Vitamin D deficiency in South-East Asian children: a systematic review

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ABSTRACT

Objective To describe the prevalence and determinants of vitamin D deficiency (VDD) among healthy children aged between 0 and 18 years living in South-East Asia (SEA).

Design We systematically searched Ovid MEDLINE and Ovid EMBASE for observational studies assessing VDD among healthy children in the SEA region as the primary or secondary outcome from database inception to 6 April 2021. PubMed was used for e-pubs and publications not indexed in Medline. Publications that included abstracts in English were included. We performed a systematic review to describe the prevalence of VDD in SEA children.

Results Our initial search identified 550 publications with an additional 2 publications from manual screening. Of these, 21 studies from 5 different countries (Thailand, Indonesia, Vietnam, Malaysia and Cambodia) were summarised and included in forest plots. The prevalence of VDD (<50 nmol/L) ranged from 0.9% to 96.4%, with >50% of newborns having VDD, and severe VDD (<30 nmol/L) ranged from 0% to 55.8%. Female sex and urban living were the most common determinants of VDD.

Conclusions VDD among healthy children living in the SEA region is common. Efforts to detect VDD and the implementation of preventive measures, including education on safe sun exposure and oral vitamin D supplementation or food fortification, should be considered for key target groups, including adolescent females and pregnant and lactating women to improve the vitamin D status of newborns.

Protocol registration number This study is registered with PROSPERO (CRD42020181600).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vitamin D deficiency (VDD) is a global public health issue.
⇒ VDD has been recently linked with increased risks for various skeletal and non-skeletal diseases.
⇒ Multicountry data on prevalence of VDD among South-East Asian (SEA) children are lacking.

WHAT THIS STUDY ADDS

⇒ VDD in healthy SEA children varies among countries and age groups but is most common in newborns (52%–90%).
⇒ Detection and preventive measures of VDD, particularly among newborns and adolescent females, should be implemented to reduce the risks arising from VDD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Global consensus on an agreed threshold level for VDD and standardisation of assays to measure vitamin D are urgently needed.
⇒ In subpopulations in SEA where prevalence of VDD (<30 nmol/L) exceeds 20%, public health interventions are crucial to reduce the burden of VDD.
⇒ Interventions, such as safe sunlight exposure, food fortification and supplementation, are encouraged, particularly for high-risk groups, and should be developed through multisectoral programmes.

INTRODUCTION

Vitamin D deficiency (VDD) is a global public health issue. During periods of rapid growth, such as infancy and prepuberty, severe VDD can lead to demineralisation of the skeleton and deformities, a condition known as rickets. In young children, rickets may present as bow legs, delayed eruption of teeth and hypocalcaemic seizures, while in adolescence, it presents as diffuse bone and muscle pain, deformities of lower extremities and generalised muscle weakness despite normal radiological findings. Rickets has recently re-emerged in children possessing darker skin tones, who have low exposure to direct sunlight and poor vitamin D intake.

More recently, the non-osseous complications of VDD have also been highlighted including increases in acute respiratory infections, cardiovascular diseases and all-cause mortality. Children with VDD have been reported to be at risk of developing severe pneumonia, or failing to respond to standard pneumonia therapy, due to weakened immunity and softened ribs which limit effective breathing and clearance of pathogens.

Vitamin D studies in the South-East Asia (SEA) region have highlighted the importance of VDD in the region, but synthetic estimates of regional VDD burden in children are not yet available. Despite abundant sunlight, there are lifestyle and cultural beliefs that contribute to VDD in the region. Strategies to maintain adequate vitamin D levels in
METHODS

Search strategy and eligibility criteria

We systematically searched Ovid MEDLINE and Ovid EMBASE, from database inception to 6 April 2021, using thesaurus and keywords; and PubMed using keywords-only to retrieve e-pubs and items not-indexed in Medline, for studies assessing the prevalence of VDD in children from the SEA region (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, The Philippines, Singapore, Thailand, Timor-Leste and Vietnam). Eligibility criteria included original studies with an abstract available in English, including case-control studies, cross-sectional surveys and cohort studies that reported the prevalence/incidence of VDD among healthy children aged 0–18 years residing in the SEA region. For randomised controlled trials (RCTs) and case-control studies, only vitamin D status of the control/non-intervention groups were included. We excluded case reports/series, letters or reviews. A healthy child was defined as any child without any known significant health problems, or conditions, or medications that would otherwise affect the metabolism of vitamin D.

