Association of Vitamin D Status and Cardio-Metabolic Risk Factors in Children and Adolescents: The CASPIAN-V Study

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Research
Abstract

Background: Metabolic syndrome (MetS) starts from early life, and is one of the important underlying factors for non-communicable disease (NCDs) in adulthood. Controversial evidence exists on the role of vitamin D deficiency in increasing risk of pediatric MetS.

Objective: This study aimed to assess the relationship between vitamin D level with MetS and its components in children and adolescents.

Methods: This cross-sectional nationwide study was performed as part of a surveillance program in Iran. Participants were 2596 students, aged 7 to 18 years, living in 30 provinces. In addition to filling questionnaires, physical examination was conducted, and blood samples were collected. Serum concentration of 25-hydroxy vitamin D (25(OH)D) was measured using direct competitive immunoassay chemiluminescence method.

Results: 2596 students with mean age of 12.2 y (55.1% boys) were recruited. Prevalence of vitamin D deficiency and insufficiency in participants was 10.6% (n=276), and 60.5% (n=1570), respectively. Prevalence of MetS was higher in vitamin D deficient group. Students with deficient vitamin D level had higher odds of MetS (OR: 4.25, 95%CI: 2.26-7.98), abdominal obesity (OR: 2.24, 95%CI: 1.61-3.12), low HDL-C (OR: 1.65, 95%CI: 1.18-2.30) and high fasting blood sugar (OR: 2.56, 95%CI: 1.43-4.57) in comparison to those with sufficient level of vitamin D.

Conclusion: Vitamin D deficiency was associated with increased odds of MetS and its components in Iranian pediatric population. These findings underscore the importance of prevention and control of vitamin D deficiency in preventative programs against NCDs.

Introduction

The metabolic syndrome (MetS) is a clinical condition and is characterized by risk factors including dyslipidemia, elevated blood pressure, obesity and impaired glucose regulation. Several factors including unhealthy diet, physical inactivity and obesity can affect MetS (1).

Vitamin D levels are generally assessed using the blood concentration of 25-hydroxyvitamin D (25(OH)D). It is essential in homeostasis of calcium and phosphorus and affects bone mineralization. Recent evidence suggests extraskeletal effects of vitamin D on cardio-metabolic outcomes. Vitamin D deficiency may increase the risk of non-communicable diseases (NCDs) and associated with MetS components (2). However, compared with adults, there is conflicting and inadequate evidence about the association between vitamin D deficiency and MetS in children and adolescents. Some studies showed an inverse association between plasma vitamin D and metabolic syndrome components (3, 4) while others did not reveal any association (5, 6).
Vitamin D deficiency is widespread and is more common in young populations because of sedentary life. In addition, NCDs often begin in childhood or young adulthood (7). Thus, assessment the link between vitamin D deficiency and cardio-metabolic risk factors in the young is important. Particularly, studies with a large nationally representative sample are needed to clarify conflicting evidence regarding the relationship between plasma vitamin D and prevalence of metabolic syndrome and its components (8).

Low serum 25(OH)D concentration has been correlated with obesity and MetS, However, few studies have investigated these associations in the Iranian pediatric population where the prevalence of vitamin D deficiency, obesity and related metabolic disorders in pediatric population is high. We conducted a cross-sectional study to examine the association between plasma vitamin D status and cardio-metabolic risk factors in a large nationally representative sample of Iranian children and adolescents.

**Methods And Materials**

**Study population**

This cross-sectional study nationwide was performed as part of the fifth survey of a national school-based surveillance program entitled “Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable disease” (CASPIAN-V study). The study was conducted among students aged 7–18 years from primary and secondary schools in urban and rural areas of 30 provinces of the country; details of the study protocol have been described previously (9). From 14400 students which have been enrolled, vitamin D measurement has been done on 2596 students randomly. Written informed consent and verbal assent were obtained from the parents and students after explaining the aim of study. The study protocol was approved by the Research and Ethics Council of National Institute for Medical Research Development (NIMAD) and it was in compliance with the declaration of Helsinki.

**Data collection**

All students participated in a demographic survey, anthropometric measurements and blood testing. The demographic survey included questions about the age, region of residence, consumption of vitamin D supplement, family’s socioeconomic status and leisure time activity. The physical activity (PA) and screen time (ST) of students during the prior week were assessed using a validated questionnaire. Students were asked about the frequency of their leisure time PA outside of school, which caused sweating or increase in heart rate lasting at least 30 minutes. PA was classified into three groups; low, moderate and high PA were defined as having activity 0–2, 3–5 and 6–7 days per week, respectively (10). ST was considered as the average number of hours per day spent watching television, using computer or playing electronic games. ST was categorized into two groups (low: less than 2 h/d and high: equal or more than 2 h/d) based on international ST recommendations. Questions about the parental educational level and occupational status, school type (public/private), having private car, and possessing personal computer...
have been considered in questionnaire for estimating the family’s socioeconomic status (SES) in three levels (low/moderate/high).

