Clinical Nutrition 38 (2019) 2161–2167

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Vitamin D levels are associated with metabolic syndrome in adolescents and young adults: The BCAMS study

Junling Fu [a, 1], Lanwen Han [b, 1], Yanglu Zhao [c], Ge Li [a], Yingna Zhu [b], Yu Li [a], Ming Li [a, *], Shan Gao [b, **], Steven M. Willi [d]

[a] Department of Endocrinology, NHC Key Laboratory of Endocrinology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China
[b] Department of Endocrinology, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100043, China
[c] Epidemiology Department, Fielding School of Public Health, University of California Los Angeles, Los Angeles 90024, USA
[d] Division of Endocrinology, The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

ARTICLE INFO

Article history:
Received 13 March 2018
Accepted 30 August 2018

Keywords:
Vitamin D
Metabolic syndrome
Cardiometabolic risk factors
Adolescents
Young adults

SUMMARY

Background and aims: The relationship between vitamin D deficiency and metabolic syndrome (MS) remains controversial with relatively sparse data among youth. Therefore, we attempted to explicate the association of 25-hydroxyvitamin D [25(OH)D] levels with MS in Chinese adolescents and young adults.
Methods: A cohort of 559 subjects at elevated risk of MS were recruited at 14–28 years of age as a follow-up to the Beijing Child and Adolescent Metabolic Syndrome Study. Subjects underwent clinical assessment including a 2h-oral glucose tolerance test. The concentrations of 25(OH)D, glucose, insulin and lipids were determined. MS was defined using the 2009 harmonized definition.
Results: The prevalence of vitamin D deficiency (< 20 ng/ml) was 78.3%. After adjusting for age, gender and season, 25(OH)D concentrations were negatively correlated with neck circumference, percent body fat, LDL cholesterol, fasting and 2h-glucose levels (all $P < 0.05$). 25(OH)D levels were significantly lower in participants with obesity, high triglycerides, type 2 diabetes, or MS, compared to their respective counterparts (all $P < 0.05$). After adjusting for potential confounders (e.g., body mass index), participants in the lowest 25(OH)D tertile were 2.5 times more likely to exhibit MS than were those in the highest tertile (Odds Ratio: 2.48; 95% CI: 1.13–5.45, $P < 0.05$).
Conclusions: Vitamin D deficiency was very common in this young Chinese population at risk for MS. Given this association between low vitamin D levels and MS, the role of vitamin D supplementation in Chinese youths needs further examination, particular in those at risk for MS.

1. Introduction

The metabolic syndrome (MS) is characterized by a constellation of cardiovascular risk factors, including obesity, impaired glucose regulation, elevated triglycerides, decreased high-density lipoprotein cholesterol (HDL-C), and elevated blood pressure [1]. In recent decades, MS has emerged as a global public health problem, as well as a clinical dilemma [1]. Evidence of an association between vitamin D deficiency and the MS, and its individual components (obesity, hyperglycemia, dyslipidemia) has been mounting in recent years [2–4].

Vitamin D plays a pivotal role in calcium and phosphorus homeostasis. Studies have uncovered various extra-skeletal effects of vitamin D on cardiac, endothelial, and smooth muscle functions; suggesting an important role in cardiovascular health [5]. Vitamin D deficiency, usually defined as serum 25-hydroxyvitamin D [25(OH)D] concentrations below 20 ng/ml, is highly prevalent throughout the world [2]. Over 50% of the population of Asia is vitamin D deficient [6] and nearly 75% of the Middle East is deficient or insufficient [7]. Due to increased sedentary lifestyle, it has been suggested that vitamin D deficiency is more common in young populations, even among those with abundant sun exposure [2].

* Corresponding author. Department of Endocrinology, NHC Key Laboratory of Endocrinology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China.
** Corresponding author. Department of Endocrinology, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100043, China.
E-mail addresses: liming@pumch.cn (M. Li), gaoshanmw@163.com (S. Gao).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.clnu.2018.08.039
0261-5614/

Nonetheless, the relationship between vitamin D deficiency and obesity, diabetes, and MS remains controversial, as some studies reveal an association [2–4,8,9], while others do not [10,11]. Given that few studies have focused on younger populations, and that their findings remain inconsistent [10,11], we sought to investigate the relationship between 25(OH)D levels and MS, as well as its individual components, among Chinese adolescents and young adults at risk for MS.

