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INADEQUATE VITAMIN D LEVELS AND ASSOCIATED RISK FACTORS AMONG CHILDREN UNDER FIVE YEARS IN SOUTHEAST ASIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Vitamin D deficiency (VDD) and Vitamin D insufficiency (VDI) in children in Southeast Asia (SEA) pose significant public health concerns, impacting growth and non-skeletal health. This study aimed to (1) assess the prevalence of inadequate Vitamin D levels among children under five years in SEA and (2) identify associated risk factors. A meta-analysis was conducted, systematically reviewing articles from ProQuest, EBSCO, and PubMed (January 2013–October 2024). Inclusion criteria encompassed original, English-language, cross-sectional studies focusing on children under five years with documented serum 25(OH)D levels. Studies conducted outside SEA, lacking full text, addressing irrelevant topics, or containing insufficient data were excluded. Statistical analysis employed the DerSimonian and Laird random-effects model, with 95% CI calculated using the Clopper-Pearson method. A total of 13 cross-sectional studies from Thailand, Malaysia, Indonesia, Philippines, Cambodia, and Vietnam were included, with a combined sample size of 4,321 subjects. The prevalence of VDD among children under five years in SEA was 35% (95% CI, 24%-45%; I2, 98.15%), and VDI was found in 34% (25%-44%; I2, 89.67%). The mean serum vitamin D level (nmol/L) was 57.97 (48.83–67.10; I2, 99.99%). Maternal VDD or VDI was found to be associated with inadequate Vitamin D levels among children under five years in SEA, with a Pooled Odds Ratio of 4.25 (95% CI: 1.76–6.74; I2 =87.57%). This study underscores the high prevalence of inadequate Vitamin D levels among children under five in SEA, highlighting the urgent need for targeted public health interventions to mitigate this growing concern.

Keywords: Children, Southeast Asia, vitamin D deficiency, vitamin D insufficiency.

Introduction

Vitamin D deficiency (VDD) and Vitamin D insufficiency (VDI) are notable health issues, particularly in regions like Southeast Asia (SEA), where they can lead to severe health consequences such as rickets, a condition characterized by skeletal demineralization and deformities.[1] VDD and VDI are commonly seen in children during phases of rapid growth like infancy and prepuberty, leading to symptoms such as bowed legs, delayed tooth development, seizures due to low calcium levels, and muscle weakness during adolescence.[2,3] The recurrence of VDD and VDI has been noted in children with darker skin tones, inadequate sunlight exposure, and insufficient vitamin D consumption.[3,4]

Apart from bone-related issues, VDD and VDI are associated with non-bone complications such as higher rates of acute respiratory infections, cardiovascular conditions, and overall mortality.[5-7] Children suffering from VDD and VDI face an increased risk of severe pneumonia or inadequate response to typical pneumonia treatments due to compromised immunity and a weakened rib structure.[7,8]

Although SEA receives ample sunlight, lifestyle choices, and cultural beliefs play a significant role in the prevalence of VDD and VDI in the area.[9,10] It is essential to implement public health initiatives that promote sufficient vitamin D levels through cost-effective, realistic, and enduring approaches.[9] Identifying vulnerable age groups prone to VDD and VDI and the factors influencing this condition is vital for planning successful preventive or intervention strategies.[11] This study aimed to: 1) assess the prevalence of inadequate Vitamin D levels among children under five years in SEA, and 2) identify the factors associated with inadequate Vitamin D levels in this population.

Materials and Methods

Study design and sample

The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] Searches were conducted in three databases; ProQuest, EBSCO, and PubMed to identify relevant studies published from January 2013 to October 2024.

