Association of vitamin D deficiency with cardiovascular disease risk in children: implications for the Asia Pacific Region

Indah K Murni MD, PhD1, Dian C Sulistyoningrum MSc2, Vicka Oktaria MD, MPH1

1Department of Pediatrics, DR Sardjito Hospital/Faculty of Medicine Universitas Gadjah Mada, Yogyakarta, Indonesia
2Department of Nutrition and Health, Faculty of Medicine Universitas Gadjah Mada, Yogyakarta, Indonesia

Background and Objectives: Vitamin D deficiency significantly affects cardiovascular disease risk. Cardiovascular disease is epidemic in nature. Because the prevalence of cardiovascular disease has been increasing in children, it has been changing from an adulthood disease to a childhood disease. Therefore, formulating an effective prevention strategy against cardiovascular disease development in children is crucial. Methods and Study Design: From PubMed, we identified and reviewed studies evaluating the association of vitamin D deficiency with cardiovascular disease risk in children. Results: The mechanism through which vitamin D protects against cardiovascular disease has yet to be fully elucidated. Vitamin D deficiency may be associated with various risk factors for cardiovascular disease that are already manifested in childhood, including obesity, hypertension, dyslipidemia, insulin resistance, and metabolic syndrome. Vitamin D deficiency has been associated with cardiovascular disease because it promotes vascular stiffness and calcification, leading to atherosclerosis. However, studies investigating the effectiveness of vitamin D in preventing cardiovascular disease risk by using an ideal study design are scant. Conclusions: Vitamin D deficiency in children may increase cardiovascular disease risk, which tends to manifest in childhood. Because data on the association of vitamin D deficiency with cardiovascular disease risk among children are limited and inconclusive, additional studies are required to investigate this association in children in general and in a setting with naturally abundant sun exposure.

Key Words: vitamin D deficiency, sunlight exposure, cardiovascular disease risk, children

INTRODUCTION
Cardiovascular disease has become a major public health problem worldwide and has caused considerable morbidity and mortality. The development of atherosclerosis, hypertension, and metabolic syndrome contributes to cardiovascular disease. Cardiovascular disease is epidemic in nature. Moreover, because the prevalence of cardiovascular disease has been increasing in children, it has been changing from an adulthood disease to a childhood disease. Therefore, identifying risk factors for cardiovascular disease in children has been emphasised.

Vitamin D has been associated with cardiovascular disease. However, the mechanism through which vitamin D protects against cardiovascular disease has yet to be fully elucidated. Vitamin D deficiency might be common in children, even in those living in countries with abundant sun exposure, because of increased sedentary activities. Therefore, collating evidence from studies evaluating whether vitamin D deficiency is associated with cardiovascular disease risk in children is crucial. Herein, we review the literature on the association between vitamin D status and cardiovascular disease risk in children. Furthermore, we highlight the evidence gaps and areas that should be focused on in future research.

METHODS
Search strategy
We systematically searched Pubmed for studies investigating the association between vitamin D deficiency and cardiovascular disease risk in children (aged <18 years) by using the following keywords: ‘vitamin D’ OR ‘vitamin D deficiency’ OR ‘vitamin D’ (MeSH) OR ‘vitamin D deficiency’ (MeSH) AND ‘cardiovascular risk’ (ti) OR ‘hypertension’ (ti) OR ‘cardiovascular disease’ (ti) OR ‘dyslipidemia’ (ti) OR ‘diabetes’ (ti) OR ‘atherosclerosis’ (ti).

In the search, a word followed by an asterisk (*) denotes searching for all terms that begin with this word. The search was limited to articles published in English but not to particular publication dates. Relevant articles included in the bibliographic references of identified studies were also sought. All studies that evaluated the association between vitamin D status and cardiovascular dis-
Vitamin D and cardiovascular disease risk in children were included. Intervention trials with the following designs were included: randomised clinical trials (RCTs) and quasi-experimental or sequential trials. Furthermore, observational studies evaluating the association of vitamin D deficiency with cardiovascular disease risk were included if there was limited evidence in children in interventional study designs. Studies with duplicated data were excluded.

Data extraction and outcome measures
After reading the full texts, we assessed the eligibility of all studies identified using the aforementioned inclusion criteria. By using a standardised data-extraction form, we summarised study details including authors, year of publication, country or countries where the study was performed, time frame of the study, patient population (infant or early childhood, children, or adolescents), study design (cross sectional, case control, cohort, RCT, or quasi-experimental), measured outcomes, and results.