2. Subjects and methods

2.1. Subjects and ethics

A cross-sectional sample was obtained from the Beijing Child and Adolescent Metabolic Syndrome (BCAMS) study cohort. The BCAMS is as an ongoing prospective study of obesity and related cardiometabolic abnormalities in a representative sample of Beijing school-aged children which has been described in detail elsewhere [12], and was registered at www.clinicaltrails.gov (NCT03421444). The baseline survey (n = 19,593, 6 to-18 years old, 50 percent male) was conducted in 2004. Within this cohort, 4,500 participants were identified to be at elevated risk for cardiovascular disease due to the presence of one or more of the following: being overweight [body mass index (BMI) > 85th percentile], blood pressure $\geq 90^{th}$ percentile, total cholesterol $\geq$ 5.2 mmol/L, triglycerides $\geq$ 1.7 mmol/L, or fasting glucose $\geq$ 5.6 mmol/L based on a capillary blood test. The present study is part of a 10-year follow-up study beginning in 2012, wherein a total of 559 adolescents and young adults aged 14–28 years were recruited consecutively to undergo medical examination in Beijing Chaoyang Hospital. The present study was approved by the Ethics Committee at Beijing Chaoyang Hospital for approval consistency. Informed consent was obtained from all participants and/or their parents/guardians.

2.2. Clinical measurements

Subjects' height, weight, neck circumference, waist circumference and body fat percentage were measured by trained recruiters. Weight (nearest 0.1 kg), height (nearest 0.1 cm) and body fat percentage were measured using a TANITA Body Composition Analyzer (ModelTBF-300A). Neck circumference was measured at the midway point of the neck between mid-cervical spine and mid-anterior neck to 0.5 cm just below the laryngeal prominence. Waist circumference was measured exact at midway between the lowest rib and the peak of the iliac crest. Measurements of systolic and diastolic blood pressure (SBP and DBP) were performed with a standard method. BMI was calculated as weight (kg)/height $(m)^2$. Lifestyle factors (physical activity, sunscreen use, alcohol consumption, and cigarette smoking) were obtained by standardized questionnaires.

2.3. Biochemical measurements

Venous blood samples were taken in the morning after an overnight ($\geq$10h) fast. Each participant underwent a 2h oral glucose tolerance test using 75 g glucose load, and blood samples were collected at 0h, 0.5h, and 2h for measurements of glucose and insulin levels. The concentrations of glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), were assayed using the Hitachi 7060 C automatic biochemistry analysis system. HbA1c was measured using the TOSOH G7 automatic analysis system with high pressure liquid chromatography. Serum 25(OH)D levels were measured by electro-chemiluminescence immunoassay. The intra-assay and inter-assay coefficient of variations (CVs) were < 7.5% and < 6.8%, respectively. Insulin levels were measured by an in-house monoclonal antibody based ELISA [12], which was developed in the Key Laboratory of Endocrinology, Peking Union Medical College Hospital. The assay had no cross-reactivity to proinsulin, and the inter-assay CV was <9.0%. All the measurements of biochemicals except for insulin were performed in the biochemistry laboratory of Beijing Chaoyang Hospital.

2.4. Definitions and diagnostic criteria

The diagnosis of prediabetes, including impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), and T2DM were based on current guidelines of the American Diabetes Association [13]. IFG: fasting blood glucose (FBG) level = 5.6–6.9 mmol/L; IGT: 2h-blood glucose (2h-BG) level = 7.8–11.0 mmol/L; T2DM: FBG $\geq$ 7.0 mmol/L or 2h-BG $\geq$ 11.1 mmol/L.

Insulin resistance was assessed by following indexes: 1) the homeostasis model assessment of insulin resistance (HOMA-IR) = fasting insulin (FINS) (mU/L) $\times$ FBG (mmol/L)/22.5; 2) the Matsuda insulin sensitive index (ISIM) = 10,000/(FBG $\times$ FINS) $\times$ (mean serum glucose $\times$ mean serum insulin) [14]. Beta-cell function was estimated by the insulinogenic index (IGI = ΔIns30/ΔGluc30), and the oral disposition index (DIO). The DIO was the product of insulin sensitivity (ISIM) and insulin secretion (IGI), touted to be a better measure of beta-cell function [15].