Study selection

The research aimed to analyze the mean blood vitamin D levels in children under five years within the region and to identify the factors associated with inadequate levels. For this investigation, VDD was defined as a serum 25(OH)D level <20 ng/mL or <50 nmol/L, while VDI was between 20-29 ng/mL or 50-74.9 nmol/L, and hypovitaminosis D (VDD and VDI).[14] The search strategy employed specific keywords to identify original articles published between January 2013 and October 2024: "((Children[MeSH Terms]) AND (Risk factors[MeSH Terms])) AND (Vitamin D deficiency[MeSH Terms])". Only original English-language articles involving human subjects were included, with a focus on cross-sectional studies. Studies conducted outside Southeast Asia (Thailand, Malaysia, Indonesia, Philippines, Cambodia, Vietnam, Myanmar, Singapore, Brunei Darussalam, and Laos) were excluded during the filtering process. Additionally, articles were excluded if they lacked full text, addressed irrelevant topics, or contained data unsuitable for extraction or analysis. Two authors (RDN and NPS) independently reviewed the titles and abstracts of potentially relevant articles. Studies meeting the inclusion criteria underwent a full-text assessment to facilitate the meta-analysis, with disagreements resolved through consensus.

Data extraction and quality assessment

The information from the articles was organized into tables containing details such as author names, country of origin, study designs, subjects' ages, sample sizes, Vitamin D measurement methods, prevalence of Vitamin D status, average Vitamin D levels, and risk factors. Data extraction was conducted independently by two authors (RDN and NPS), with any discrepancies resolved through consultation with a third author (LCM). In cases where additional data were needed, the study authors were contacted for clarification. Visual representations in the form of PRISMA flowcharts were utilized to outline the article retrieval process (Figure 1).

The assessment of bias risk in prevalence studies was carried out using the Joanna Briggs Institute (JBI) criteria. Studies were categorized based on their scores: 0 to 3 as low-risk, 4 to 6 as moderate-risk, and 7 to 9 as high-risk (Figure 2).[14]