Vitamin D deficiency status was defined as a serum 25-hydroxyvitamin D [25(OH)D] level of <50 nmol/L, and adequate vitamin D status was defined as a serum 25(OH)D level of ≥50 nmol/L. A data item in nanomoles per litre (nmol/L) was converted into nanograms per millilitre (ng/mL) by dividing it by 2.496. Outcomes were risk factors for cardiovascular diseases including obesity, hypertension, dyslipidaemia, insulin resistance, metabolic syndrome, and atherosclerosis. Hypertension was defined if the blood pressure was above the 95th percentile in at least a single measurement, which was adjusted for sex, age, and height. Dyslipidaemia was defined if there was an abnormal fasting lipid panel including high low-density lipoprotein (LDL) cholesterol (≥110 mg/dL), elevated triglycerides (≥100 mg/dL), and low high-density lipoprotein (HDL) cholesterol (≤45 mg/dL). Insulin resistance was calculated using the formula for the homeostasis model assessment of insulin resistance (HOMA-IR). Metabolic syndrome was defined as having three or more of the following signs: (1) waist circumference above the 90th percentile for their age and sex; (2) triglyceride levels of ≥110 mg/dL; (3) HDL cholesterol levels of ≤40 mg/dL; (4) either systolic or diastolic blood pressure above the 90th percentile for their age, sex, and height; and (5) fasting glucose levels of ≥100 mg/dL. Atherosclerosis was measured using the carotid artery intima-media thickness (CIMT).

RESULTS
Of the identified 690 articles, 25 met the inclusion criteria (Figure 1). Of these 25 eligible studies, 2 were RCTs, 2 were nonrandomised interventional before–after studies, 7 were cohort studies, 1 was a case–control study, and 13 were cross-sectional studies. Furthermore, eight studies were conducted in European countries, seven in the United States, one in North America, one in Argentina, one in Turkey, and one in Iran. Only six studies have been conducted in Asia Pacific regions including one in Australia, one in India, and four in Korea. The results of this systematic review revealed that the association of vitamin D deficiency in children with cardiovascular disease risk remains inconclusive (Table 1). Furthermore, most of the studies have been conducted on adolescents. No study has evaluated the association of vitamin D deficiency with cardiovascular risk in early childhood.

Figure 1. Search strategy
<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Study design</th>
<th>Study population</th>
<th>Outcome</th>
<th>Associations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodam et al, 2015, Italy&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Cross sectional</td>
<td>6 – 18 years</td>
<td>575</td>
<td>Metabolic syndrome components</td>
<td>25(OH)D level was inversely associated with total cholesterol, LDL cholesterol and triglycerides</td>
</tr>
<tr>
<td>Lee et al, 2015, Korea&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Cross sectional</td>
<td>10 - 18 years</td>
<td>2880</td>
<td>Insulin resistance, metabolic syndrome</td>
<td>Low 25(OH)D level was associated with increased insulin resistance and metabolic syndrome</td>
</tr>
<tr>
<td>Kao et al, 2015, Australia&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Cross sectional</td>
<td>3 – 18 years</td>
<td>229</td>
<td>Metabolic syndrome component</td>
<td>Lower 25(OH)D was associated with greater adiposity and higher blood pressure</td>
</tr>
<tr>
<td>Singh et al, 2015, USA&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Cross sectional</td>
<td>9 – 11 years</td>
<td>25</td>
<td>hsCRP and CIMT</td>
<td>25(OH) D levels did not associated with hsCRP or CIMT</td>
</tr>
<tr>
<td>Kwon et al, 2015, Korea&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Cross sectional</td>
<td>7 – 9 years</td>
<td>205</td>
<td>Metabolic syndrome component</td>
<td>25(OH)D levels were negatively associated with triacylglycerol levels. 25(OH)D deficiency was associated with metabolic syndrome via the derangement of triacylglycerol</td>
</tr>
<tr>
<td>Hirschler et al, 2015, Argentina&lt;sup&gt;38&lt;/sup&gt;</td>
<td>A controlled before and after study</td>
<td>8 – 12.5 years in San Antonio de los Cobres (SAC) and 7 – 10.5 years in Buenos Aires (BA)</td>
<td>321 (192 SAC and 129 BA)</td>
<td>Triglyceride/HDL cholesterol ratio</td>
<td>Indigenous Argentinean children have a higher risk for dyslipidemia in comparison with BA children, even after vitamin D treatment</td>
</tr>
<tr>
<td>Shah et al, 2015, USA&lt;sup&gt;37&lt;/sup&gt;</td>
<td>RCT</td>
<td>11 – &lt;18 years</td>
<td>40 (20 vitamin D and 20 placebo) Only 31 (78%) completed the study</td>
<td>Inflammatory cytokines, adiponectin, hs-CRP, lipids, hemoglobin A1C, and BMI</td>
<td>25(OH)D were not associated with inflammatory and cardiovascular markers</td>
</tr>
</tbody>
</table>

25(OH)D: 25-hydroxyvitamin D; CIMT: carotid-intima media thickness; CRP: C-reactive protein; hsCRP: high sensitivity C-reactive protein; HDL: high density lipoproteins; LDL: low density lipoproteins; BMI: body mass index; MetS: metabolic syndrome; HOMA – IR: homeostatic model assessment – insulin resistance; FMD: flow mediated dilatation; PTH: parathyroid hormone; CVD: cardiovascular disease.
### Table 1. Studies assessing the association of serum-25-OH-D concentration with occurrence of cardiovascular events in children (cont.)