Keywords and appropriately related Medical Subject Headings terms were used and modified to suit each database (online supplemental file 1). A manual search of each database was conducted to complement the systematic search with similar keywords.

Selecting studies and collecting data

Titles and abstracts were screened independently by two investigators (VO and DADP) using Covidence (https://www.covidence.org/) and all publications that met the eligibility criteria were retrieved in full-text format. Data extraction, that is, author’s name, study design, location, age, vitamin D quantification methods and determinants of VDD were recorded by two investigators (VO and DADP). Any discrepancies were resolved through discussions with a third investigator (ZI). If the required information was not available in the published articles, data were personally requested from the authors.

Risk of bias assessment

Risk of bias was assessed using the bias tool by Hoy et al18 and modified according to the recent published meta-analysis study in African children.19 Each study was assessed, and categorised into low, moderate or high risk.

Outcome measures

VDD was defined as serum (or plasma) 25-hydroxyvitamin D (25(OH)D) concentrations <50 nmol/L (equivalent to <20 ng/dL) with the main consideration being a vitamin D level adequate enough to maintain optimal bone health without contributing to other health outcomes.20 In the subgroup analysis, we reported the prevalence of VDD below <30 nmol/L if >20% of the target population had a level below 30 nmol/L,21 as this was the chosen cut-off for public health intervention. These data were only included when original data from authors were obtainable. Studies that reported serum vitamin D levels with ng/dL were converted to nmol/L, with every 1 ng/dL having an equivalent value of ~2.5 nmol/L.

When needed, recalculations for prevalence of VDD or mean serum vitamin D levels were performed, for example:

- Studies using different cut-off criteria to define VDD, such as 25(OH)D level <30 nmol/L as deficient and 30–49.9 nmol/L as insufficient. In such cases, percentages from both groups were combined to fulfil the current study criteria for VDD <30 nmol/L.
- Prevalence (or mean) that was reported in a subgroup (ie, rural/urban) was calculated by the following formula:

  \[ p = \frac{1}{N} \sum_{i=1}^{N} x_i \]

  \[ p = \text{VDD prevalence reported in the study.} \]

  \[ x = \text{mean of 25(OH)D level from all participants in the study.} \]

  \[ n = \text{the number of participants in the subgroup.} \]

  \[ N = \text{total participants tested for vitamin D level.} \]