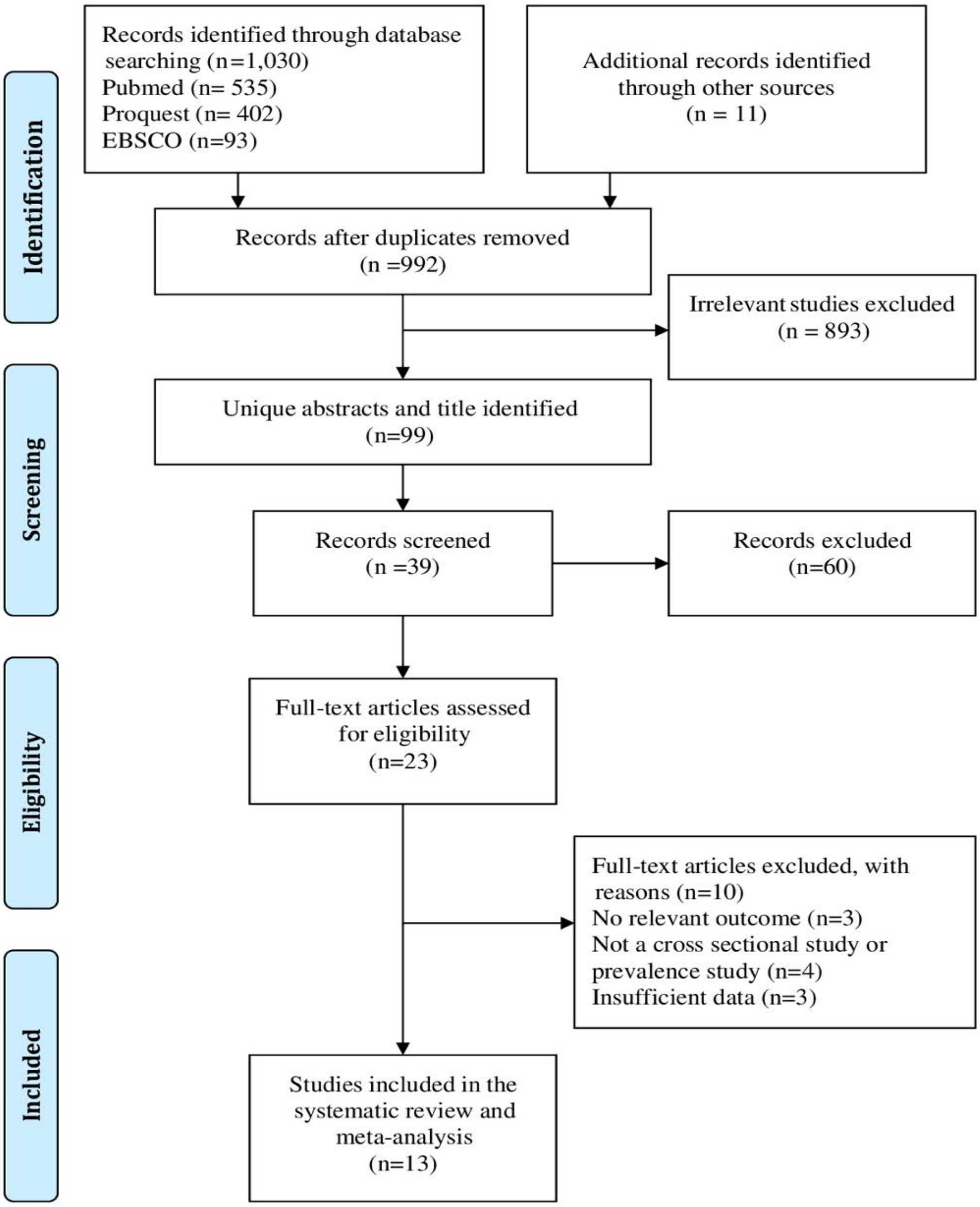

Figure 1. PRISMA flow chart

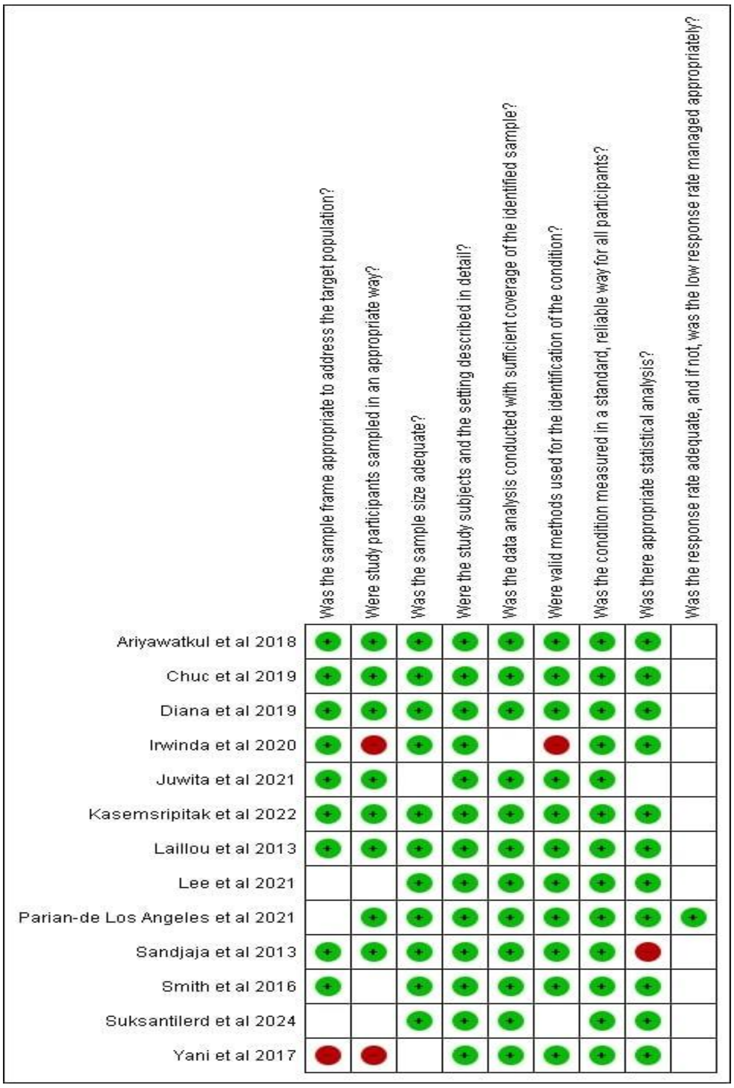

Figure 2. Quality of the publications using Joanna Briggs Institute (JBI) criteria

