

Review Article

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, dyslipidaemia, 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 'metabolic syndrome' (ti) OR 'dyslipidemia' (ti) OR 'diabet*' (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-

Corresponding Author: Dr Indah K Murni, Jalan Kesehatan No 1, Sekip, Yogyakarta, Indonesia, 55284.

Tel: +62 274 561616; Fax: +62 274 583745

Email: indah.kartika.m@ugm.ac.id

Manuscript received 16 October 2016. Initial review completed 09 December 2016. Revision accepted 12 December 2016.

doi: 10.6133/apjcn.122016.s1

ease 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.

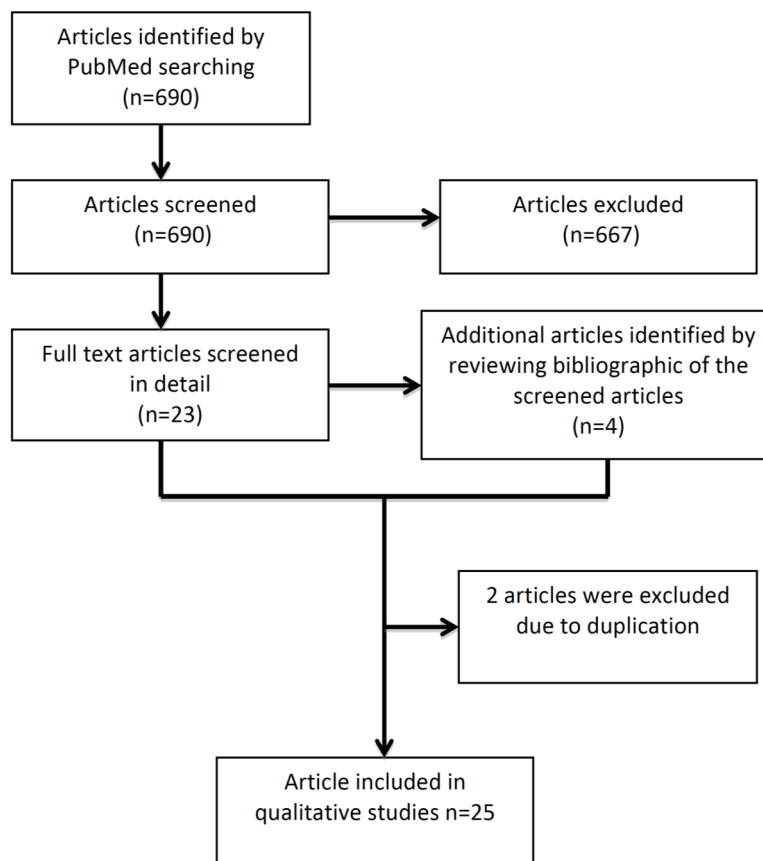


Figure 1. Search strategy

Table 1. Studies assessing the association of serum-25-OH-D concentration with occurrence of cardiovascular events in children