Anthropometric measurements were done according to the standard protocol. Height was measured without shoes. Weight was measured using a digital scale (SECA, Germany) with minimal clothing and without shoes. Body mass index (BMI) was calculated as weight in kg divided by squared height in m². Waist circumference (WC) was measured using a non-elastic tape at the midpoint between the lower margin of the rib cage and top of the iliac crest to the nearest 0.1 cm. Blood pressure (BP) was measured in sitting position two times with five-minute interval using a standardized mercury sphygmomanometer. The first and fifth Korotkoff sounds were considered as systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively. The average of two measurements was recorded.

Students were asked to fast overnight for 12 hours before collecting blood samples. Biochemical variables including fasting blood glucose (FBG), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) were measured by enzymatic methods using Hitachi auto-analyzer (Tokyo, Japan). Serum concentration of 25-hydroxy vitamin D (25(OH)D) was measured using direct competitive immunoassay chemiluminescence method with LIASON 25-OH vitamin D assay TOTAL (DiaSorin,Inc.) according to the manufacturer’s instructions. The coefficient of variation (CV) of this test was 9.8%.

**Definition of terms**

MetS was diagnosed based on the Adult Treatment Panel III (ATP III) criteria with modification for the pediatric age group. Students were classified as having MetS if they had three or more of the following components: 1- Serum TG concentration ≥ 150 mg/dl; 2- Serum HDL-C concentration ≤ 40 mg/dL; 3- Serum FBG concentration ≥ 100 mg/dl; 4- Abdominal obesity as waist to height ratio > 0.5; 5- Either SBP or DBP ≥ 90th percentile for age, gender, and height (1). Vitamin D deficiency is defined as a serum 25(OH)D concentration of less than 10 ng/mL, and vitamin D insufficiency is defined as a serum 25(OH)D concentration between 10 to 30 ng/mL. Serum 25(OH)D level greater than 30 ng/mL was considered as vitamin D sufficiency (11).

**Statistical analysis**

Data are presented as mean ± standard deviation or number (percentage). Demographic characteristics and biochemical variables were compared according to gender using independent sample t-test and Chi-square test. Prevalence of MetS and its components was compared according to vitamin D status by Chi-square test. Mean levels of MetS components were compared among vitamin D status groups using Analysis of variance (ANOVA) test. Associations between MetS components and vitamin D levels were examined by linear regression models controlling for potential confounders including age, gender, living area, ST, PA and SES.
Association between vitamin D status and MetS and its components were assessed using multinomial logistic regression analysis. Results are presented as odds ratio (OR) and 95% confidence interval (CI). Three models were defined; Model I: crude, Model II: adjusted for age, gender, living area, and Model III: additionally adjusted for ST, PA and SES. Data analysis was performed using STATA Statistical Software version 11.0 (StataCorp LP. Package, College Station, TX, USA). Significance level was defined as P values below 0.05.

Results

Participants consisted of 2596 students with mean (SD) age of 12.2 (3.0) y, including 55.1% boys. The mean of age, WC, SBP and TG, PA level, and family SES were significantly different according to gender (P < 0.05). No significant difference was existed between boys and girls in terms of place of residence, ST, as well as level of vitamin D, HDL-C, FBG and DBP. The demographic characteristics of students according to gender are presented in Table 1.
Table 1
Participants’ demographic characteristics, according to gender: the CASPIAN-V study