Data analysis

To calculate the prevalence rate, the total count of children under five years old with documented vitamin D levels was divided by the number identified as VDD and VDI. The statistical analysis utilized the DerSimonian and Laird random-effects model, and the 95% confidence interval (CI) was calculated using the Clopper-Pearson method.[15] Publication bias was assessed using Egger's test. The analysis of the data was conducted utilizing Stata 17.0 software.

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Results

The review of the studies identified 13 cross-sectional studies conducted in regions including Thailand, Malaysia, Indonesia, the Philippines, Cambodia, and Vietnam, with a combined sample size of 4,321 subjects (Table 1).[16-28]

Table 1. Review of included studies

Author	Year	Country	Study design	Subject's age	Sample size	Method of measuring Vitamin D	Prevalence of Vitamin D status (%)			Mean of Vitamin D level (nmol/L)	Risk factors
							VDD	VDI	HVD		
Suksantilerd et al[16]	2024	Thailand	Cross-sectional	4 mo	109	ECLIA	35.78	33.03	68.81	35.93±8.4	Child sun exposure (≤ 15 min/day), maternal Vitamin D supplement
Kasemsripitak et al[17]	2022	Thailand	Cross-sectional	6-12 mo	120	CMIA	9	19	28	64±24.5	Child sun exposure (≤ 15 min/day), maternal VDD or VDI
Lee et al[18]	2021	Malaysia	Cross-sectional	Newborn	110	ECLIA	N/A	42.7	N/A	36.9±15.3	Child sun exposure (≤ 15 min/day)
Juwita et al[19]	2021	Indonesia	Cross-sectional	23-29 mo	109	ELISA	50.5	36.7	87.2	50.7±10.5	N/A
Parian-de Los Angeles et al[20]	2021	Philippines	Cross-sectional	<6 mo	131	ECLIA	77	N/A	N/A	N/A	Infant age ≤ 11 mo, maternal VDD or VDI
Irwinda et al[21]	2020	Indonesia	Cross-sectional	Newborn	30	LCMS	52.4	N/A	N/A	53.75±12.5	N/A
Diana et al[22]	2019	Indonesia	Cross-sectional	6 mo	116	LCMS	10	N/A	N/A	89.71±1.57	N/A
Chuc et al[23]	2019	Vietnam	Cross-sectional	1-3 y	327	ELISA	47.7	N/A	N/A	81.3±26.48	N/A
Ariyawatkul et al[24]	2018	Thailand	Cross-sectional	Newborn	94	CMIA	33.3	54.2	87.5	37.1±12.83	Maternal VDD or VDI
Yani et al[25]	2017	Indonesia	Cross-sectional	<5 y	100	ELISA	21	N/A	N/A	N/A	N/A
Smith et al[26]	2016	Cambodia	Cross-sectional	24-59 mo	495	ELISA	10.3	24.4	34.7	87.9±35.4	Infant age ≤ 11 mo, maternal Vitamin D supplement
Laillou et al[27]	2013	Vietnam	Cross-sectional	<5 y	532	HPLC	36.7	N/A	N/A	44.50±0.74	N/A
Sandjaja et al[28]	2013	Indonesia	Cross-sectional	2-4.9 y	2,048	ELISA	34.9	N/A	N/A	56.0±3.0	N/A
Total sample					**4,321**						

CMIA, Chemiluminescent microparticle immunoassay; ECLIA, Electrochemiluminescence immunoassay; ELISA, Enzyme-linked immunosorbent assay; HPLC, High-performance liquid chromatography; LCMS, Liquid chromatography-tandem mass spectroscopy; N/A, not available; y, years; mo, months; VDD, Vitamin D Deficiency; VDI, Vitamin D insufficiency; HVD, hypovitaminosis D.