Author, year, country	Study design	Study population			Outcome	Associations	Notes
		Age	Total cases	Setting			
Prodam et al, 2015, Italy ¹⁹	Cross sectional	6 – 18 years	575	Overweight or obese children attended to endocrine clinics, a tertiary hospital	Metabolic syndrome components	25(OH)D level was inversely associated with total cholesterol, LDL cholesterol and triglycerides	Confounders associated with vitamin D status and outcomes (sex, age, puberty, BMI, waist circumference, UV exposure) were adjusted
Lee et al, 2015, Korea ⁷	Cross sectional	10 - 18 years	2880	Healthy children, community based	Insulin resistance, metabolic syndrome	Low 25(OH)D level was associated with increased insulin resistance and metabolic syndrome	Factors associated with both vitamin D status and outcome were not adjusted
Kao et al, 2015, Australia ¹⁸	Cross sectional	3 – 18 years	229	Overweight and obese children attended to obesity clinics, tertiary paediatrics hospital	Metabolic syndrome component	Lower 25(OH)D was associated with greater adiposity and higher blood pressure	Factors associated with vitamin D status were not adjusted
Singh et al, 2015, USA ⁸	Cross sectional	9 – 11 years	25	Obese and non-obese without history and current systemic infections and steroid use	hsCRP and CIMT	25(OH) D levels did not associated with hsCRP or CIMT	A preliminary study
Kwon et al, 2015, Korea ³⁶	Cross sectional	7 – 9 years	205	Healthy children, community based cohort	Metabolic syndrome component	25(OH)D levels were negatively associated with triacylglycerol levels. 25(OH)D deficiency was associated with metabolic syndrome via the derangement of triacylglycerol	Confounders associated with vitamin D status and outcomes (sex, age, BMI, birth order, maternal education level, and fruit/fruit juice intake) were adjusted
Hirschler et al, 2015, Argentina ³⁸	A controlled before and after study	8 – 12.5 years in San Antonio de los Cobres (SAC) and 7 – 10.5 years in Buenos Aires (BA)	321 (192 SAC and 129 BA)	Intervention: Indigenous SAC children were supplemented with 5000 IU of vitamin D3 per week during 8 weeks once a week BA children were not given supplementation	Triglyceride/HDL cholesterol ratio	Indigenous Argentinean children have a higher risk for dyslipidemia in comparison with BA children, even after vitamin D treatment	None of the children had received any vitamin supplementation previously. Confounders associated with vitamin D status and outcomes (age, gender, BMI, insulin, and group (SAC- BA)) were adjusted
Shah et al, 2015, USA ³⁷	RCT	11 – <18 years	40 (20 vitamin D and 20 placebo) Only 31 (78%) completed the study	Overweight and obese children and 25(OH)D of 10 and 60 ng/mL. Intervention: vitamin D2 150,000 IU every 3 months for 6 months	Inflammatory cytokines, adiponectin, hs-CRP, lipids, hemoglobin A1C, and BMI	25(OH)D were not associated with inflammatory and cardiovascular markers	A preliminary study Supplementation of vitamin D were not resulted in increased vitamin D status

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.)

Author, year country	Study design	Study population		Setting	Outcome	Associations	Notes
		Age	Total cases				
Banzato et al, 2014, Italy ²¹	Cross sectional	7 – 16 years	32	Obese Caucasian children admitted to Department of Pediatrics at a tertiary teaching hospital	Hypertension	Low 25(OH)D in obese children were associated with a higher BP burden, especially at night	Factors associated with vitamin D status were not adjusted
Atabek et al, 2014, Turkey ²⁰	Cross sectional	8 – 16 years	247	Obese children admitted to outpatient clinics at a tertiary teaching hospital	Insulin resistance, metabolic syndrome components, and CIMT	Low 25(OH)D were associated with increased CIMT and metabolic syndrome	Factors associated with both vitamin D status and outcomes were not adjusted
Robinson et al, 2014, North America ³²	Cross sectional	14 – 16 years	201	Children with systemic lupus erythematosus	hsCRP and CIMT	25(OH)D deficiency was associated increased hsCRP, but not CIMT	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
Tornhammar et al, 2014, Sweden ³¹	Prospective cohort	25(OH)D was measured in neonates and CVD risks were measured at aged 35 years	284	Population based, healthy neonates screened for metabolic disorders	Metabolic syndrome components	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	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
Kelishadi et al, 2014, Iran ²⁷	RCT	10 – 16 years	50 (25 vitamin D and 25 placebo) 43 (86%) completed the study	Children with BMI > 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	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	Vitamin D supplementation were associated with decreased serum insulin, triglyceride, HOMA-IR and cMetS	Used an intention to threat analysis

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.)