<table>
<thead>
<tr>
<th>Author, year country</th>
<th>Study design</th>
<th>Study population</th>
<th>Outcome</th>
<th>Associations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banzato et al, 2014, Italy21</td>
<td>Cross sectional</td>
<td>7 – 16 years</td>
<td>Hypertension</td>
<td>Low 25(OH)D in obese children were associated with a higher BP burden, especially at night</td>
<td>Factors associated with vitamin D status were not adjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32</td>
<td>Obese Caucasian children admitted to Department of Pediatrics at a tertiary teaching hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atabek et al, 2014, Turkey20</td>
<td>Cross sectional</td>
<td>8 – 16 years</td>
<td>Insulin resistance, metabolic syndrome components, and CIMT</td>
<td>Low 25(OH)D were associated with increased CIMT and metabolic syndrome</td>
<td>Factors associated with both vitamin D status and outcomes were not adjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>247</td>
<td>Obese children admitted to outpatient clinics at a tertiary teaching hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robinson et al, 2014, North America22</td>
<td>Cross sectional</td>
<td>14 – 16 years</td>
<td>hsCRP and CIMT</td>
<td>25(OH)D deficiency was associated increased hsCRP, but not CIMT</td>
<td>Confounders both associated with vitamin D status and outcomes (race, season, latitude, multivitamin use, BMI and socioeconomic status, disease-specific factors including duration of illness, disease activity, and proteinuria; and traditional CVD risk factors including fasting lipids) were adjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>201</td>
<td>Children with systemic lupus erythematos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tornhammar et al, 2014, Sweden11</td>
<td>Prospective cohort</td>
<td>25(OH)D was measured in neonates and CVD risks were measured at aged 35 years</td>
<td>Metabolic syndrome components</td>
<td>Higher neonatal 25(OH)D was associated with higher fasting insulin, triglyceride, and cholesterol (in women) concentrations and with a higher risk of overweight at 35 y of age but not with other adult cardiovascular disease risk factors</td>
<td>Confounders both associated with vitamin D status and outcomes (season of birth, sex, preterm birth, maternal age at delivery, education, exercise, fish consumption, smoking, and vitamin D at follow-up) were adjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>284</td>
<td>Population based, healthy neonates screened for metabolic disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kelishadi et al, 2014, Iran27</td>
<td>RCT</td>
<td>10 – 16 years</td>
<td>Insulin resistance, and a continuous value of metabolic syndrome (cMetS). cMetS score was calculated as the sum of the standardized residuals (Z-scores) for waist circumference, HDL-cholesterol, triglycerides, fasting blood glucose, and mean arterial blood pressure (MAP) by regressing them based on age and gender to account for age- and gender-related differences</td>
<td>Vitamin D supplementation were associated with decreased serum insulin, triglyceride, HOMA-IR and cMetS</td>
<td>Used an intention to threat analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 (25 vitamin D and 25 placebo)</td>
<td>Children with BMI &gt; 3 Z-scores and presence of metabolic syndrome Intervention: oral vitamin D (300,000 IU) and the other group received placebo per week for 12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>43 (86%) completed the study</td>
<td>Population based, healthy neonates screened for metabolic disorders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

25(OH)D: 25-hydroxyvitamin D; CIMT: carotid-intima media thickness; CRP: C-reactive protein; hsCRP: high sensitivity C-reactive protein; HDL: high density lipoproteins; LDL: low density lipoproteins; BMI: body mass index; MetS: metabolic syndrome; HOMA – IR: homeostatic model assessment – insulin resistance; FMD: flow mediated dilatation; PTH: parathyroid hormone; CVD: cardiovascular disease.
Table 1. Studies assessing the association of serum-25-OH-D concentration with occurrence of cardiovascular events in children (cont.)