In Figure 3, the prevalence of VDD among children under five years in SEA was 35% (95% CI, 24%-45%; I^2, 98.15%), while VDI was found in 34% (25%-44%; I^2, 89.67%), and HVD was present in 61% (35%-88%; I^2, 98.71%). The average serum vitamin D level (nmol/L) was 57.97 (48.83– 67.10; I^2, 99.99%) (Figure 3).

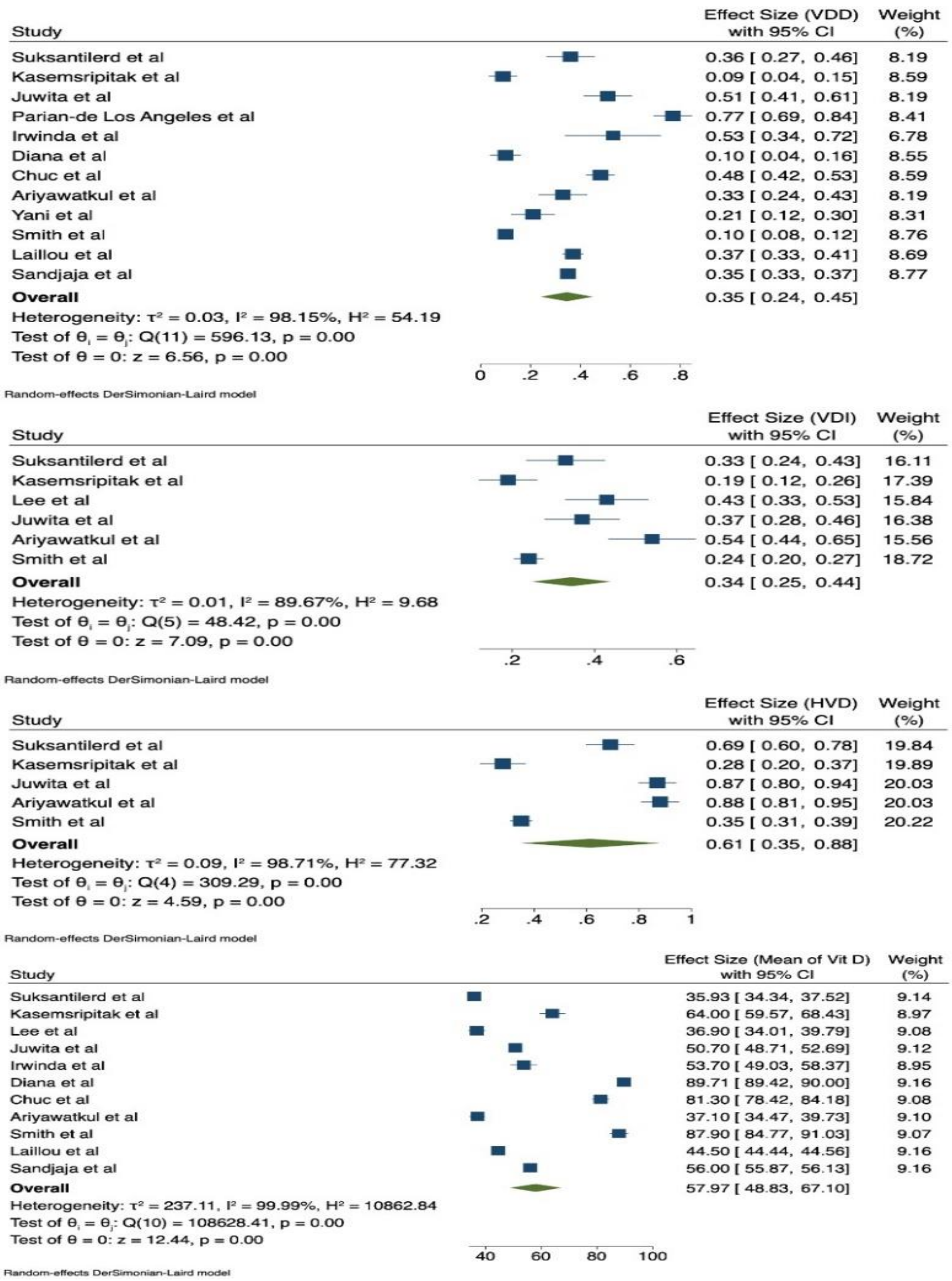

Figure 3. Prevalence of inadequate Vitamin D levels among children under five years in SEA