Author, year country	Study design	Study population		Setting	Outcome	Associations	Notes
		Age	Total cases				
Williams et al, 2014, UK ²⁶	Prospective cohort	25(OH)D was measured at 7 – 12 years and CVD risk in 15.4 years	2470	A healthy, population based cohort	Hypertension, triglyceride, HDL, glucose, insulin, and CRP	Total 25(OH)D concentration <50 nmol/l had lower HDL-C and higher fasting insulin compared with participants with total 25(OH)D ≥72 nmol/l	Factors associated with vitamin D status (age, gender, socioeconomic status, BMI, parathyroid hormone, calcium, and phosphate) were adjusted
Lee et al, 2013, Korea ²⁸	Cross sectional	9 years	1660	A school-based health examination	Metabolic syndrome	Low 25(OH)D were associated with obesity and metabolic syndrome	Adjusted for BMI
Williams et al, 2013, UK ²⁵	Prospective cohort	25(OH)D was measured at pregnancy and CVD risk at 9.9 years and 15.4 years	4109	A healthy, population based cohort	Hypertension, lipids, apolipoproteins, CRP, interleukin (at 9.9 years) and insulin resistance, glucose (at 15.4 years)	Maternal 25(OH)D was inversely associated with systolic blood pressure, Apo-B, and CRP at age 9.9 years	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
Stanley et al, 2013, USA ⁵¹	Cross sectional	12 – 18 years	30 (15 obese girls and 15 matched normal weight)	Population based study	Insulin resistance and hsCRP	In obese girls, PTH/25(OH)D is positively associated with measures of insulin sensitivity and hsCRP	Adjusted for BMI
Nam et al, 2012, Korea ⁴¹	Cross sectional	12 – 19 years	713	Population-based study	Abdominal obesity, overweight or obese, and metabolic syndrome	25(OH)D deficiency was associated with increased risk for abdominal obesity, obesity, and metabolic syndrome	Adjusted for age, sex, and regular physical exercise
Cheraghi et al, 2012, USA ⁴	Cross sectional	10 – 17 years	74	Children who attended to a Preventive Cardiology Clinic for evaluation of obesity, dyslipidemia and other atherosclerosis-promoting risk factors	Cardiometabolic risk, vascular distensibility and CIMT 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 <45 mg/dL, insulin ≥18 uIU/mL, and history of tobacco exposure	25(OH)D levels inversely associated with cardiometabolic risk factor score, but no vascular distensibility and CIMT	Adjusted for sex, age and race

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.)

Author, year country	Study design	Study population			Outcome	Associations	Notes
		Age	Total cases	Setting			
Williams et al, 2012, UK ²⁴	Prospective cohort	Mean age 9.9 years	4274	A healthy, population based cohort	Hypertension, lipids (triglycerides, LDL, HDL cholesterol), apolipoproteins (Apo-A1 and Apo-B), adiponectin, leptin, CRP, and IL-6	25(OH)D was associated with levels of HDL cholesterol, Apo-A1, and adiponectin	Adjusted for age, gender, ethnicity, socioeconomic status, waist circumference, BMI, parathyroid hormone, calcium and phosphate
Williams et al, 2011, UK ³²	Cross sectional	12 – 19 years	5609	A healthy, population based cohort	Metabolic syndrome components	Higher calcium levels is more important predictor of increased cardiovascular risk than lower 25(OH)D or parathyroid hormone levels	Adjusted for age, sex, ethnicity, poverty income ratio, waist circumference, and BMI
Creo et al, 2013, USA ³⁹	Prospective cohort	2 – 6 years	83	Obese children attended to obesity care at a tertiary referral hospital	Insulin resistance, metabolic syndrome components	25(OH)D was not associated with insulin resistance and cardiovascular disease risks	Adjusted for age, sex, BMI, and season
Ganji et al, 2011, USA ⁶	Prospective cohort	12 – 19 years	5867	A healthy, population based cohort	Metabolic syndrome and cardiometabolic risk factors	25(OH)D was inversely associated with waist circumference, systolic blood pressure, and HOMA-IR regardless of obesity	Adjusted for age, sex, race-ethnicity, BMI, poverty-income ratio, season of survey, use of supplements, smoking, and alcohol intake
Pacifico et al, 2011, Italy ⁵	Cross sectional	Mean age 11 – 11.5 years	452	A population-based, healthy Caucasian	Metabolic syndrome components, flow-mediated vasodilatation (FMD), and CIMT	Low 25(OH)D levels are inversely associated with total adiposity, metabolic syndrome, and hypertension, but no association with FMD and CIMT	Adjusted for age, sex, and Tanner stage
Khrisnaveni et al, 2011, India ⁴⁰	Cross sectional	25(OH)D was measured at pregnancy and CVD risks were measured at 5 years and 9.5 years	539 (at 5 years n=506 and at 9.5 years n=469)	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	Fasting insulin resistance was calculated using the HOMA-IR equation.	Intra-uterine exposure to low 25(OH)D concentrations is associated with higher insulin resistance. At 9.5 years old, children of vitamin D deficient mothers had higher fasting insulin concentrations and HOMA-IR than children of non-deficient women	Adjusted for age, sex, maternal parity, religion, BMI, gestational diabetes status and socio-economic score
Ashraf et al, 2011, USA ³³	A before and after study	12 – 16 years	80 (53 African American and 27 Caucasian American)	Obese postmenarchal adolescent females attending a weight management clinic at a tertiary teaching hospital	Blood pressures, lipid profile, CRP, alanine transaminases (ALT) and aspartate transaminases followed by an oral glucose tolerance test, and HOMA-IR	25(OH)D was inversely associated with fasting glucose Relationships of 25(OH)D with fasting insulin and ALT were ethnic specific. The positive relationship with LDL and ALT were suggestive of possible adverse influences of vitamin D	Adjusted for BMI