<table>
<thead>
<tr>
<th>Author, year country</th>
<th>Study design</th>
<th>Study population</th>
<th>Outcome</th>
<th>Associations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams et al, 2014, UK</td>
<td>Prospective cohort</td>
<td>26(OH)D was measured at 7 – 12 years and CVD risk in 15.4 years</td>
<td>Hypertension, triglyceride, HDL, glucose, insulin, and CRP</td>
<td>Total 25(OH)D concentration &lt;50 nmol/l had lower HDL-C and higher fasting insulin compared with participants with total 25(OH)D ≥72 nmol/l</td>
<td>Factors associated with vitamin D status (age, gender, socioeconomic status, BMI, parathyroid hormone, calcium, and phosphate) were adjusted</td>
</tr>
<tr>
<td>Lee et al, 2013, Korea</td>
<td>Cross sectional</td>
<td>9 years</td>
<td>Metabolic syndrome</td>
<td>Low 25(OH)D were associated with obesity and metabolic syndrome</td>
<td>Adjusted for BMI</td>
</tr>
<tr>
<td>Williams et al, 2013, UK</td>
<td>Prospective cohort</td>
<td>25(OH)D was measured at pregnancy and CVD risk at 9.9 years and 15.4 years</td>
<td>Hypertension, lipids, apolipoproteins, CRP, interleukin (at 9.9 years) and insulin resistance, glucose (at 15.4 years)</td>
<td>Maternal 25(OH)D was inversely associated with systolic blood pressure, Apo-B, and CRP at age 9.9 years</td>
<td>Confounders associated with vitamin D status and outcomes (maternal age, education, BMI, smoking, physical activity, parity, socioeconomic position, ethnicity, offspring gestational age at 25(OH)D sampling, gender, age, and BMI at outcome assessment) were adjusted</td>
</tr>
<tr>
<td>Stanley et al, 2013, USA</td>
<td>Cross sectional</td>
<td>12 – 18 years</td>
<td>Insulin resistance and hsCRP</td>
<td>In obese girls, PTH/25(OH)D is positively associated with measures of insulin sensitivity and hsCRP</td>
<td>Adjusted for BMI</td>
</tr>
<tr>
<td>Nam et al, 2012, Korea</td>
<td>Cross sectional</td>
<td>12 – 19 years</td>
<td>Abdominal obesity, overweight or obese, and metabolic syndrome</td>
<td>25(OH)D deficiency was associated with increased risk for abdominal obesity, obesity, and metabolic syndrome</td>
<td>Adjusted for age, sex, and regular physical exercise</td>
</tr>
<tr>
<td>Cheraghi et al, 2012, USA</td>
<td>Cross sectional</td>
<td>10 – 17 years</td>
<td>Cardiometabolic risk, vascular distensibility and CIMT</td>
<td>Cardiometabolic risks = BMI ≥95th percentile for age and sex, systolic blood pressure ≥95th percentile for age, sex and height, total cholesterol ≥170 mg/dL, triglyceride ≥100 mg/dL, HDL &lt;45 mg/dL, insulin ≥18 uIU/mL, and history of tobacco exposure</td>
<td>25(OH)D levels inversely associated with cardiometabolic risk factor score, but no vascular distensibility and CIMT</td>
</tr>
</tbody>
</table>

25(OH)D: 25-hydroxyvitamin D; CIMT: carotid-intima media thickness; CRP: C-reactive protein; hsCRP: high sensitivity C-reactive protein; HDL: high density lipoproteins; LDL: low density lipoproteins; BMI: body mass index; MetS: metabolic syndrome; HOMA – IR: homeostatic model assessment – insulin resistance; FMD: flow mediated dilatation; PTH: parathyroid hormone; CVD: cardiovascular disease.
### Table 1. Studies assessing the association of serum-25-OH-D concentration with occurrence of cardiovascular events in children (cont.)

<table>
<thead>
<tr>
<th>Author, year country</th>
<th>Study design</th>
<th>Study population</th>
<th>Outcome</th>
<th>Associations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams et al, 2012, UK</td>
<td>Prospective cohort</td>
<td>Mean age 9.9 years</td>
<td>4274</td>
<td>A healthy, population based cohort</td>
<td>Hypertension, lipids (tri-glycerides, LDL, HDL cholesterol), apolipoproteins (Apo-A1 and Apo-B), adiponectin, leptin, CRP, and IL-6</td>
</tr>
<tr>
<td>Williams et al, 2011, UK</td>
<td>Cross sectional</td>
<td>12 – 19 years</td>
<td>5609</td>
<td>A healthy, population based cohort</td>
<td>Metabolic syndrome components</td>
</tr>
<tr>
<td>Creo et al, 2013, USA</td>
<td>Prospective cohort</td>
<td>2 – 6 years</td>
<td>83</td>
<td>Obese children attended to obesity care at a tertiary referral hospital</td>
<td>Insulin resistance, metabolic syndrome components</td>
</tr>
<tr>
<td>Ganji et al, 2011, USA</td>
<td>Prospective cohort</td>
<td>12 – 19 years</td>
<td>5867</td>
<td>A healthy, population based cohort</td>
<td>Metabolic syndrome and cardiometabolic risk factors</td>
</tr>
<tr>
<td>Pacifico et al, 2011, Italy</td>
<td>Cross sectional</td>
<td>Mean age 11 – 11.5 years</td>
<td>452</td>
<td>A population-based, healthy Caucasian</td>
<td>Metabolic syndrome components, flow-mediated vasodilatation (FMD), and CIMT</td>
</tr>
<tr>
<td>Khrisnaveni et al, 2011, India</td>
<td>Cross sectional</td>
<td>25(OH)D was measured at pregnancy and CVD risks were measured at 5 years and 9.5 years</td>
<td>539</td>
<td>Pregnant women and their offspring’s who matching eligibility criteria (no known history of diabetes) had an oral glucose tolerance test at 28 to 32 weeks gestation</td>
<td>Fasting insulin resistance was calculated using the HOMA-IR equation.</td>
</tr>
<tr>
<td>Ashraf et al, 2011, USA</td>
<td>A before and after study</td>
<td>12 – 16 years</td>
<td>80 (53 African American and 27 Caucasian American)</td>
<td>Obese postmenarchal adolescent females attending a weight management clinic at a tertiary teaching hospital</td>
<td>Blood pressures, lipid profile, CRP, alanine transaminases (ALT) and aspartate transaminases followed by an oral glucose tolerance test, and HOMA-IR</td>
</tr>
</tbody>
</table>