Figure 4 displays the factors associated with inadequate Vitamin D levels among children under five years in SEA. Maternal VDD or VDI is associated with inadequate Vitamin D levels among children under five years in SEA, with a Pooled Odds Ratio of 4.25 (95% CI, 1.76–6.74; I², 87.57%) (Figure 4).

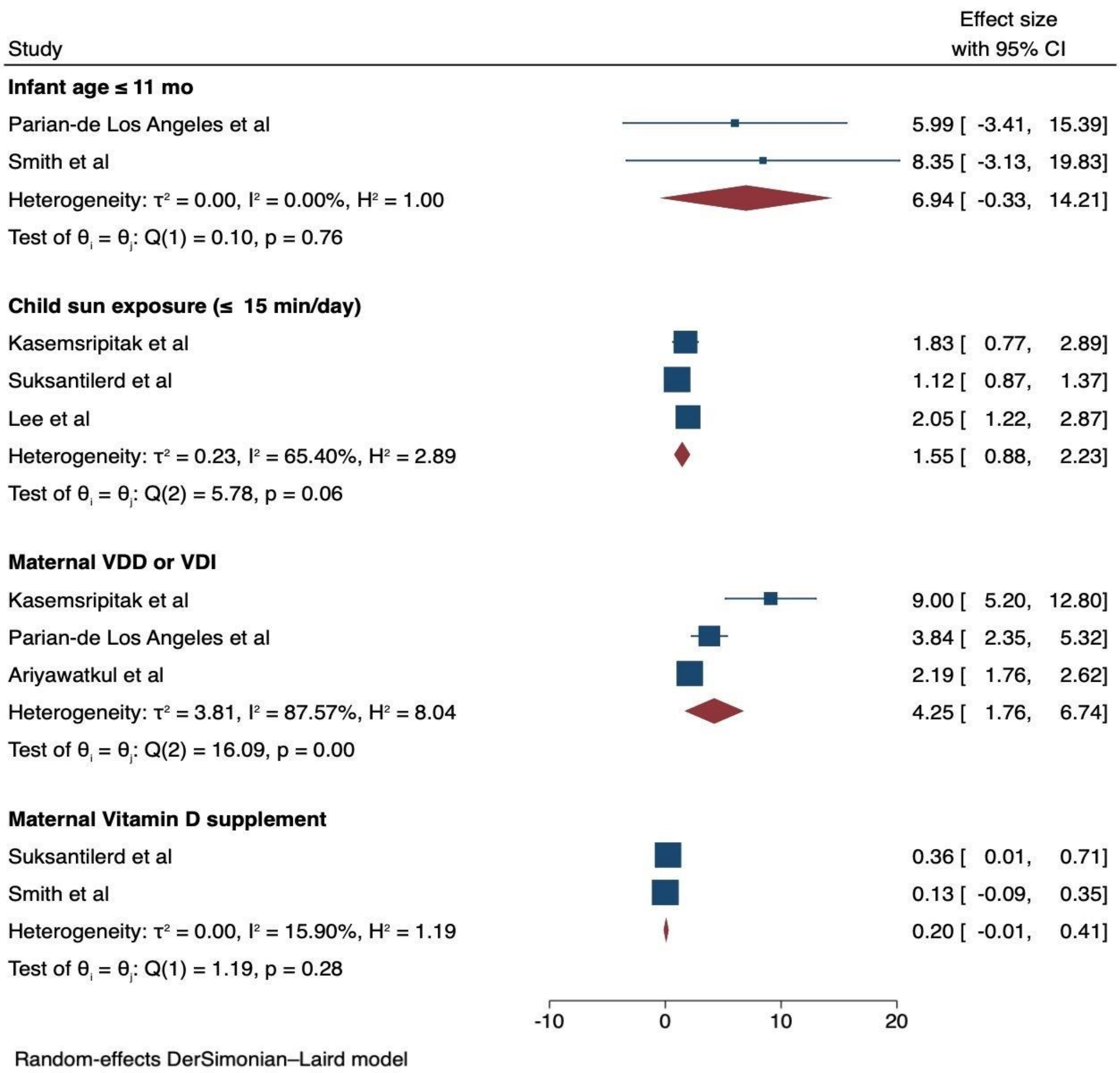

Figure 4. Factors associated with inadequate Vitamin D levels among children under five years in SEA

Meta-regression analysis outcomes presented in Table 2 indicate the prevalence of VDD based on different factors. When measuring Vitamin D using ELISA, the prevalence was 33% (95% CI, 17%-48%; I², 98.76%),

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which was slightly lower compared to non-ELISA methods at 36% (19%-54%; I^2, 97.76%). Moreover, for sample sizes less than 100, the prevalence was 41% (22%-61%; I^2, 70.63%), higher than sample sizes of 100 or more, which showed a prevalence of 33% (22%-45%; I^2, 98.74%). According to the JBI criteria, the prevalence in the low category was 34% (22%-46%; I^2, 98.63%), lower than the moderate category at 35% (19%-51%; I^2, 82.55%). The study also revealed that newborns had the highest prevalence of VDD at 41% (22%-61%; I^2, 70.63%), followed by children under five years old at 34% (21%-46%; I^2, 98.53%), and infants at 33% (2%-64%; I^2, 98.78%). Additionally, there was no evidence of publication bias among the studies included in the analysis, as assessed across various factors (Table 2).

Table 2. Meta-regression analysis results

Criteria	Prevalence (95% CI)	p-value	I^2	Egger's test
Method of measuring Vitamin D				
ELISA	33 (17-48)	<0.001	98.76	0.362
Non-ELISA	36 (19-54)	<0.001	97.76	0.376
Sample size				
<100	41 (22-61)	<0.001	70.63	0.065
≥100	33 (22-45)	<0.001	98.74	0.258