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)D₂ 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)D₂, 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%,⁴ 34.5%,⁵ 49%,⁶ and 75%⁷ 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^{6,7,18,24} 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].²⁵ 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).⁵ 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}

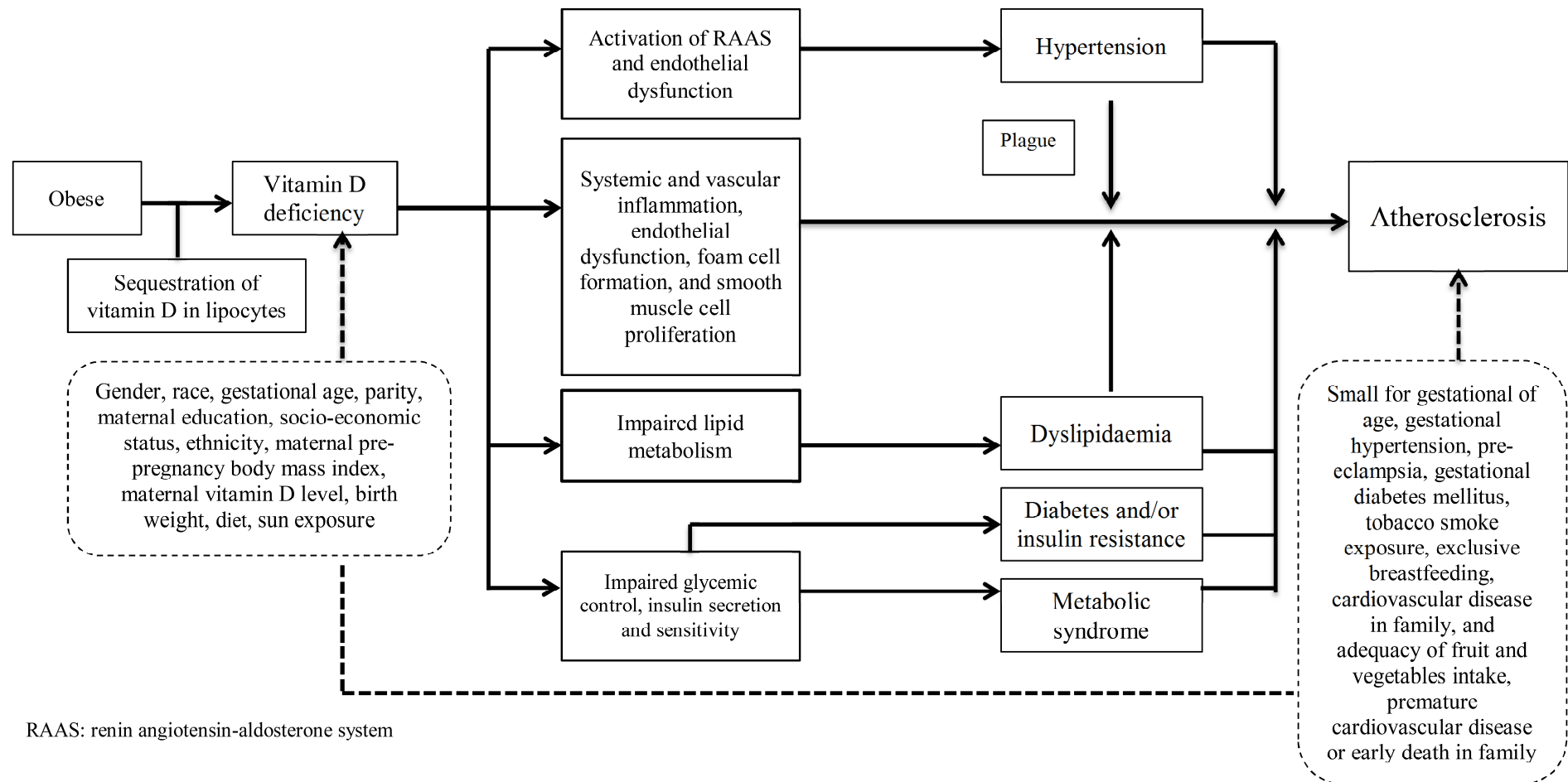


Figure 2. Possible mechanisms of developing cardiovascular disease risk in children with vitamin D deficiency. In obese, vitamin D may trap in lipocytes leading to vitamin D deficiency. Other factors contributing to vitamin D deficiency are gender, race, gestational age, parity, maternal education, socio-economic 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 in hypertension. It also may cause impaired lipid metabolism leading to dyslipidaemia, and impaired glycaemic 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.

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.¹⁹ 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 ($\rho=-0.073$, $p<0.001$) and was inversely correlated with the insulin sensitivity index ($\rho=0.095$, $p<0.001$).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 ; $p=0.03$).²⁶ 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 ($r=-0.42$, $p=0.03$).³³

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: hypertriglyceridemia, low HDL cholesterol level, high blood glucose level, excessive waist circumference, or hypertension.^{5-7,18,20,28} 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, $p<0.01$).⁶ 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.^{29,30} These processes can lead to the development of plaques as a degenerative vascular process that starts in childhood.^{8,42,43} 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 ($Q=2.55$; $p=0.47$). 