25(OH)D: 25-hydroxyvitamin D; CIMT: carotid-intima media thickness; CRP: C-reactive protein; hsCRP: high sensitivity C-reactive protein; HDL: high density lipoproteins; LDL: low density lipoproteins; BMI: body mass index; MetS: metabolic syndrome; HOMA – IR: homeostatic model assessment – insulin resistance; FMD: flow mediated dilatation; PTH: parathyroid hormone; CVD: cardiovascular disease.
Vitamin D deficiency in children
The most common forms of vitamin D are ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D3 can be synthesised in the skin under ultraviolet-B exposure from the sun. In the skin, 7-dehydrocholesterol is converted into precholecalciferol (pre-vitamin D), which is unstable. This previtamin D is then converted into cholecalciferol through thermal isomerisation. Other forms of vitamin D can be obtained from diet as vitamin D2 or vitamin D3, which are present in foods such as oily fish, egg yolk, and fortified foods. After entering the body circulation, both forms of vitamin D are bound to the vitamin D-binding protein and transported to the liver, which rapidly converts them into 25(OH)D, the major circulating form of the vitamin. Subsequently, 25(OH)D is transported around the body while being bound to the vitamin D-binding protein. Furthermore, the active form of vitamin D [1, 25(OH)2D or calcitriol] is produced mainly in the mitochondria of the renal cortex, which is controlled by the parathyroid hormone (PTH) for the maintenance of calcium homeostasis. The most accurate marker of vitamin D status is the serum 25(OH)D level because it has a long circulating half-life of approximately 3 weeks, it has a high concentration in circulation at approximately 1000 times of 1,25(OH)2D, and its production is not influenced by the level of calcium.\(^1,2\) The stages of individual vitamin D status can be classified according to the circulating 25(OH)D level.\(^3\) Vitamin D status is evaluated by measuring the levels of 25(OH)D. Vitamin D deficiency is defined as having a 25(OH)D level of <20 ng/mL. Vitamin D deficiency was variably common in 20%, 34.5%, 49%, and 75% of adolescents aged 10–18 years. A study reported that 4% of early adolescents aged 9–11 years had vitamin D deficiency [25(OH)D < 20 ng/mL]. However, an inadequate vitamin D level [25(OH)D = 20–30 ng/mL] was observed in 68% of adolescents.\(^8\)

A study conducted in Indonesia reported that almost 50% of children aged 2–5 years and 5–12 years had vitamin D levels of <50 nmol/L.\(^9\) Another study including children aged 7–12 years reported that more than 75% of the children had vitamin D levels of 37.5 and 77.5 nmol/L.\(^10\)

Relevance of Asian food culture and personal behaviors
Vitamin D can be optimally obtained from the sun in countries where sun exposure is adequate. Therefore, there might be only a small requirement of vitamin D intake from food. Out of these small selections of foods, many are from animal-derived where the precursor of vitamin D which is dehydrocholesterol is found, as well as fungi such as mushrooms which contain the other precursor of vitamin D, ergosterol.\(^11\) However, vitamin D deficiency might be common because of reduced sun exposure, owing to increased indoor activities, high latitudes, sunscreen usage, and dark skin pigmentation.\(^12,13\) Indonesian infants may also have a risk of vitamin D deficiency. This might be attributed to the avoidance of sunlight and wearing of scarves by many Indonesian women. In addition, this risk may be caused by maternal vitamin D deficiency, which increases the risk of vitamin D deficiency at the birth of their babies. Moreover, mothers are strongly encouraged to engage in exclusive breastfeeding in the first 6 months of life and to continue breastfeeding up to 2 years of age. However, breast milk is a poor source of vitamin D, particularly when the mother has vitamin D deficiency.\(^14,15\) Furthermore, infants have very limited exposure to direct sunlight and may receive insufficient intake through their diet once solids are introduced.

Vitamin D deficiency and obesity
Several factors may contribute to vitamin D deficiency in obesity including the sequestration of vitamin D in lipocytes because of the presence of receptors in adipose tissue, decrease in vitamin D bioavailability in the target organ, increase in the inflammation process, and decrease in sun exposure because of increased sedentary activities. Furthermore, a low level of vitamin D in obese children has been associated with visceral adiposity.\(^16,17\) These possible etiologies resulting in vitamin D deficiency may be common in obese children living in countries with abundant sun exposure. The results indicated that vitamin D deficiency is common and that it was observed in 45%–53% of obese adolescents aged 7–18 years.\(^18,21\)

Vitamin D and hypertension
Vitamin D deficiency is associated with hypertension because of the activation of the renin–angiotensin–aldosterone system (RAAS) and the dysfunction of the endothelial system (Figure 2). The disruption of the vitamin D pathway increases the renin level, whereas an increase in the vitamin D level reduces the renin level. RAAS regulates electrolyte and volume homeostasis. Therefore, excessive RAAS stimulation is associated with hypertension.\(^22\) Inappropriate RAAS stimulation has also been associated with heart attack and stroke.\(^23\)

Vitamin D provides adequate nitric oxide, which is a potent vasodilator. Nitric oxide deficiency may lead to hypertension. Vitamin D may cause endothelial dysfunction and increased arterial stiffness leading to increased blood pressure.\(^22\) Furthermore, vitamin D deficiency may prevent secondary hyperparathyroidism by reducing the PTH level, which is associated with hypertension.