Data analysis

The data analysis was performed using a STATA, V.16 (StataCorp, Texas, USA). When multiple publications used a similar study dataset (overlapping of samples) with a single vitamin D measurement performed in participants, only the publication with the most complete dataset was included. We initially attempted to perform a meta-analysis with the random-effects models; plotting the pooled prevalence of VDD in forest plots, and showing the estimated size effect of prevalence or baseline prevalence (for prospective studies) of VDD with a 95% CI. However, due to high between-study heterogeneity, with I² values >75%, prevalence or incidence ranges were presented instead. Substantial between-study heterogeneities were also present during meta-analysis for VDD prevalence by age group, gender, countries and residency. Publication bias were assessed based on visual or analytical detection of asymmetry in a funnel plot. We used the Egger’s test for bias with p<0.05 considered as significant publication bias.
Table 1  Vitamin D deficiency (VDD) among children in SEA region (n=30)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of study</th>
<th>Design</th>
<th>N§</th>
<th>Location</th>
<th>Age (years)</th>
<th>Quantification methods</th>
<th>Prevalence/ Cumulative incidence VDD§ (50 nmol/L) (%)</th>
<th>Prevalence/Cumulative incidence VDD§ (30 nmol/L) (%)</th>
<th>Mean of serum 25(OH)D (nmol/L)</th>
<th>Risk factors associated with VDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febriani A et al^46</td>
<td>2019</td>
<td>Case-control</td>
<td>40</td>
<td>Indonesia</td>
<td>0.5–5</td>
<td>ELISA</td>
<td>n/a</td>
<td>n/a</td>
<td>49.77 (control)</td>
<td></td>
</tr>
<tr>
<td>Invinda and Andardi^47</td>
<td>2017–2019</td>
<td>Cross-sectional</td>
<td>30</td>
<td>Indonesia</td>
<td>Newborn</td>
<td>LC-MS/MS</td>
<td>52.4</td>
<td>44</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Chuc et al^14</td>
<td>2017</td>
<td>Cross-sectional</td>
<td>327</td>
<td>Vietnam</td>
<td>1–3</td>
<td>ELISA</td>
<td>47.7</td>
<td>0</td>
<td>81.3</td>
<td>Older age</td>
</tr>
<tr>
<td>Ariyawanul and Lersbauini^48</td>
<td>2016–2017</td>
<td>Cross-sectional</td>
<td>94</td>
<td>Thailand</td>
<td>Newborn</td>
<td>Chemiluminescent microparticle immunoassay</td>
<td>89.3</td>
<td>20.2</td>
<td>37.1</td>
<td>Low maternal vitamin D level</td>
</tr>
<tr>
<td>Oktaria et al^11††</td>
<td>2015–2017</td>
<td>Cohort</td>
<td>344(at birth)</td>
<td>Indonesia</td>
<td>Newborn and 6 months</td>
<td>LC-MS/MS</td>
<td>90 (at birth) 13 (6 months)</td>
<td>55.8 (at birth) 4.3 (6 months)</td>
<td>30 (at birth) 77 (6 months)</td>
<td>Lower cumulative skin-sun exposure score, severe VDD at birth and exclusive breast feeding</td>
</tr>
<tr>
<td>Loeb et al^49</td>
<td>2013–2016</td>
<td>RCT (baseline)</td>
<td>1095</td>
<td>Vietnam</td>
<td>3–17</td>
<td>Diasorin</td>
<td>16.8</td>
<td>n/a</td>
<td>65.5</td>
<td>Female sex, Indian ethnicity, urban living and obesity (wider waist circumference)</td>
</tr>
<tr>
<td>Yani et al^12</td>
<td>2014–2015</td>
<td>Cross-sectional</td>
<td>100</td>
<td>Indonesia</td>
<td>&lt;5</td>
<td>ELISA</td>
<td>21</td>
<td>1.78</td>
<td>67.5</td>
<td>Female sex</td>
</tr>
<tr>
<td>Quah et al^10†</td>
<td>2014</td>
<td>Cohort</td>
<td>1016</td>
<td>Malaysia</td>
<td>15</td>
<td>Automated direct competitive chemiluminescent immunoassay</td>
<td>33</td>
<td>2.6</td>
<td>59.4</td>
<td>Female sex, Malay and Indian ethnicity, and wearing long sleeves</td>
</tr>
<tr>
<td>Smith et al^11†</td>
<td>2014</td>
<td>Cross-sectional</td>
<td>781</td>
<td>Cambodia</td>
<td>0.5–5</td>
<td>ELISA</td>
<td>13.4</td>
<td>n/a</td>
<td>91.1</td>
<td>Urban living and older age</td>
</tr>
<tr>
<td>Diana et al^13††</td>
<td>2013–2014</td>
<td>Cohort</td>
<td>116</td>
<td>Indonesia</td>
<td>6 and 12 months</td>
<td>Isotope-dilution LC tandem MS</td>
<td>0.9 (6 months) 4.3 (12 months)</td>
<td>0 (6 months) 12 (months)</td>