JBI criteria				
Low	34 (22-46)	<0.001	98.63	0.238
Moderate	35 (19-51)	<0.001	82.55	0.055
Age groups				
Newborn (0-28 days)	41 (22-61)	<0.001	70.63	0.065
Infant (28 days-12 months)	33 (2-64)	<0.001	98.78	0.319
Under-five years old (1-5 years)	34 (21-46)	<0.001	98.53	0.411

Discussion

The research emphasizes the critical necessity of tackling VDD and VDI among SEA children under five years, given its substantial health repercussions and prevalent occurrence. Vitamin D plays a pivotal role in maintaining the health of both skeletal and non-skeletal organs, with its inadequacy linked to a diverse array of health issues such as rickets, psoriasis, muscle weakness, and an elevated risk of various conditions including infections, autoimmune diseases, and cancer.[4,5]

The COVID-19 pandemic has further accentuated the significance of Vitamin D inadequacy, as studies have indicated a potential correlation between VDD and heightened mortality rates in severe COVID-19 cases.[1,13,29]

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This underscores the vital role of ensuring optimal Vitamin D levels in Indonesian children not only for their overall well-being but also for potentially mitigating the severity of infectious diseases like COVID-19. Consequently, it is imperative to implement initiatives and targeted programs focusing on increasing Vitamin D sufficiency in SEA children through strategies like supplementation programs, dietary guidance, increased sunlight exposure, and educational campaigns emphasizing the importance of Vitamin D.[1,29] By raising awareness and enacting specific measures, the health outcomes and quality of life for SEA can be significantly enhanced, thereby reducing the burden of preventable health conditions associated with VDD and VDI.[1,13]