Nine studies have evaluated the association between vitamin D status and hypertension in children. The total 25(OH)D level has been reported to be inversely associated with systolic blood pressure\(^24,25\) and diastolic blood pressure.\(^7,18\) Furthermore, low levels of vitamin D in obese children were associated with hypertension, especially at night.\(^21\) The 25(OH)D level was inversely associated with systolic blood pressure [−0.48 mm Hg difference per 50 nmol/L increase in 25(OH)D; 95% confidence interval (CI): −0.95 to −0.01].\(^23\) Furthermore, 25(OH)D deficiency (<17 ng/mL) was associated with hypertension, with the adjusted odds ratio (95% CI) of 1.72 (1.02–2.92).\(^3\) By contrast, some studies have reported no association between vitamin D and hypertension.\(^26–28\)

Vitamin D and dyslipidaemia
Vitamin D is useful for maintaining adequate levels of apolipoprotein AI, which is a major component in the lipoprotein of HDL cholesterol. Low 25(OH)D levels may also cause hypertriglyceridaemia and impaired lipid metabolism (Figure 2). This association may be mediated by inflammation.\(^29,30\)
Vitamin D and cardiovascular disease risk in children

Figure 2. Possible mechanisms of developing cardiovascular disease risk in children with vitamin D deficiency. In obese, vitamin D may traps in lipocytes leading to vitamin D deficiency. Other factors contributing to vitamin D deficiency are gender, race, gestational age, parity, maternal education, socio-economic status, ethnicity, maternal pre-pregnancy body mass index, maternal vitamin D level, birth weight, diet, sun exposure. Vitamin D deficiency may cause an activation of RAAS and endothelial dysfunction resulting hypertension. It also may cause impaired lipid metabolism leading to dyslipidaemia, and impaired glycemic control, insulin secretion and sensitivity causing diabetes, insulin resistance, and metabolic syndrome. Deficiency of vitamin D also causes systemic and vascular inflammation, endothelial dysfunction, foam cell formation, and smooth muscle cell proliferation leading to atherosclerosis. Other factors contributing to atherosclerosis include Small for gestational of age, gestational hypertension, pre-eclampsia, gestational diabetes mellitus, tobacco smoke exposure, exclusive breastfeeding, cardiovascular disease in family, and adequacy of fruit and vegetables intake, premature cardiovascular disease or early death in family.

RAAS: renin angiotensin-aldosterone system
Fifteen studies have evaluated the association of vitamin D status with dyslipidaemia. There was ten studies have reported that vitamin D deficiency might be associated with dyslipidaemia including high triglyceride, high LDL cholesterol, and low HDL cholesterol levels. The 25(OH)D level was inversely associated with total cholesterol, LDL cholesterol, and triglyceride levels. High 25(OH)D levels in neonates was associated with high triglyceride and cholesterol levels in women.\(^{31}\) In addition, baseline vitamin D deficiency was associated with the LDL cholesterol level in children with systemic lupus erythematosus (SLE) in a univariable analysis.\(^ {32}\)

An interventional study evaluated the effect of vitamin D supplementation on metabolic syndrome components. This study compared the treatment group [received supplementation of vitamin D (300,000 IU)] and the control group (received placebo per week for 12 weeks). They reported that compared with the baseline and the control group, the serum triglyceride level decreased significantly in the treatment group after the intervention. The total serum cholesterol, LDL cholesterol, HDL cholesterol, and fasting blood glucose and blood pressure did not significantly differ between the treatment and control groups.\(^ {27}\)

Low 25(OH)D levels have been reported to be inversely associated with total serum cholesterol.\(^ {5}\) In addition, studies have reported an association of the serum 25(OH)D level with the HDL cholesterol level.\(^ {6,24}\) Vitamin D deficiency has been positively associated with LDL cholesterol, independent of race, and BMI.\(^ {33}\) A prospective cohort study reported an association of high 25(OH)D levels in childhood with high HDL cholesterol levels in adolescence.\(^ {26}\) However, some studies have demonstrated no association between vitamin D and dyslipidaemia.\(^ {7,18,20,25,28}\)

