data meta-analysis. *PLoS Med* 2019; 16(9): e1002907.  
<http://dx.doi.org/10.1371/journal.pmed.1002907> PMID: 31509529
- [51] Wang Y. A meta-analysis on associations between vitamin D receptor genetic variants and tuberculosis. *Microb Pathog* 2019; 130: 59-64.  
<http://dx.doi.org/10.1016/j.micpath.2019.02.027> PMID: 30822458
- [52] Yadav U, Kumar P, Rai V. FokI polymorphism of the vitamin D receptor (VDR) gene and susceptibility to tuberculosis: Evidence through a meta-analysis. *Infect Genet Evol* 2021; 92: 104871.  
<http://dx.doi.org/10.1016/j.meegid.2021.104871> PMID: 33901685
- [53] Li B, Wen F, Wang Z. Correlation between polymorphism of vitamin D receptor TaqI and susceptibility to tuberculosis. *Medicine* 2022; 101(16): e29127.  
<http://dx.doi.org/10.1097/MD.00000000000029127> PMID: 35482984
- [54] Xu X, Shen M. Associations between vitamin D receptor genetic variants and tuberculosis: A meta-analysis. *Innate Immun* 2019; 25(5): 305-13.  
<http://dx.doi.org/10.1177/1753425919842643> PMID: 30987490
- [55] Huang L, Liu C, Liao G, *et al.* Vitamin D receptor gene FokI polymorphism contributes to increasing the risk of tuberculosis. *Medicine* 2015; 94(51): e2256.  
<http://dx.doi.org/10.1097/MD.0000000000002256> PMID: 26705207
- [56] Santos-Mena A, González-Muñiz OE, Jacobo-Delgado YM, Rivas-Santiago B. Shedding light on vitamin D in tuberculosis: A comprehensive review of clinical trials and discrepancies. *Pulm Pharmacol Ther* 2024; 85: 102300.  
<http://dx.doi.org/10.1016/j.pupt.2024.102300> PMID: 38723942
- [57] Al-Jaberi FAH, Crone CG, Lindenström T, *et al.* Reduced vitamin D-induced cathelicidin production and killing of *Mycobacterium tuberculosis* in macrophages from a patient with a non-functional vitamin D receptor: A case report. *Front Immunol* 2022; 13:

1038960.  
<http://dx.doi.org/10.3389/fimmu.2022.1038960> PMID: 36405761
- [58] Das P, Banerjee A, Karak DP. Molecular interplay between vitamin D and immunity can aid antitubercular treatment vitamin D in immunomodulation of TB. *Def Life Sci J* 2022; 7(3): 209-20.  
<http://dx.doi.org/10.14429/dlsj.7.17566>
- [59] Shoemaker ME, Huynh LM, Smith CM, Mustad VA, Duarte MO, Cramer JT. Immunomodulatory effects of vitamin D and prevention of respiratory tract infections and COVID-19. *Topics Clin Nutr* 2022; 37(3): 203-17.  
<http://dx.doi.org/10.1097/TIN.0000000000000284> PMID: 35761885
- [60] Gaudet M, Plesa M, Mogas A, Jalaaliddine N, Hamid Q, Al Heialy S. Recent advances in vitamin D implications in chronic respiratory diseases. *Respir Res* 2022; 23(1): 252.  
<http://dx.doi.org/10.1186/s12931-022-02147-x> PMID: 36117182
- [61] Li Y, Ding S. Serum 25-Hydroxyvitamin D and the risk of mortality in adult patients with Sepsis: A meta-analysis. *BMC Infect Dis* 2020; 20(1): 189.  
<http://dx.doi.org/10.1186/s12879-020-4879-1> PMID: 32131740
- [62] Ahmad S, Arora S, Khan S, *et al.* Vitamin D and its therapeutic relevance in pulmonary diseases. *J Nutr Biochem* 2021; 90: 108571.  
<http://dx.doi.org/10.1016/j.jnutbio.2020.108571> PMID: 33388351
- [63] Rekha RS, Mily A, Sultana T, *et al.* Immune responses in the treatment of drug-sensitive pulmonary tuberculosis with phenylbutyrate and vitamin D<sub>3</sub> as host directed therapy. *BMC Infect Dis* 2018; 18(1): 303.  
<http://dx.doi.org/10.1186/s12879-018-3203-9> PMID: 29973153
- [64] Wen Y, Li L, Deng Z. Calcitriol supplementation accelerates the recovery of patients with tuberculosis who have vitamin D deficiency: A randomized, single-blind, controlled clinical trial. *BMC Infect Dis* 2022; 22(1): 436.  
<http://dx.doi.org/10.1186/s12879-022-07427-x> PMID: 35513795
- [65] Tamara L, Kartasasmita CB, Alam A, Gurnida DA. Effects of Vitamin D supplementation on resolution of fever and cough in children with pulmonary tuberculosis: A randomized double-blind controlled trial in Indonesia. *J Glob Health* 2022; 12: 04015.  
<http://dx.doi.org/10.7189/jogh.12.04015> PMID: 35198149
- [66] Chandra H, Rahman A, Yadav P, Maurya G, Kumar Shukla S. Effect of adjunct Vitamin D treatment in vitamin D deficient pulmonary tuberculosis patients: A randomized, double blind, active controlled clinical trial. *Indian J Tuberc* 2024; 71(2): 170-8.  
<http://dx.doi.org/10.1016/j.ijtb.2023.04.026> PMID: 38589121
- [67] Ganmaa D, Uyanga B, Zhou X, *et al.* Vitamin D supplements for prevention of tuberculosis infection and disease. *N Engl J Med* 2020; 383(4): 359-68.  
<http://dx.doi.org/10.1056/NEJMoa1915176> PMID: 32706534
- [68] Sudfeld CR, Mugusi F, Muhihi A, *et al.* Efficacy of vitamin D<sub>3</sub> supplementation for the prevention of pulmonary tuberculosis and mortality in HIV: A randomised, double-blind, placebo-controlled trial. *Lancet HIV* 2020; 7(7): e463-71.  
[http://dx.doi.org/10.1016/S2352-3018\(20\)30108-9](http://dx.doi.org/10.1016/S2352-3018(20)30108-9) PMID: 32621874