| Variables*            | Total (n = 2596) | Boys (n = 1430) | Girls (n = 1166) | p-value |
|-----------------------|------------------|-----------------|------------------|---------|
| Age, years$^1$        | 12.18(3.04)      | 12.32(3.01)     | 11.99(3.07)      | < 0.001 |
| Region$^2$            |                  |                 |                  | 0.79    |
| Urban                 | 1850(71.3)       | 1022(71.5)      | 828(71)          |         |
| Rural                 | 746(28.7)        | 408(28.5)       | 338(29)          |         |
| PA$^2$                |                  |                 |                  | 0.01    |
| Low                   | 817(33.4)        | 417(31.2)       | 400(36.1)        |         |
| Moderate              | 794(32.5)        | 435(32.6)       | 359(32.4)        |         |
| High                  | 833(34.1)        | 483(36.2)       | 350(31.6)        |         |
| ST$^2$                |                  |                 |                  | 0.24    |
| Low                   | 2164(85.5)       | 1179(84.8)      | 985(86.4)        |         |
| High                  | 367(14.5)        | 212(15.2)       | 155(13.6)        |         |
| SES$^2$               |                  |                 |                  | < 0.001 |
| Low                   | 808(32.6)        | 405(29.4)       | 403(36.6)        |         |
| Moderate              | 827(33.4)        | 496(36)         | 331(30.1)        |         |
| High                  | 843(34)          | 477(34.6)       | 366(33.3)        |         |
| WC, cm$^1$            | 66.75(12.38)     | 67.31(13.02)    | 66.05(11.51)     | < 0.001 |
| Vitamin D ng/dl$^1$   | 25.94(11.33)     | 26.11(11.10)    | 25.74(11.62)     | 0.40    |
| SBP, mmHg$^1$         | 98.45(12.98)     | 99.14(13.16)    | 97.59(12.72)     | < 0.001 |
| DBP, mmHg$^1$         | 63.46(10.15)     | 63.64(10.39)    | 63.25(9.86)      | 0.32    |
| HDL-C, mg/dl$^1$      | 46.62(10.12)     | 46.72(10.24)    | 46.49(9.96)      | 0.55    |
| TG, mg/dl$^1$         | 86.45(46.93)     | 84.86(46.19)    | 88.41(47.78)     | 0.05    |
| FBG, mg/dl$^1$        | 91.99(12.48)     | 92.35(13.25)    | 91.56 (11.45)    | 0.11    |
Variables*  
(n = 2596)  
Boys  
(n = 1430)  
Girls  
(n = 1166)  
p-value

1.Data are presented as mean (standard deviation).

2.Data are presented as Number (%)

BMI = body mass index; WC: Waist circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; HDL = high density lipoprotein; LDL = low density lipoprotein; TG = triglycerides; FBG = fasting blood glucose; PA = physical activity; ST = screen time; SES = socioeconomic statue

Prevalence of vitamin D deficiency, insufficiency and sufficiency in students was 10.6% (n = 276), 60.5% (n = 1570) and 28.9% (n = 750), respectively. Prevalence of MetS and its component according to vitamin D status is presented in Table 2. Prevalence of MetS, high FBG, low HDL, high TG and abdominal obesity was higher in vitamin D deficient group compared to vitamin D sufficient and insufficient groups (P < 0.01). As shown in Table 3, mean of WC and TG was higher in vitamin D deficient group compared to two other groups and HDL concentration was lower in vitamin D deficient and insufficient groups compared to sufficient group (P < 0.001).

Table 2

| Variable         | Vitamin D status | P-Value |
|------------------|------------------|---------|
|                  | Deficient | Insufficient | Sufficient |
| Abdominal Obesity | 97(35.4) | 319(20.3) | 147(19.5) | < 0.001 |
| High TG          | 89(32.5)  | 379(24.2) | 193(25.6) | 0.01    |
| Low HDL          | 94(34.3)  | 455(29)   | 168(22.3) | < 0.001 |
| High SBP         | 5(1.8)    | 46(2.9)   | 15(2)     | 0.29    |
| High DBP         | 27(9.9)   | 134(8.5)  | 83(11)    | 0.15    |
| High BP          | 28(10.2)  | 153(9.8)  | 86(11.4)  | 0.47    |
| High FBG         | 23(8.3)   | 58(3.7)   | 26(3.5)   | < 0.001 |
| MetS             | 32(11.7)  | 48(3.1)   | 18(2.4)   | < 0.001 |

Abdominal obesity = Waist to height ratio ≥ 0.5; High TG = TG > 100; Low HDL = HDL-C < 40 mg/dl except in boy 15-19y; high systolic BP = SBP at or above the 90th for age, gender and height; high diastolic BP = DBP at or above the 90th for age, gender and height; High BP = either high SBP / DBP at or above the 90th for age, gender and height; Metabolic syndrome = defined according to ATP-III criteria; SBP = systolic blood pressure; DBP = diastolic blood pressure; FBG = fasting blood sugar; TG = triglycerides; HDL = high density cholesterol.
Table 3
Mean levels of metabolic syndrome components according to vitamin D levels: the CASPIAN-V study