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.⁴⁵ Initially, at approximately 3 years of age, almost all children with atherosclerosis have at least some degree of aortic fatty streaks,⁴⁶ which can increase after 8 years of age.⁴⁷ Finally, atherosclerotic plaques can be found in the coronary arteries during adolescence.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.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.⁵⁰

In this review, few studies evaluating the association of low serum vitamin D with increased CIMT have provided inconclusive results.^{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 ($p=0.03$).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.⁸ In addition, the distensibility index of $2.62\% \pm 0.87\%$ per 10 mmHg and the CIMT of 0.54 ± 0.06 mm were not related to vitamin D deficiency.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- α (TNF- α), 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- α), adiponectin, and high-sensitivity CRP (hs-CRP), which are the biomarkers of inflammation, were not associated with vitamin D deficiency.³⁷ Moreover, Singh et al reported the same conclusion that 25(OH)D levels were not associated with hsCRP.⁸ 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.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.²⁵ In obese girls, PTH or 25-(OH)D was positively associated with hsCRP.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.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

1. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation*. 2008;117:503-11. doi: 10.1161/CIRCULATIONAHA.107.706127
2. Muldowney S, Kiely M. Vitamin D and cardiometabolic health: a review of the evidence. *Nutr Res Rev*. 2011;24:1-20. doi: 10.1017/S0954422410000259.
3. Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. *Prog Biophys*