In contrast to our findings, South Asia, which includes countries like India, Pakistan, and Bangladesh, has also reported high prevalence rates of VDD. For instance, in India, despite the country's geographical latitude allowing for ample sunshine, studies have reported a prevalence of over 70% of VDD in all age groups, including toddlers. This is particularly concerning in urban areas and among lower socioeconomic strata, where the prevalence of VDD is even higher.[9]

In the United States, approximately 5.9% of the population is affected by severe VDD, characterized by 25(OH)D levels below 30 nmol/L. Furthermore, the prevalence of individuals with levels below 50 nmol/L is reported to be 24%, indicating a substantial portion of the U.S. population, including children, may be vulnerable to VDD.[30]

Programs of vitamin D supplementation, dietary modification, and educational campaigns play a crucial role in effectively addressing VDD and VDI in the pediatric population.[1] Firstly, implementing routine Vitamin D supplementation programs for children at high risk of inadequate Vitamin D levels, such as those with dark skin, limited sunlight exposure, or diets low in Vitamin D content, is essential.[2,5]

Secondly, educating individuals on the importance of consuming Vitamin D-rich foods, such as fatty fish, eggs, fortified dairy products, and other sources of Vitamin D, is vital. Promoting a balanced diet that includes sufficient Vitamin D intake to support children's bone health and immune systems is crucial.[13,15]

Thirdly, conducting educational campaigns on the significance of adequate sunlight exposure for Vitamin D synthesis in the skin is essential. Providing information to the public about the symptoms of VDD and VDI in children under five years, as well as the long-term health consequences of VDD, is imperative.[8,9] Furthermore, collaborating with educational institutions, healthcare services, and governmental bodies to disseminate information on preventing and addressing VDD and VDI at the community level is essential. By integrating and sustaining programs focused on supplementation, dietary adjustments, and educational initiatives, it is anticipated that community awareness will increase, access to Vitamin D sources will improve, and the occurrence of VDD and VDI in children under five years will decrease significantly.[10,11,13]

Our study also found that maternal VDD or VDI is associated with inadequate Vitamin D levels among children under five years in SEA, with a Pooled Odds Ratio of 4.25. Maternal Vitamin D status during pregnancy and breastfeeding directly influences the fetal and neonatal Vitamin D supply, as the fetus relies entirely on maternal stores for its Vitamin D needs.[3,4,6] Insufficient maternal Vitamin D levels can result in suboptimal transfer of this essential nutrient to the child, predisposing them to deficiency or insufficiency. Previous studies in SEA have reported high rates of maternal VDD and VDI due to limited sun exposure, cultural practices, and inadequate dietary intake of Vitamin D-rich foods.[1,2]

The study's strength lies in its pioneering role as the first to perform a meta-analysis evaluating the prevalence of VDD, VDI, and hypovitaminosis in children under five years across SEA. Furthermore, it successfully identified instances of inadequate Vitamin D levels by meticulously analyzing a broad spectrum of studies, each boasting substantial sample sizes and encompassing a wide array of demographic characteristics within the Southeast Asian region.

It is important to note that this meta-analysis has several limitations. The included studies were cross-sectional in nature, which limits the ability to establish causality between vitamin D levels and associated factors. Additionally, there was substantial heterogeneity among the studies, which may be attributed to variations in study populations, methodologies, and geographical locations. Despite these limitations, this study provides valuable insights into the occurrence of inadequate vitamin D levels among children under five years in SEA and underscores the need for further research and public health interventions to address this issue.

The study's findings have significant implications for public health interventions in SEA. Targeted strategies such as supplementation programs, dietary modifications, and educational campaigns are essential to address VDI and VDI effectively and improve the overall health outcomes of children under five years in the region. Future studies in this area could assess the long-term impact of VDD and VDI on children's health outcomes in SEA. Additionally, exploring the effectiveness of different intervention strategies and their impact on reducing the prevalence of VDD and VDI would be valuable for guiding public health policies and practices.

Ethical Considerations: As this study utilized publicly available data and previously published literature, no ethical concerns or violations were involved.

Conflict of Interest: The authors declare no conflict of interest.

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