| Variable | Vitamin D status | Mean (SD)   | P-Value |
|----------|------------------|-------------|---------|
| WC       | Deficient        | 69.24(13.29) | < 0.001 |
|          | Insufficient     | 66.80 (12.08)|         |
|          | Sufficient       | 65.73 (12.55)|         |
| SBP      | Deficient        | 98.46(13.10) | 0.96    |
|          | Insufficient     | 98.49(12.79)|         |
|          | Sufficient       | 98.34(13.33)|         |
| DBP      | Deficient        | 63.63(9.88)  | 0.37    |
|          | Insufficient     | 63.24(10.16)|         |
|          | Sufficient       | 63.86(10.23)|         |
| FBG      | Deficient        | 92.90(11.08) | 0.43    |
|          | Insufficient     | 91.84(13.60)|         |
|          | Sufficient       | 91.99(10.32)|         |
| TG       | Deficient        | 95.96(56.82) | < 0.001 |
|          | Insufficient     | 85.10(4.86) |         |
|          | Sufficient       | 85.81(46.86)|         |
| HDL      | Deficient        | 45.47(9.20)  | < 0.001 |
|          | Insufficient     | 45.77(9.29) |         |
|          | Sufficient       | 48.79(11.64)|         |

Data are presented as mean (standard deviation).

SBP = systolic blood pressure; DBP = diastolic blood pressure; FBG = fasting blood sugar; TG = triglycerides; HDL = high density cholesterol; WC: Waist circumference

Results of linear regression models in Table 4 showed that WC, HDL and TG were significantly associated with vitamin D deficiency (P < 0.001). Moreover, WC and HDL were significantly associated with vitamin D insufficiency (P < 0.05). Results of logistic regression analysis investigating the association between vitamin D status and MetS and its components are presented in Table 5. Odds of MetS were higher in the vitamin D deficient group compared with the vitamin D sufficient group; this difference remained significant after adjusting for confounding factors (OR: 4.25, 95%CI: 2.26–7.98). Students with deficient
vitamin D level had a higher odds of abdominal obesity in comparison to those with sufficient vitamin D level (OR: 2.24, 95%CI: 1.61–3.12). Deficient vitamin D group had higher odds of low HDL-C compared with sufficient vitamin D group (OR: 1.65, 95%CI: 1.18–2.30). Odds of high FBG in deficient vitamin D group was 2.56 times higher than sufficient vitamin D group (OR: 2.56, 95%CI: 1.43–4.57). In vitamin D insufficient group only odds of low HDL was higher than sufficient vitamin D group (OR: 1.40, 95%CI: 1.12–1.74).
Table 4
Association between metabolic syndrome components and vitamin D levels in linear regression models: the CASPIAN-V study

| Vitamin D status | Deficient$^1$ | Insufficient$^1$ |
|------------------|---------------|-----------------|
|                  | $\beta$ | SE      | p-value | $\beta$ | SE      | p-value |
| WC               | Model 1     | 3.51 | 0.87  | < 0.001 | 1.06  | 0.54  | 0.05  |
|                  | Model 2     | 3.44 | 0.75  | < 0.001 | 1.17  | 0.47  | 0.01  |
|                  | Model 3     | 3.32 | 0.81  | < 0.001 | 1.16  | 0.50  | 0.02  |
| SBP              | Model 1     | 0.12 | 0.91  | 0.89    | 0.15  | 0.57  | 0.78  |
|                  | Model 2     | 0.08 | 0.85  | 0.92    | 0.22  | 0.53  | 0.66  |
|                  | Model 3     | 0.45 | 0.89  | 0.61    | 0.58  | 0.55  | 0.29  |
| DBP              | Model 1     | -0.23 | 0.71 | 0.74  | -0.62  | 0.45  | 0.16  |
|                  | Model 2     | -0.25 | 0.68 | 0.70  | -0.55  | 0.43  | 0.20  |
|                  | Model 3     | -0.00 | 0.72 | 0.99  | -0.34  | 0.45  | 0.44  |
| HDL-C            | Model 1     | -3.32  | 0.70 | < 0.001 | -3.01  | 0.44  | < 0.001 |
|                  | Model 2     | -3.36  | 0.70 | < 0.001 | -3.06  | 0.44  | < 0.001 |
|                  | Model 3     | -3.74  | 0.75 | < 0.001 | -2.96  | 0.46  | < 0.001 |
| TG               | Model 1     | 10.15  | 3.30 | < 0.001 | -0.70  | 2.07  | 0.73  |
|                  | Model 2     | 9.96  | 3.30 | < 0.001 | -0.59  | 2.07  | 0.77  |
|                  | Model 3     | 9.39  | 3.42 | < 0.001 | -0.44  | 2.12  | 0.83  |
| FBG              | Model 1     | 0.91  | 0.88  | 0.30  | -0.14  | 0.55  | 0.79  |
|                  | Model 2     | 0.89  | 0.88  | 0.30  | -0.18  | 0.55  | 0.74  |
|                  | Model 3     | 0.94  | 0.96  | 0.32  | -0.32  | 0.59  | 0.58  |