- Mol Biol. 2006;92:39-48.
4. Cheraghi N, Dai H, Raghuvveer G. Vitamin D deficiency is associated with atherosclerosis-promoting risk factor clustering but not vascular damage in children. *Met Sci Monit.* 2012;18:CR687-92. doi: 10.1016/j.pbiomolbio.2006.02.001.
 5. Pacifico L, Anania C, Osborn JF, Ferraro F, Bonci E, Olivero E et al. Low 25(OH)D3 levels are associated with total adiposity, metabolic syndrome, and hypertension in Caucasian children and adolescents. *Eur J Endocrinol.* 2011; 165:603-11. doi: 10.1530/EJE-11-0545.
 6. Ganji V, Zhang X, Shaikh N, Tangpricha V. Serum 25-hydroxyvitamin D concentrations are associated with prevalence of metabolic syndrome and various cardiometabolic risk factors in US children and adolescents based on assay-adjusted serum 25-hydroxyvitamin D data from NHANES 2001-2006. *Am J Clin Nutr.* 2011;94:225-33. doi: 10.3945/ajcn.111.013516.
 7. Lee DY, Kwon AR, Ahn JM, Kim YJ, Chae HW, Kim DH et al. Relationship between serum 25-hydroxyvitamin D concentration and risks of metabolic syndrome in children and adolescents from Korean National Health and Nutrition Examination survey 2008-2010. *Ann Pediatr Endocrinol Metab.* 2015;20:46-52. doi: 10.6065/apem.2015.20.1.46.
 8. Singh J, Merrill ED, Sandesara PB, Schoeneberg L, Dai H, Raghuvveer G. Vitamin D, low-grade inflammation and cardiovascular risk in young children: a pilot study. *Pediatr Cardiol.* 2015;36:1338-43. doi: 10.1007/s00246-015-1162-0.
 9. Sandjaja S, Budiman B, Harahap H, Ernawati F, Soekatri M, Widodo Y et al. Food consumption and nutritional and biochemical status of 0.5-12-year-old Indonesian children: the SEANUTS study. *Br J Nutr.* 2013;110(Suppl 3):S11-20. doi: 10.1017/S0007114513002109.
 10. Soesanti F, Pulungan A, Tridjaja B, Batubara J. Vitamin D profile in healthy children aged 7-12 years old in Indonesia. *Int J Pediatr Endocrinol.* 2013;Suppl:167. doi:10.1186/1687-9856-2013-S1-P167.
 11. Wahlqvist ML. Vitamin D status and food security in North-East Asia. *Asia Pac J Clin Nutr.* 2013;22:1-5. doi: 10.6133/apjcn.2013.22.1.21.
 12. Matsuoka LY, Ide L, Wortsman J, MacLaughlin JA, Holick MF. Sunscreens suppress cutaneous vitamin D3 synthesis. *J Clin Endocrinol Metab.* 1987;64:1165-8. doi: 10.1210/jcem-64-6-1165.
 13. Poh BK, Rojroongwasinkul N, Nguyen BK, Sandjaja, Ruzita AT, Yamborisut U et al. 25-hydroxy-vitamin D demography and the risk of vitamin D insufficiency in the South East Asia Nutrition Surveys (SEANUTS). *Asia Pac J Clin Nutr.* 2016;25:538-48. doi: 10.6133/apjcn.092015.02.
 14. Ziegler E, Hollis B, Nelson S, Jeter J. Vitamin D Deficiency in Breastfed Infants in Iowa. *Pediatrics.* 2006;118:603-10.
 15. Choi Y, Kim M, Jeong S. Vitamin D deficiency in infants aged 1 to 6 months. *Korean J Pediatr.* 2013;56:205-10. doi: 10.1542/peds.2006-0108.
 16. Cheng S, Massaro JM, Fox CS, Larson MG, Keyes MJ, McCabe EL et al. Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study. *Diabetes.* 2010;59:242-8. doi: 10.2337/db09-1011.
 17. Mozos I, Marginean O. Links between vitamin D deficiency and cardiovascular diseases. *Biomed Res Int.* 2015;2015: 109275. doi: 10.1155/2015/109275.
 18. Kao KT, Abidi N, Ranasinha S, Brown J, Roda C, McCallum Z et al. Low vitamin D is associated with hypertension in paediatric obesity. *J Paediatr Child Health.* 2015;51:1207-13. doi: 10.1111/jpc.12935.