<td>89.71 (6 months) 83.21 (12 months)</td>
<td>Female sex, overweight/obese</td>
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<tr>
<td>Al-Sadat et al^46†</td>
<td>2012</td>
<td>Cross-sectional</td>
<td>1361</td>
<td>Malaysia</td>
<td>12–13</td>
<td>ECUA</td>
<td>92.6</td>
<td>n/a</td>
<td>29.2</td>
<td>Female sex, Indian ethnicity, urban living and obesity (wider waist circumference)</td>
</tr>
<tr>
<td>Rahmadhani et al^46</td>
<td>2012</td>
<td>Cross-sectional</td>
<td>678</td>
<td>Malaysia</td>
<td>13</td>
<td>ECUA</td>
<td>70</td>
<td>n/a</td>
<td>42.3</td>
<td>Female sex, high BMI</td>
</tr>
<tr>
<td>Pulungan et al^14†</td>
<td>2012</td>
<td>Cross-sectional</td>
<td>120</td>
<td>Indonesia</td>
<td>7–12</td>
<td>Diasonin</td>
<td>39.2</td>
<td>1.6</td>
<td>54.6</td>
<td>Less time spent outdoors</td>
</tr>
<tr>
<td>Nguyen et al^16†‡</td>
<td>2012–2016</td>
<td>Cross-sectional</td>
<td>794</td>
<td>Vietnam</td>
<td>6–14</td>
<td>HPLC/MS</td>
<td>30.6</td>
<td>n/a</td>
<td>67.39</td>
<td>Female sex, overweight/obese</td>
</tr>
<tr>
<td>Poh et al^17†</td>
<td>2010–2011</td>
<td>Cross-sectional</td>
<td>2016</td>
<td>Indonesia, Malaysia, Thailand, Vietnam</td>
<td>&gt;2</td>
<td>Diasonin (Malaysia, Thailand), HPLC (Vietnam), immunoactivity detection system (Indonesia)</td>
<td>42.14</td>
<td>n/a</td>
<td>56.1</td>
<td>Female sex, older age, urban living, religion, higher BMI and region</td>
</tr>
<tr>
<td>Senaprom et al^20</td>
<td>2011</td>
<td>Cross-sectional</td>
<td>477</td>
<td>Thailand</td>
<td>3–13</td>
<td>Diasorin</td>
<td>31.9</td>
<td>n/a</td>
<td>60.1</td>
<td>Female sex, Muslim religion, obesity, sun exposure &lt;30 min/day in weekdays (end)</td>
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<td>Emawati and Budiman et al^46</td>
<td>2011</td>
<td>Cross-sectional</td>
<td>349</td>
<td>Indonesia</td>
<td>2–13</td>
<td>ELIA</td>
<td>45.1</td>
<td>n/a</td>
<td>52.6</td>
<td>Female sex, older age, less time spent outdoors</td>
</tr>
<tr>
<td>Reesukumal et al^28†</td>
<td>2011–2012</td>
<td>Cross-sectional</td>
<td>159</td>
<td>Thailand</td>
<td>6–12</td>
<td>ECUA</td>
<td>19.5</td>
<td>0.6</td>
<td>64</td>
<td>Higher BMI, higher body fat percentage, higher parathyroid hormone</td>
</tr>
<tr>
<td>Sandaja et al^33</td>
<td>2011</td>
<td>Cross-sectional</td>
<td>276</td>
<td>Indonesia</td>
<td>2–12</td>
<td>Not specified</td>
<td>43.6</td>
<td>n/a</td>
<td>52.5</td>
<td>Female sex</td>
</tr>
<tr>
<td>Rojroongnasinkul et al^38</td>
<td>2011</td>
<td>Cross-sectional</td>
<td>628</td>
<td>Thailand</td>
<td>3–13</td>
<td>Diasonin</td>
<td>33.5</td>
<td>n/a</td>
<td>n/a</td>
<td>Urban living</td>
</tr>
<tr>
<td>Le Nguyen et al^14†‡</td>
<td>2011</td>
<td>Cross-sectional</td>
<td>574</td>
<td>Vietnam</td>
<td>6–12</td>
<td>HPLC</td>
<td>50.4</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>Nguyen Bao et al^30</td>
<td>2010–2011</td>
<td>Cross-sectional</td>
<td>384</td>
<td>Indonesia, Malaysia, Thailand, Vietnam</td>
<td>1–12</td>
<td>Diasonin (Malaysia, Thailand), HPLC (Vietnam), immunoactivity detection system (Indonesia)</td>
<td>45.8</td>
<td>17.5</td>
<td>55.7</td>
<td>Higher dairy daily consumption</td>
</tr>
<tr>
<td>Poh et al^37†</td>
<td>2010–2011</td>
<td>Cross-sectional</td>
<td>2936</td>
<td>Malaysia</td>
<td>4–12</td>
<td>Diasonin</td>
<td>47.5</td>
<td>n/a</td>
<td>54.7</td>
<td>Female sex, urban living, older age</td>
</tr>
<tr>
<td>Laillou et al^15†</td>
<td>2010</td>
<td>Cross-sectional</td>
<td>485</td>
<td>Vietnam</td>
<td>&lt;5</td>
<td>HPLC</td>
<td>57.3</td>
<td>20.6</td>
<td>43.4</td>
<td>n/a</td>
</tr>
<tr>
<td>Poomthavon et al^31†</td>
<td>2008–2009</td>
<td>Cross-sectional</td>
<td>179</td>
<td>Thailand</td>
<td>&lt;18</td>
<td>HPLC</td>
<td>11 (obese) 10 (non-obese) 0 (obese and non-obese) 70.4 (obese) 68.9 (non-obese)</td>
<td>60.4</td>
<td>Older age, lower weight circumference</td>
<td></td>
</tr>
</tbody>
</table>