$^1$ In all model sufficient is reference group

Model 1: crude model; Model 2: Adjusted for age, gender and living area; Model 3: additionally adjusted to SES; PA and ST

SBP = systolic blood pressure; DBP = diastolic blood pressure; FBG = fasting blood sugar; TG = triglycerides; HDL = high density cholesterol; WC: Waist circumference
### Table 5
Association of Vitamin D status with MetS in logistic regression analysis

| Vitamin D status | Deficient | Insufficient |       |       |       |       |
|------------------|-----------|--------------|-------|-------|-------|-------|
|                  | OR        | CI95%        | p-value| OR    | CI95% | p-value|
| MetS             |           |              |        |       |       |       |
| Model 1          | 4.88      | 2.70–8.77    | < 0.001| 1.21  | 0.70–2.08 | 0.48  |
| Model 2          | 4.76      | 2.64–8.60    | < 0.001| 1.19  | 0.69–2.05 | 0.51  |
| Model 3          | 4.25      | 2.26–7.98    | < 0.001| 1.17  | 0.67–2.05 | 0.56  |
| Abdominal Obesity|           |              |        |       |       |       |
| Model 1          | 2.23      | 1.65–3.03    | < 0.001| 1.02  | 0.82–1.28 | 0.79  |
| Model 2          | 2.20      | 1.62–2.99    | < 0.001| 1.01  | 0.81–1.26 | 1.01  |
| Model 3          | 2.24      | 1.61–3.12    | < 0.001| 1.03  | 0.81–1.30 | 0.79  |
| High SBP         |           |              |        |       |       |       |
| Model 1          | 0.67      | 0.22–2.03    | 0.48   | 1.38  | 0.77–2.46 | 0.26  |
| Model 2          | 0.66      | 0.22–2.01    | 0.47   | 1.35  | 0.76–2.41 | 0.30  |
| Model 3          | 1.05      | 0.33–3.34    | 0.93   | 1.84  | 0.94–3.62 | 0.07  |
| High DBP         |           |              |        |       |       |       |
| Model 1          | 0.93      | 0.59–1.46    | 0.76   | 0.77  | 0.58–1.03 | 0.08  |
| Model 2          | 0.93      | 0.59–1.47    | 0.77   | 0.77  | 0.58–1.04 | 0.09  |
| Model 3          | 1.11      | 0.68–1.80    | 0.66   | 0.83  | 0.60–1.14 | 0.26  |
| High BP          |           |              |        |       |       |       |
| Model 1          | 0.93      | 0.59–1.45    | 0.75   | 0.86  | 0.65–1.14 | 0.30  |
| Model 2          | 0.93      | 0.59–1.45    | 0.76   | 0.86  | 0.65–1.14 | 0.31  |
| Model 3          | 1.10      | 0.68–1.77    | 0.67   | 0.92  | 0.68–1.25 | 0.60  |
| Low HDL-C        |           |              |        |       |       |       |
| Model 1          | 1.70      | 1.26–2.31    | < 0.001| 1.39  | 1.13–1.70 | < 0.001|
| Model 2          | 1.72      | 1.26–2.33    | < 0.001| 1.40  | 1.14–1.72 | < 0.001|
| Model 3          | 1.65      | 1.18–2.30    | < 0.001| 1.40  | 1.12–1.74 | < 0.001|
| High TG          |           |              |        |       |       |       |
| Model 1          | 1.36      | 1.01–1.84    | 0.04   | 0.90  | 0.74–1.11 | 0.34  |
| Model 2          | 1.35      | 1.00–1.82    | 0.05   | 0.91  | 0.74–1.11 | 0.38  |
| Model 3          | 1.28      | 0.92–1.77    | 0.13   | 0.88  | 0.71–1.09 | 0.27  |
| High FBS         |           |              |        |       |       |       |
| Model 1          | 2.53      | 1.41–4.51    | < 0.001| 1.06  | 0.66–1.71 | 0.78  |
| Model 2          | 2.56      | 1.43–4.57    | < 0.001| 1.06  | 0.66–1.71 | 0.78  |
| Model 3          | 1.89      | 0.96–3.70    | 0.06   | 1.10  | 0.66–1.81 | 0.70  |
### Discussion

The present study examined the association between plasma vitamin D status and cardio-metabolic risk factors in Iranian children and adolescents. Inverse association was observed between plasma vitamin D and the prevalence of MetS. In addition, plasma vitamin D was inversely related to the number of MetS components. High FBG, low HDL, high TG and abdominal obesity was higher in vitamin D deficient group compared to vitamin D sufficient and insufficient groups.