 19. Prodam F, Zanetta S, Ricotti R, Marolda A, Giglione E, Monjani A et al. Influence of Ultraviolet Radiation on the Association between 25-Hydroxy Vitamin D Levels and Cardiovascular Risk Factors in Obesity. *J Pediatr.* 2016; 171:83-9. doi: 10.1016/j.jpeds.2015.12.032.
 20. Atabek ME, Eklioglu BS, Akyürek N, Alp H. Association between vitamin D level and cardiovascular risk in obese children and adolescents. *J Pediatr Endocrinol Metab.* 2014; 27:661-6. doi: 10.1515/jpem-2013-0379.
 21. Banzato C, Maffei C, Maines E, Cavarzere P, Gaudino R, Fava C et al. Hypovitaminosis D and nocturnal hypertension in obese children: an interesting link. *J Hum Hypertens.* 2014;28:360-6. doi: 10.1038/jhh.2013.122.
 22. Silva JS, Pereira SE, Sobrinho CJS, Ramalho A. Obesity, related diseases and their relationship with vitamin D deficiency in adolescents. *Nutr Hosp.* 2016;33:856-64. doi: 10.20960/nh.381.
 23. Li YC. Vitamin D regulation of the renin-angiotensin system. *J Cell Biochem.* 2003;88:327-31. doi: 10.1002/jcb.10343
 24. Williams DM, Fraser A, Sayers A, Fraser WD, Hingorani A, Deanfield J et al. Associations of 25-hydroxyvitamin D2 and D3 with cardiovascular risk factors in childhood: cross-sectional findings from the Avon Longitudinal Study of Parents and Children. *J Clin Endocrinol Metab.* 2012;97: 1563-71. doi: 10.1210/jc.2011-2335.
 25. Williams DM, Fraser A, Fraser WD, Hypponen E, Davey Smith G, Deanfield J et al. Associations of maternal 25-hydroxyvitamin D in pregnancy with offspring cardiovascular risk factors in childhood and adolescence: findings from the Avon Longitudinal Study of Parents and Children. *Heart.* 2013;99:1849-56. doi: 10.1136/heartjnl-2013-303678.
 26. Williams DM, Fraser A, Sayers A, Fraser WD, Hypponen E, Smith GD et al. Associations of childhood 25-hydroxyvitamin D2 and D3 and cardiovascular risk factors in adolescence: prospective findings from the Avon Longitudinal Study of Parents and Children. *Eur J Prev Cardiol.* 2014;21:281-90. doi: 10.1177/2047487312465688.
 27. Kelishadi R, Salek S, Salek M, Hashemipour M, Movahedian M. Effects of vitamin D supplementation on insulin resistance and cardiometabolic risk factors in children with metabolic syndrome: a triple-masked controlled trial. *J Pediatr (Rio J).* 2014;90:28-34. doi: 10.1016/j.jped.2013.06.006.
 28. Lee SH, Kim SM, Park HS, Choi KM, Cho GJ, Ko BJ et al. Serum 25-hydroxyvitamin D levels, obesity and the metabolic syndrome among Korean children. *Nutr Metab Cardiovascular Dis.* 2013;23:785-91. doi: 10.1016/j.numecd.2012.04.013.
 29. Sulistyoningrum DC, Gasevic D, Green TJ, Lear SA, Devlin AM. Adiposity and the relationship between vitamin D and blood pressure. *Metabolism.* 2013;62:1795-802. doi: 10.1016/j.metabol.2013.07.009.
 30. Sulistyoningrum DC, Green TJ, Lear SA, Devlin AM. Low Vitamin D Status is Associated with Increased Adiposity and Ethnicity. *PLoSOne.* 2012;7(e43159).
 31. Tornhammar P, Ueda P, Hult M, Simila H, Eyles D, Norman M. Season of birth, neonatal vitamin D status, and cardiovascular disease risk at 35 y of age: a cohort study from Sweden. *Am J Clin Nutr.* 2014;99:472-8. doi: 10.3945/ajcn.113.072520.
 32. Robinson AB, Tangpricha V, Yow E, Gurion R, McComsey GA, Schanberg LE. Vitamin D deficiency is common and associated with increased C-reactive protein in children and young adults with lupus: an Atherosclerosis Prevention in Pediatric Lupus Erythematosus substudy. *Lupus Sci Med.* 2014;1:e000011. doi: 10.1136/lupus-2014-000011.
 33. Ashraf AP, Alvarez JA, Gower BA, Saenz KH, McCormick