Continued
### Table 1 Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of study</th>
<th>Design</th>
<th>N ($)</th>
<th>Location</th>
<th>Age (years)</th>
<th>Quantification methods</th>
<th>Prevalence/Cumulative incidence VDD (&lt; 50 nmol/L) (%)</th>
<th>Prevalence/Cumulative incidence VDD (&lt; 30 nmol/L) (%)</th>
<th>Mean of serum 25(OH)D (nmol/L)</th>
<th>Risk factors associated with VDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khor et al.¶</td>
<td>2008</td>
<td>Cross-sectional</td>
<td>402</td>
<td>Malaysia</td>
<td>7–12</td>
<td>Diasorin</td>
<td>72.4</td>
<td>n/a</td>
<td>n/a</td>
<td>Higher BMI in boys, female sex</td>
</tr>
<tr>
<td>Houghton et al.¶</td>
<td>2002–2003</td>
<td>Cross-sectional</td>
<td>529</td>
<td>Thailand</td>
<td>6–14</td>
<td>LC-MS/MS</td>
<td>4</td>
<td>n/a</td>
<td>72.71</td>
<td>Older female</td>
</tr>
<tr>
<td>Tanggam et al.</td>
<td>n/a</td>
<td>Cross-sectional</td>
<td>28</td>
<td>Thailand</td>
<td>4.8–17.2</td>
<td>Chemiluminescence assay</td>
<td>96.4</td>
<td>n/a</td>
<td>66.5**</td>
<td>n/a</td>
</tr>
<tr>
<td>Soesanti et al.¶</td>
<td>n/a</td>
<td>Cross-sectional</td>
<td>120</td>
<td>Indonesia</td>
<td>7–12</td>
<td>Not specified</td>
<td>39.2</td>
<td>n/a</td>
<td>n/a</td>
<td>Female sex</td>
</tr>
<tr>
<td>Hussain and Elnajeh¶</td>
<td>n/a</td>
<td>Cross-sectional</td>
<td>361</td>
<td>Malaysia</td>
<td>13–18</td>
<td>CUA</td>
<td>60.1</td>
<td>16.3</td>
<td>49</td>
<td>Female sex, Malay ethnicity</td>
</tr>
</tbody>
</table>

VDD was defined when serum 25(OH)D <50 nmol/L.

*Data from MyHeARTs, both studies were included because eventhough data were derived from the same study, the time point was different.

†Geometric mean.