Many cross-sectional studies have well documented relationship between low serum 25(OH) D level and MetS in pediatric population. However, there is inadequate evidence to support a causal link (12). Study on 6311 US children and adolescents aged 6–18 years showed a potential adverse association between low serum 25(OH) D level and MetS components. However, the underlying mechanisms require further investigation (13).

Study on 3577 US adolescents showed a strong association between low serum 25(OH) D and hypertension, hyperglycemia, MetS, overweight and abdominal obesity (14). Serum vitamin D levels were inversely associated with FBS, insulin, total cholesterol and TG in the Korean pediatric population (15). Study on Iranian adolescents demonstrated that vitamin D levels associated with FBS (16). Study on 5867 US adolescents, aged 12–19 y showed inverse association between serum 25(OH)D and prevalence of MetS phenotype, WC, SBP, and HOMA-IR (17). Findings on 452 Caucasian children (304 overweight/obese and 148 healthy, normal weight) showed that low 25(OH) D levels were reversely associated with hypertension, total adiposity and MetS (18).

Findings of a systematic review that examine the association between vitamin D status and cardio-metabolic outcomes in generally healthy adults showed positive association between vitamin D insufficiency and disease risk. However, this association was not significant because of heterogeneity across the studies (19). Other systematic reviews showed opposite relationship between vitamin D and cardiovascular risks (20, 21). In a meta-analysis of 28 studies including 99745 participants, 43% reduction in cardio-metabolic disorders was associated with the highest levels of serum vitamin D (OR 0.57, 95% CI: 0.48–0.68) (22).

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| Vitamin D status | Deficient | Insufficient |
|------------------|-----------|--------------|
|                  | OR        | CI95% | p-value | OR  | CI95%  | p-value |
| 1                | In all model sufficient is reference group |

Model 1: crude model; Model 2: Adjusted for age, sex and living area; Model 3: additionally adjusted to SES, PA and ST

MetS = metabolic syndrome; SBP = systolic blood pressure; DBP = diastolic blood pressure; FBS = fasting blood sugar; TG = triglycerides; HDL = high density cholesterol; WC: Waist circumference
The dose-response meta-analysis on adult population reported opposite association between serum 25(OH) D and MetS. This association was shown in cross-sectional studies but not longitudinal studies (23).

Differences in age, sex, country of the studied subjects and mean serum vitamin D levels among participants lead to inconsistency in results (8).

The biological mechanisms by which vitamin D may affect the MetS have not been completely clarified and is complex. Insufficient serum 25(OH) D can change metabolite function and lead to perturbation of many cellular functions including endocrine pancreas. Vitamin D status can be associated with cardiometabolic risk factors because of immunomodulatory and anti-inflammatory properties of vitamin D. Vitamin D mediate down-regulation of the production of pro-inflammatory cytokines, stimulate insulin production and improve insulin sensitivity (24, 25). Vitamin D insufficiency increases C-reactive protein (CRP) level that has been linked to an increased risk of cardiovascular disease, obesity and MetS (26).

In the present study vitamin D deficiency associated with dyslipidemia. The main component of HDL is apolipoprotein A-1. Vitamin D is essential for maintaining adequate levels of apolipoprotein A-1. In addition, vitamin D need for increasing activity of lipoprotein lipase. So, serum vitamin D can be correlated with dyslipidemia (27).

Our results did not show any significant association between low serum vitamin D and blood pressure. Framingham Offspring Study (28) and study on NHANES III data (29) showed an inverse association between 25(OH) D and hypertension or prehypertension. The potential mechanism of these association may be correlated with antihypertensive properties of vitamin D include renoprotective effects, suppression of the renin–angiotensin–aldosterone system, direct effects on vascular cells, and effects on calcium metabolism. However, additional studies is needed before recommendation of widespread vitamin D supplementation in the primary prevention of hypertension especially in pediatric population (30).

Metabolic syndrome is influenced by many factors such as obesity. A review of human, animal, and cellular studies showed inconsistent findings that a low serum vitamin D level was correlated with the cause of obesity (31). The mechanisms of association between vitamin D deficiency and MetS in obese children should be elucidated in prospective studies and provide health strategies for decreasing the risk of obesity and metabolic syndrome among children and adolescents (32).