**Vitamin D and diabetes and insulin resistance**

Vitamin D plays a role in the mechanism of type 2 diabetes, which is one of the critical risk factors for cardiovascular disease. The lower the 25(OH)D levels are, the higher is the risk for diabetes. Vitamin D deficiency might affect insulin sensitivity or beta cell function because the receptor of 25(OH)D is found in pancreatic beta cells. In addition, vitamin D deficiency was identified to be associated with impaired insulin secretion and might cause insulin resistance (Figure 2).\(^ {34}\) Vitamin D may improve insulin sensitivity to glucose transport by stimulating the expression of insulin receptors. Moreover, vitamin D may play a role in improving insulin responsiveness in skeletal and adipose tissues.\(^ {22,35}\)

Ten studies have examined glucose tolerance or insulin resistance with inconclusive results. These studies have reported that 25(OH)D levels were not associated with insulin resistance formulated using HOMA-IR.\(^ {5,6,19,20,27,33,36-39}\) However, Lee et al demonstrated that 25(OH)D deficiency was correlated with HOMA-IR (\(p=0.073, p<0.001\)) and was inversely correlated with the insulin sensitivity index (\(p=0.095, p=0.001\)).\(^ {7}\) In addition, a study reported an inverse association of 25(OH)D deficiency with fasting insulin levels (a relative difference of \(-4.59\%\) per doubling; 95% CI: \(-8.37\) to \(-0.59; \(p=0.03\)).\(^ {36}\) Khrisnaveni et al. demonstrated that at the age of 9.5 years, the children of vitamin D-deficient mothers had high fasting insulin levels and insulin resistance.\(^ {40}\) In a study evaluating patients of different races, the 25(OH)D level was inversely associated with the fasting insulin level in Caucasian Americans, after adjustment for BMI (\(r=-0.42, p=0.03\)).\(^ {35}\)

**Vitamin D deficiency and metabolic syndrome**

Most of studies have applied the same criteria for metabolic syndrome; that is, having three or more of the following signs: hypertriglyceridaemia, low HDL cholesterol level, high blood glucose level, excessive waist circumference, or hypertension.\(^ {7,18,20,28}\) Approximately 47.9%\(^ {20}\) to 54.5%\(^ {18}\) of obese adolescents had metabolic syndrome. The prevalence of metabolic syndrome in healthy children aged 9 years was 6.4%.\(^ {28}\)

Low 25(OH)D levels have been reported to be inversely associated with metabolic syndrome.\(^ {5,20,28,41}\) Metabolic syndrome was significantly associated with low serum 25(OH)D levels, with an odds ratio of 1.71 (95% CI: 1.11–2.65, \(p<0.01\)).\(^ {4}\) The prevalence of metabolic syndrome was significantly higher in children with vitamin D deficiency [25(OH)D < 20.86 ng/mL] than in children with a vitamin D level of ≥20.86 ng/mL (\(p=0.029\)).\(^ {7}\)

**Vitamin D deficiency and cardiovascular disease**

A study reported an association of vitamin D deficiency with adverse cardiovascular risk factors in children and adolescents.\(^ {29}\) The receptors of vitamin D are found in vascular smooth muscles, the endothelium, and cardiomyocytes. Vitamin D has been associated with cardiovascular disease because vitamin D promotes vascular stiffness and calcification, which lead to atherosclerosis. In addition, lack of vitamin D is associated with hypertension because of the activation of the RAAS system and the dysfunction of the endothelial system.\(^ {30,31}\) These processes can lead to the development of plaques as a degenerative vascular process that starts in childhood.\(^ {42,43}\) Later, in adulthood, this might cause myocardial infarction or stroke.\(^ {17}\)

A systematic review and meta-analysis evaluated the association of serum vitamin D with cardiovascular disease risk in adults. This review included nine studies; of these studies, four have investigated nonfatal cardiovascular events or combined outcomes of fatal and nonfatal cardiovascular events reporting the incidence of cardiovascular diseases, and five have focused on mortality-related cardiovascular diseases. All these studies included healthy adults from nontropical countries. This meta-analysis suggested an association of the lowest 25-OH-D level with cardiovascular events [pooled hazard ratio (HR)=1.54 (1.22–1.95)]. However, this association did not differ significantly across the studies (Q=2.55; \(p=0.047\)). Furthermore, this meta-analysis indicated a significant association of low 25-OH-D levels with mortality-related cardiovascular events [HR=1.83 (1.19–2.80)], and a significant heterogeneity was detected among the studies (Q=21.01, \(p=0.0003\)). Finally, the combination of the incidence and mortality studies yielded a pooled HR of 1.64 (1.27–2.11), which supports the association of low 25-OH-D levels with cardiovascular disease outcomes.\(^ {44}\)

Atherosclerosis, which is observed as lipid accumula-
tion in the intima arteries, can start at a younger age.\textsuperscript{45} Initially, at approximately 3 years of age, almost all children with atherosclerosis have at least some degree of aortic fatty streaks,\textsuperscript{46} which can increase after 8 years of age.\textsuperscript{47} Finally, atherosclerotic plaques can be found in the coronary arteries during adolescence.\textsuperscript{48} CIMT is widely used as a marker of subclinical atherosclerosis in adults. Abnormal CIMT is associated with an increased risk of developing cardiovascular disease. CIMT is similar to the aorta intima media thickness (aIMT) and can be used to noninvasively identify early vascular changes.\textsuperscript{49} These early changes involve the thickening of vessel walls and the impairment of arterial vasodilatory function related to cardiovascular disease risk. However, aIMT had a stronger association with cardiovascular disease risk, particularly in those aged <18 years.\textsuperscript{50}