‡Data from SEANUTS. Poh et al. was chosen as SEANUTS representative, as it provides most of the countries prevalence and meet our criteria to define VDD.

‡Data from IPADS, both papers present the same result, Oktaria et al. was chosen as it is the first one published.

BMI, body mass index; ECLIA, electrochemiluminescence immunoassay; EIA, enzyme immunoassay; HPLC, high performance liquid chromatograph; IPADS, The Indonesian Pneumonia and vitamin D Study; LC-MS/MS, liquid chromatography-mass spectrometry; MyHeARTs, Malaysian Health and Adolescents Longitudinal Research Study; n/a, not available; 25(OH)D, 25-hydroxyvitamin D.

### RESULTS

This study is registered with PROSPERO (CRD420181600).

The protocol was approved by the Ethics Committee of the University of Malaya Medical Centre. All participants were enrolled after written informed consent was obtained. The study was conducted according to the Declaration of Helsinki. This study is registered with PROSPERO (CRD42020181600).

Twenty-one included studies were further summarized and plotted into forest plots for study selection as provided in Figure 1. The proportion of studies was assessed as having a moderate risk of bias.

[Continued]
Original research

Study characteristics

The majority of studies (24/30; 80%) were cross-sectional in design except for four cohort studies, and one reported baseline data from an RCT, with a wide range of vitamin D assays used (table 1). Eight of 30 studies included were part of the South-East Asian Nutrition Survey (SEANUTS), a comprehensive survey, studying growth, nutrition and food intake, conducted in Indonesia, Malaysia, Thailand and Vietnam. The age range among studies was diverse, from newborns to 18 years of age (table 2).

Study prevalence of VDD

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence of VDD with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khor et al, 2011</td>
<td>72.40 [68.03, 76.77]</td>
</tr>
<tr>
<td>Poomthavorn et al, 2012</td>
<td>10.30 [ 8.5, 12.3]</td>
</tr>
<tr>
<td>Laillou et al, 2013</td>
<td>57.30 [52.90, 61.70]</td>
</tr>
<tr>
<td>Soesanti et al, 2013</td>
<td>39.20 [30.47, 47.93]</td>
</tr>
<tr>
<td>Houghton et al, 2014</td>
<td>4.00 [ 2.33, 5.67]</td>
</tr>
<tr>
<td>Reesukumal et al, 2015</td>
<td>19.50 [13.34, 25.66]</td>
</tr>
<tr>
<td>Al-Sadat et al, 2016</td>
<td>92.60 [91.21, 93.99]</td>
</tr>
<tr>
<td>Poh BK et al, 2016</td>
<td>42.10 [39.94, 44.26]</td>
</tr>
<tr>
<td>Smith et al, 2016</td>
<td>13.40 [ 9.01, 15.79]</td>
</tr>
<tr>
<td>Rahmadhani et al, 2017</td>
<td>70.00 [66.55, 73.45]</td>
</tr>
<tr>
<td>Loeb et al, 2018</td>
<td>16.80 [14.59, 19.01]</td>
</tr>
<tr>
<td>Arisayawati et al, 2018</td>
<td>89.30 [83.05, 95.55]</td>
</tr>
<tr>
<td>Quah et al, 2016</td>
<td>33.80 [30.89, 36.71]</td>
</tr>
<tr>
<td>Tanggam et al, 2018</td>
<td>96.40 [95.1, 97.5]</td>
</tr>
<tr>
<td>Chuc et al, 2019</td>
<td>2.10 [ 0.55, 3.65]</td>
</tr>
<tr>
<td>Diana et al, 2019a</td>
<td>1.10 [ 0.6, 2.0]</td>
</tr>
<tr>
<td>Diana et al, 2019b</td>
<td>4.80 [ 1.41, 8.19]</td>
</tr>
<tr>
<td>Oktaria et al, 2020a</td>
<td>90.00 [86.83, 93.17]</td>
</tr>
<tr>
<td>Oktaria et al, 2020b</td>
<td>13.00 [ 8.87, 17.13]</td>
</tr>
<tr>
<td>Irwinda R, 2020</td>
<td>52.40 [34.53, 70.27]</td>
</tr>
<tr>
<td>Hussain et al, 2020</td>
<td>60.10 [55.05, 65.15]</td>
</tr>
<tr>
<td>Pulungan et al, 2021</td>
<td>39.20 [30.47, 47.93]</td>
</tr>
</tbody>
</table>