The prevalence of vitamin D deficiency among children and adolescents dependent on some factors including ethnicity, sex, physical inactivity, low sun exposure, increased TV watching, low milk intake and high soft drink intake that are also play a role in increased risk of MetS (32, 33). The association between low serum 25(OH) D and MetS is a concern in pediatric population because children and adolescents with MetS are at high risk of future cardiovascular disease and type II diabetes. More studies for assessment the effect of vitamin D supplementation on MetS components and prevention of cardiovascular disease is suggested (17).
The strengths of the present study are the large sample size. Some limitations are cross-sectional, lack of imaging procedures and observational design thus we are unable to investigate causality. In addition, some potential confounders might affect our findings.

**Conclusion**

The present study demonstrates inverse association between plasma vitamin D level and cardio-metabolic risk factors in children and adolescents. Additional research is essential to support a causal link and determine whether low serum vitamin D levels in childhood may affect the subsequent development of cardiovascular diseases during adulthood.

**List Of Abbreviations**

Metabolic syndrome (MetS), non-communicable disease (NCDs), 25-hydroxy vitamin D (25(OH)D), physical activity (PA), screen time (ST), socioeconomic status (SES), Body mass index (BMI), fasting blood glucose (FBG), high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG), coefficient of variation (CV)

**Declarations**

**Ethics approval and consent to participate**

Written informed consent and verbal assent were obtained from the parents and students after explaining the aim of study. The study protocol was approved by the Research and Ethics Council of National Institute for Medical Research Development (NIMAD) and it was in compliance with the declaration of Helsinki.

**Consent for publication**

Written consent was obtained from the parents and students or their legal guardians regarding the use of the acquired data for publication purposes.

**Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author in response to reasonable requests and with the permission of the patients, for authentication purposes.

**Competing interests**

The authors declare that they have no competing interests

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Author contributions

M.Q. designed the research analysis and edited the manuscript. M.H and H.E wrote, edited and reviewed the manuscript. G.S designed the research analysis and edited the manuscript. F.G. and S.T performed the research. M.K, N.M., M.E, H.A and M.J wrote, and edited the manuscript. R.H edited and reviewed the manuscript. All authors have read and approved the manuscript.

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References

1. Weihe P, Weihrach-Bluher S. Metabolic Syndrome in Children and Adolescents: Diagnostic Criteria, Therapeutic Options and Perspectives. Current obesity reports. 2019;8(4):472-9.

2. Taheri E, Saedisomeolia A, Djalali M, Qorbani M, Madani Civi M. The relationship between serum 25-hydroxy vitamin D concentration and obesity in type 2 diabetic patients and healthy subjects. Journal of diabetes and metabolic disorders. 2012;11(1):16.

3. Saedisomeolia A, Taheri E, Djalali M, Moghadam AM, Qorbani M. Association between serum level of vitamin D and lipid profiles in type 2 diabetic patients in Iran. Journal of diabetes and metabolic disorders. 2014;13(1):7.

4. Fu J, Han L, Zhao Y, Li G, Zhu Y, Li Y, et al. Vitamin D levels are associated with metabolic syndrome in adolescents and young adults: The BCAMS study. Clinical nutrition (Edinburgh, Scotland). 2019;38(5):2161-7.

5. Jari M, Qorbani M, Moafi M, Motlagh ME, Keikha M, Ardalan G, et al. Association of 25-hydroxy Vitamin D levels with indexes of general and abdominal obesity in Iranian adolescents: The CASPIAN-III study. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences. 2015;20(2):122-6.

6. Kim S, Lim J, Kye S, Joung H. Association between vitamin D status and metabolic syndrome risk among Korean population: based on the Korean National Health and Nutrition Examination Survey IV-2, 2008. Diabetes research and clinical practice. 2012;96(2):230-6.

7. Murni IK, Sulistyoningrum DC, Oktaria V. Association of vitamin D deficiency with cardiovascular disease risk in children: implications for the Asia Pacific Region. Asia Pacific journal of clinical nutrition. 2016;25(Suppl 1):S8-S19.
8. Kim YS, Hwang JH, Song MR. The Association Between Vitamin D Deficiency and Metabolic Syndrome in Korean Adolescents. Journal of pediatric nursing. 2018;38:e7-e11.

9. Motlagh ME, Ziaodini H, Qorbani M, Taheri M, Aminaei T, Goodarzi A, et al. Methodology and Early Findings of the Fifth Survey of Childhood and Adolescence Surveillance and Prevention of Adult Noncommunicable Disease: The CASPIAN-V Study. International journal of preventive medicine. 2017;8:4.

10. Kelishadi R, Majdzadeh R, Motlagh ME, Heshmat R, Aminaee T, Ardalan G, et al. Development and Evaluation of a Questionnaire for Assessment of Determinants of Weight Disorders among Children and Adolescents: The Caspian-IV Study. International journal of preventive medicine. 2012;3(10):699-705.

11. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. The American journal of clinical nutrition. 2006;84(1):18-28.

12. Alsharairi NA. Serum 25-hydroxyvitamin D is associated with obesity and metabolic parameters in US children. Public health nutrition. 2020;23(7):1223-5.

13. Fu Z, Xu C, Shu Y, Xie Z, Lu C, Mo X. Serum 25-hydroxyvitamin D is associated with obesity and metabolic parameters in US children. Public health nutrition. 2020;23(7):1214-22.

14. Reis JP, von Muhlen D, Miller ER, 3rd, Michos ED, Appel LJ. Vitamin D status and cardiometabolic risk factors in the United States adolescent population. Pediatrics. 2009;124(3):e371-9.

15. Ha CD, Cho JK, Lee SH, Kang HS. Serum vitamin D, physical activity, and metabolic risk factors in Korean children. Medicine and science in sports and exercise. 2013;45(1):102-8.

16. Rafraf M, Hasanabad SK, Jafarabadi MA. Vitamin D status and its relationship with metabolic syndrome risk factors among adolescent girls in Boukan, Iran. Public health nutrition. 2014;17(4):803-9.

17. 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. The American journal of clinical nutrition. 2011;94(1):225-33.

18. 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. European journal of endocrinology. 2011;165(4):603-11.

19. Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, et al. Systematic review: Vitamin D and cardiometabolic outcomes. Annals of internal medicine. 2010;152(5):307-14.

20. Grandi NC, Breitling LP, Brenner H. Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. Preventive medicine. 2010;51(3-4):228-33.

21. Wang L, Manson JE, Song Y, Sesso HD. Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. Annals of internal medicine. 2010;152(5):315-23.
22. Parker J, Hashmi O, Dutton D, Mavrodaris A, Stranges S, Kandala NB, et al. Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. Maturitas. 2010;65(3):225-36.

23. Ju SY, Jeong HS, Kim DH. Blood vitamin D status and metabolic syndrome in the general adult population: a dose-response meta-analysis. The Journal of clinical endocrinology and metabolism. 2014;99(3):1053-63.

24. Karkeni E, Bonnet L, Marcotorchino J, Tourniaire F, Astier J, Ye J, et al. Vitamin D limits inflammation-linked microRNA expression in adipocytes in vitro and in vivo: A new mechanism for the regulation of inflammation by vitamin D. Epigenetics. 2018;13(2):156-62.

25. Cianferotti L, Bertoldo F, Bischoff-Ferrari HA, Bruyere O, Cooper C, Cutolo M, et al. Vitamin D supplementation in the prevention and management of major chronic diseases not related to mineral homeostasis in adults: research for evidence and a scientific statement from the European society for clinical and economic aspects of osteoporosis and osteoarthritis (ESCEO). Endocrine. 2017;56(2):245-61.

26. Li Q, Dai Z, Cao Y, Wang L. Association of C-reactive protein and vitamin D deficiency with cardiovascular disease: A nationwide cross-sectional study from National Health and Nutrition Examination Survey 2007 to 2008. Clinical cardiology. 2019;42(7):663-9.

27. Schwetz V, Scharnagl H, Trummer C, Stojakovic T, Pandis M, Grubler MR, et al. Vitamin D supplementation and lipoprotein metabolism: A randomized controlled trial. Journal of clinical lipidology. 2018;12(3):588-96 e4.

28. 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(4):503-11.

29. Zhao G, Ford ES, Li C, Kris-Etherton PM, Etherton TD, Balluz LS. Independent associations of serum concentrations of 25-hydroxyvitamin D and parathyroid hormone with blood pressure among US adults. Journal of hypertension. 2010;28(9):1821-8.

30. Vaidya A, Forman JP. Vitamin D and hypertension: current evidence and future directions. Hypertension (Dallas, Tex : 1979). 2010;56(5):774-9.

31. Salo A, Logomarsino JV. Relationship of vitamin D status and cardiometabolic risk factors in children and adolescents. Pediatric endocrinology reviews : PER. 2011;9(1):456-62.

32. Alaklabi AM, Alsharairi NA. Current Evidence on Vitamin D Deficiency and Metabolic Syndrome in Obese Children: What Does the Evidence from Saudi Arabia Tell Us? Children (Basel, Switzerland). 2018;5(1).

33. Adikaram SGS, Samaranayake D, Atappatu N, Kendaragama K, Senevirathne JTN, Wickramasinghe VP. Prevalence of vitamin D deficiency and its association with metabolic derangements among children with obesity. BMC pediatrics. 2019;19(1):186.