- KL. Associations of serum 25-hydroxyvitamin D and components of the metabolic syndrome in obese adolescent females. *Obesity*. 2011;19:2214-21. doi: 10.1038/oby.2011.110.
34. Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr*. 2004;79:820-5.
35. Mitri J, Dawson-Hughes B, Hu FB, Pittas AG. Effects of vitamin D and calcium supplementation on pancreatic beta cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *Am J Clin Nutr*. 2011;94:486-94. doi: 10.3945/ajcn.111.011684.
36. Kwon JH, Lee SE, Lee HA, Kim YJ, Lee HY, Gwak HS et al. Relationship of serum 25-Hydroxyvitamin D (25[OH]D) levels and components of metabolic syndrome in prepubertal children. *Nutrition*. 2015;31:1324-7. doi: 10.1016/j.nut.2015.04.023.
37. Shah S, Wilson DM, Bachrach LK. Large doses of vitamin D fail to increase 25-hydroxyvitamin D levels or to alter cardiovascular risk factors in obese adolescents: a pilot study. *J Adolesc Health*. 2015;57:19-23. doi: 10.1016/j.jadohealth.2015.02.006.
38. Hirschler V, Molinari C, Maccallini G, Sanchez M, Gonzales C, Hidalgo M et al. Status of dyslipidemia in vitamin D supplemented argentinean indigenous children versus a non-supplemented mixed population group. *Cardiovasc Hematol Agents Med Chem*. 2015;13:129-36. doi: 10.2174/187152571302151217144156.
39. Creo AL, Rosen JS, Ariza AJ, Hidaka KM, Binns HJ. Vitamin D levels, insulin resistance, and cardiovascular risks in very young obese children. *J Pediatr Endocrinol Metab*. 2013;26:97-104.
40. Krishnaveni GV, Veena SR, Winder NR, Hill JC, Noonan K, Boucher BJ et al. Maternal vitamin D status during pregnancy and body composition and cardiovascular risk markers in Indian children: the Mysore Parthenon Study. *Am J Clin Nutr*. 2011;93:628-35. doi: 10.3945/ajcn.110.003921.
41. Nam GE, Kim do H, Cho KH, Park YG, Han KD, Choi YS et al. Estimate of a predictive cut-off value for serum 25-hydroxyvitamin D reflecting abdominal obesity in Korean adolescents. *Nutr Res*. 2012;32:395-402. doi: 10.1016/j.nutres.2012.05.002.
42. Arnson Y, Itzhaky D, Mosseri M, Barak V, Tzur B, Agmon-Levin Net et al. Vitamin D inflammatory cytokines and coronary events: a comprehensive review. *Clin Rev Allergy Immunol*. 2013;45:236-47. doi: 10.1007/s12016-013-8356-0.
43. Berenson GS, Srinivasan SR, Bao W, Newman WP, 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med*. 1998;338:1650-6. doi: 10.1056/NEJM199806043382302.
44. Grandi NC, Breitling LP, Brenner H. Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. *Prev Med*. 2010;51:228-33. doi: 10.1016/j.ypmed.2010.06.013
45. McGill HC, Jr. The pathogenesis of atherosclerosis. *Clin Chem*. 1988;34:B33-9.
46. Napoli C, Pignatola O, de Nigris F, Sica V. Childhood infection and endothelial dysfunction: a potential link in atherosclerosis? *Circulation*. 2005;111:1568-70. doi: 10.1161/01.CIR.0000161816.52136.66.
47. Strong JP, Mc GH, Jr. The natural history of coronary atherosclerosis. *Am J Pathol*. 1962;40:37-49.
48. Stary HC, Blankenhorn DH, Chandler AB, Glagov S, Insull W Jr, Richardson M et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation*. 1992;85:391-405. doi: 10.1161/01.CIR.85.1.391.
49. Holewijn S, den Heijer M, Stalenhoef AF, de Graaf J. Non-invasive measurements of atherosclerosis (NIMA): current evidence and future perspectives. *Netherlands J Med*. 2010;68:388-99.
50. Dawson JD, Sonka M, Blecha MB, Lin W, Davis PH. Risk factors associated with aortic and carotid intima-media thickness in adolescents and young adults: the Muscatine Offspring Study. *J Am Coll Cardiol*. 2009;53:2273-9. doi: 10.1016/j.jacc.2009.03.026.
51. Stanley T, Bredella MA, Pierce L, Misra M. The ratio of parathyroid hormone to vitamin D is a determinant of cardiovascular risk and insulin sensitivity in adolescent girls. *Metab Syndr Relat Disord*. 2013;11:56-62. doi: 10.1089/met.2012.0102.
52. Williams DM, Fraser A, Lawlor DA. Associations of vitamin D, parathyroid hormone and calcium with cardiovascular risk factors in US adolescents. *Heart*. 2011;97:315-20. doi: 10.1136/hrt.2010.203224.
53. Jacobs ET, Martinez ME, Jurutka PW. Vitamin D: Marker or mechanism of action? *Cancer Epidemiol Biomarkers Prev*. 2011;20:585-90. doi: 10.1158/1055-9965.EPI-10-1257.