In this review, few studies evaluating the association of low serum vitamin D with increased CIMT have provided inconclusive results.\textsuperscript{6,8,20,25,32,37,51} As shown in the previous study, CIMT was 0.104±0.016 mm in obese children aged 9–15 years with a serum vitamin D of <20 ng/mL and 0.098±0.018 mm in those with serum vitamin D of >20 ng/mL (p<0.03).\textsuperscript{20} Another study reported that CIMT was 0.50±0.04 mm in obese children aged 9–11 years, and the median was 0.52 (0.42–0.57) mm; however, 25(OH)D levels were not associated with CIMT.\textsuperscript{6} In addition, the distensibility index of 2.62±0.87% per 10 mmHg and the CIMT of 0.54±0.06 mm were not related to vitamin D deficiency.\textsuperscript{4}

The role of vitamin D deficiency in atherosclerosis development is mediated by systemic and vascular inflammation. Vitamin D deficiency has been associated with increased levels of inflammatory cytokines, such as C-reactive protein (CRP), tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)), and interleukin (IL)-6, and low levels of interleukin-10, which can predispose to myocardial ischaemia development. In addition to systemic and vascular inflammation, vitamin D deficiency may cause endothelial dysfunction, foam cell formation, and smooth muscle cell proliferation, leading to atherosclerosis (Figure 2).

Inflammatory cytokines (IL-6, IL-10, and TNF-\(\alpha\)), adiponectin, and high-sensitivity CRP (hs-CRP), which are the biomarkers of inflammation, were not associated with vitamin D deficiency.\textsuperscript{32} Moreover, Singh et al reported the same conclusion that 25(OH)D levels were not associated with hsCRP.\textsuperscript{5} Robinson et al demonstrated that vitamin D deficiency was associated with hsCRP (p<0.01) and mean maximal CIMT (p<0.01) in children with SLE in the univariable analysis; nevertheless, this independent association was not observed in the multivariable analysis.\textsuperscript{32} By contrast, the 25(OH)D level at pregnancy was inversely associated with hsCRP (~6.1% difference; 95% CI: −11.5% to −0.3%) in children aged 9.9 years.\textsuperscript{25} In obese girls, PTH or 25-(OH)D was positively associated with hsCRP.\textsuperscript{51}

**Independence of sunlight exposure and health outcomes**

It is possible that one reason why vitamin D intervention studies failed to confirm the link between vitamin D and cardiovascular disease risk and other health outcomes is that vitamin D serves as a marker for sunlight exposure rather than mechanism.\textsuperscript{53}

**Implications for patient care**

Because the data on the association of vitamin D deficiency with cardiovascular disease in children are limited and inconclusive, additional studies are required to investigate this association in children in general and in a setting with abundant natural sun exposure such as Asia Pacific region. Moreover, formulating an effective prevention strategy for the development of cardiovascular diseases in children is important. Cardiovascular disease should be screened regularly by measuring the intima-media thickness or flow-mediated dilatation to detect the arterial wall thickness and endothelial dysfunction. Children with vitamin D deficiency may have an increased risk of cardiovascular disease. Therefore, the prevention and management of modifiable risk factors, including control of blood pressure, obesity, dyslipidaemia, diabetes, insulin resistance, and metabolic syndrome, should be applied. In addition, maintenance of adequate vitamin D status either from dietary intake or sun exposure is important despite the geographical location of Asia Pacific region. Because vitamin D may play a role in mechanisms underlying the development of cardiovascular disease, substantial research must be performed in this field.

**CONCLUSION**

Vitamin D deficiency has significant consequences on cardiovascular disease risk, which can manifest early in childhood on the heart and vasculature. Current evidence on vitamin D deficiency and cardiovascular disease mostly comes from research on adults. Studies evaluating the effectiveness of vitamin D in preventing cardiovascular disease risk in children by using an ideal study design are scant. Therefore, studies investigating the association of vitamin deficiency with cardiovascular disease development are required, particularly in the field of pediatric research. Furthermore, these types of studies also are important to be conducted in Asia Pacific region despite abundance in sunlight exposure.

Variations in exposure to intrauterine levels of vitamin D possibly influence foetal development, arterial structure, and metabolic processes that affect future cardiovascular health. However, to date, no study has evaluated the association of vitamin D deficiency with cardiovascular risk in early childhood, especially in the 1000 days of early life.

**ACKNOWLEDGEMENTS**

We gratefully acknowledge the Danone Institute Indonesia for facilitating a review process.

**AUTHOR DISCLOSURES**

None declared.

**REFERENCES**


33. Ashraf AF, Alvarez JA, Gower BA, Saenz KH, McCormick
Vitamin D and cardiovascular disease risk in children