Figure 2 Forest plot: vitamin D deficiency (VDD) in South-East Asia region (n=21 studies) using a cut-off <50 nmol/L. Cohort studies with multiple vitamin D measurements were presented for each measurement (studies by Diana et al and Oktaria et al).

Study prevalence of VDD

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence of VDD with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arisayawati et al, 2018</td>
<td>89.30 [83.05, 95.55]</td>
</tr>
<tr>
<td>Oktaria et al, 2020a</td>
<td>90.00 [86.83, 93.17]</td>
</tr>
<tr>
<td>Irwinda R, 2020</td>
<td>52.40 [34.53, 70.27]</td>
</tr>
<tr>
<td>Smith et al, 2016</td>
<td>7.30 [ 5.8, 9.1]</td>
</tr>
<tr>
<td>Diana et al, 2019a</td>
<td>1.10 [ 0.6, 1.9]</td>
</tr>
<tr>
<td>Oktaria et al, 2020b</td>
<td>13.00 [ 8.87, 17.13]</td>
</tr>
</tbody>
</table>

Figure 3 Forest plot: vitamin D deficiency (VDD) in South-East Asia region (n=9 studies) using a cut-off <30 nmol/L. Cohort studies with multiple vitamin D measurements were presented for each measurement (studies by Oktaria et al).

The prevalence of VDD in SEA children

The prevalence of VDD ranged from 0.9% to 96.4% based on a cut-off of <50 nmol/L (figure 2), and from 0% to 55.8% based on a cut-off of <30 nmol/L (figure 3). Pooled results were not presented due to significant between-study heterogeneity ($I^2=99.9\%$, $p<0.001$).

Fourteen studies required prevalence recalculation, with nine studies reporting vitamin D in subgroups (ie, by gender, urban/rural or by country), and five studies employed different cut-offs for VDD (<37.5 nmol/L, $p<0.001$). Ten of 20 studies required mean re-calculation; with three studies reporting vitamin D levels in ng/dL units and seven studies reporting vitamin D level in subgroups. For each forest plot, only one SEANUTS study was included, as relevant.

The prevalence of VDD varied widely within age groups (figure 4), but was consistently high in newborns, with at least one in every two newborns having VDD. Due to limited data from the original studies, we were unable to separate adolescents (aged between 10 and 19 years) from children ≥5 years. However, four studies exclusively reported the prevalence of VDD in adolescents (online supplement file 3). The prevalence of VDD by country (online supplement file 4), sex (figure 5) or residence (online supplement file 5).

Figure 4 Subgroup analysis: vitamin D deficiency (VDD) in South-East Asia region by age group (n=20 studies). Cohort studies with multiple vitamin D measurements were presented for each measurement (studies by Diana et al and Oktaria et al), the prevalence of VDD in the study by Smith et al was reported by age group. The test of group differences for VDD by age group was $Q_(3)=49.57$, $p<0.001$.

Fourteen studies required prevalence recalculation, with nine studies reporting vitamin D in subgroups (ie, by gender, urban/rural or by country), and five studies employed different cut-offs for VDD (<37.5 nmol/L, table 1). Ten of 20 studies required mean re-calculation; with three studies reporting vitamin D levels in ng/dL units and seven studies reporting vitamin D level in subgroups. For each forest plot, only one SEANUTS study was included, as relevant.

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file 5) was hard to interpret due to a large variation among reported prevalence estimates. Four publications from three cohort studies reported multiple measurements of serum vitamin D in their participants at different time. The determinants of VDD

The most common reported risk factors for VDD in the region were female sex, living in urban areas, female teenagers starting to dress more conservatively for religious purposes, exposure to sunlight <30 min/day, and obesity (table 1). Subgroup analysis by gender and residence are presented in figure 5 and online supplemental file 5, respectively.

Publication bias of vitamin D deficiency

The funnel plot was asymmetric (online supplemental file 6) due to high between-study heterogeneity and various reported effect sizes. Egger’s test showed a p value of 0.96 indicating no statistical evidence of publication bias.

DISCUSSION

VDD is very common in SEA children, with female sex and those living in urban areas the most common reported risk factors, consistent with recent findings from an African meta-analysis. Further, there are cultural practices that are strongly affected by religion, and also society’s perception of fair skin as a standard for female beauty in the SEA region. The practice of sunlight avoidance (ie, staying in the shade or under an umbrella, wearing sun protection) or the use of covered-up garments such as veils for religious purposes, is evident among SEA females. In addition to sun-avoidance, air pollution in urban regions has been reported to be associated with VDD in children due to attenuation of UVB light reaching the earth’s surface which reduces cutaneous photosynthesis of vitamin D.

Particular attention is needed to support adequate transplacental transfer of vitamin D during the antenatal period as interventions during pregnancy are an important determinant of neonatal vitamin D status. Mothers are the only source of fetal vitamin D during intrauterine life with maternal and cord blood vitamin D levels highly correlated. Nine out of 10 newborns in Indonesia and Thailand were reported to have VDD and as expected, VDD is also common in pregnant women in Thailand and Indonesia. There is a concern that prenatal transfer of vitamin D might be impeded by maternal sunlight-exposure behaviour. It has been reported that a maternal vitamin D status ≥50 nmol/L among white skinned women living in northern latitudes protects newborn infants from very low vitamin D status at birth.

Given that the skin cancer rate in SEA is lower than Western population, cutaneous vitamin D photoconversion should be optimised as the primary source of vitamin D. A combination of larger total body surface area exposed to the sun and higher UVB intensity was correlated to higher vitamin D levels in pregnant women and infants in Indonesia. Pregnant women are recommended to get sunlight exposure for half an hour/day between 10:00 and 13:00 hours to improve the vitamin D status in their newborns (approximately 1 hour for females with covered-up garments). Infant’s skin, however, is more sensitive in nature and it is generally advised that infants, especially those with light skin, should not be exposed to direct sunlight.
In many high-income countries, vitamin D supplementation for infants, pregnant or nursing mothers are preferred over vitamin D generated by direct sunlight exposure. Dietary intake of foods that are naturally rich in vitamin D, or food fortification with vitamin D should be encouraged. Many children in the SEA consume <1% of the recommended daily vitamin D intake. The availability of natural vitamin D-rich foods in the region is limited with low and infrequent consumption of meat and dairy products. Foods with the confirmed rickets in the overall preventive public health actions. Vitamin D can be added to dairy products, edible oils, flour or co-fortified with vitamin A, but these efforts should be conducted through multisectoral programming with strong coordination between national government and private sectors.

Although the VDD cut-off threshold of <30 nmol/L is used as a signal for public health action, limited published studies have used this threshold when reporting VDD. There is also a lack of global consensus on the agreed thresholds level for VDD, insufficiency and adequacy due to complexity around precision and standardisation of various laboratory methods and assays to measure 25(OH)D. Such consensus would aid future review and meta-analyses on the burden of VDD.

Although efforts have been made for a thorough search and identification of published studies in SEA regions, some countries (eg, Laos, Brunei Darussalam and Timor Leste) were lacking relevant studies. The large heterogeneity between studies may be due to the wide variability of methods for vitamin D quantification or sociodemographic factors.

CONCLUSION

VDD is common in SEA children, with newborns and female adolescents most at risk. Improving vitamin D status might be delivered by ‘safe’ sunlight exposure practices, increasing vitamin D content in the diet or oral supplementation. The practice of vitamin D supplementation to improve vitamin D status of newborns should be started during pregnancy or postnatally during the period of breast feeding. With limited natural vitamin D-rich food sources in the SEA populations, food fortification or supplementation may need to be considered.

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