Vitamin D deficiency is defined as having a 25(OH)D level of < 20 ng/ml [2], and severe deficiency as 25(OH)D < 11 ng/ml [16].

MS was diagnosed according to the harmonized criteria when at least three out of the following five criteria were met [12,17]:1) central obesity: waist circumference for boys $\geq$ 90 cm or for girls $\geq$ 80 cm; 2) SBP $\geq$ 130 mmHg and/or DBP $\geq$ 85 mmHg; 3) HDL-C < 1.03 mmol/L for males or < 1.29 mmol/L for females; 4) triglycerides $\geq$ 1.70 mmol/L; 5) FBG $\geq$ 5.6 mmol/L and/or 2h-BG $\geq$ 7.8 mmol/L.

2.5. Statistical analyses

All analysis was performed using SPSS (version 21.0). Data exhibiting skewed distributions were logarithmically transformed prior to analysis. Data were presented as mean $\pm$ standard deviation (SD) for continuous variables, or median and inter-quartile range (IQR) for skew distributions, and counts (percentages) for categorical variables. Comparisons of demographic characteristics, clinical features and laboratory results between subjects with MS and without MS were performed using the Student's t-test or general linear model with adjustment of age and gender. Associations between 25(OH)D and continuous metabolic parameters were evaluated by Partial Correlation Analysis. General Linear Model was applied to explore the correlation between 25(OH)D and various metabolic abnormalities after adjusting for confounders, and expressed as mean $\pm$ SEM. Multiple logistic regression models were used for MS in relation to the tertile of 25(OH)D, and odds ratios (ORs) and 95% CIs were calculated after adjusting for potential confounders. In the first step, we built model 1 to adjust for age, gender and season; in subsequently, model 2, smoking status, alcohol consumption, physical activity were additionally adjusted; in model 3, BMI was further adjusted. A P value < 0.05 (two-sided) was regarded as statistically significant.

3. Results

Laboratory and demographic characteristics of the study participants were presented in Table 1. A total of 559 adolescents and young adults (52.6% male), ranging in age from 14 to 28 years

Table 1
General characteristics of study population.

Variables	No MS	MS	P-Value
N, (Male %)	498 (49.2%)	61 (80.3%)	< **0.001**
Age (years)	20.1 ± 2.9	20.6 ± 2.8	0.235
Smoking (%)	18.5	27.9	0.080
Alcohol consumption (%)	47.8	55.7	0.241
Physical activity (hours/week)	3.1 ± 3.8	2.8 ± 3.4	0.567
Sunscreen use (%)	21.1	16.4	0.412
Adjusted for age and gender			
Obese-related traits			
BMI (kg/m^2)	25.0 ± 0.23	32.0 ± 0.67	< **0.001**
waist circumference (cm)	83.4 ± 0.56	99.9 ± 1.63	< **0.001**
Neck circumference (cm)	29.1 ± 0.4	40.1 ± 1.1	< **0.001**
Percent body fat (%)	29.3 ± 0.42	39.8 ± 1.23	< **0.001**
Blood pressures (mmHg)			
Systolic	113 ± 0.5	131 ± 1.5	< **0.001**
Diastolic	72 ± 0.4	88 ± 1.2	< **0.001**
Lipids (mmol/L)			
Total cholesterol	4.28 ± 0.04	4.91 ± 0.12	< **0.001**
Triglycerides	0.85 (0.65–1.15)	1.98 (1.72–2.60)	< **0.001**
LDL-C	2.46 ± 0.03	3.11 ± 0.10	< **0.001**
HDL-C	1.46 ± 0.01	1.19 ± 0.04	< **0.001**
Glucose and insulin related traits			
Glucose 0h (mmol/L)	4.86 ± 0.03	5.37 ± 0.09	< **0.001**
Glucose 0.5h (mmol/L)	7.82 ± 0.07	8.96 ± 0.19	< **0.001**
Glucose 2h (mmol/L)	5.85 ± 0.08	7.79 ± 0.23	< **0.001**
HbA1c (%)	5.34 ± 0.02	5.73 ± 0.06	< **0.001**
Insulin 0h (mU/L)	6.25 (3.77–10.40)	15.10 (11.32–22.16)	< **0.001**
Insulin 0.5h (mU/L)	65.61 (45.65–96.60)	86.26 (63.19–143.66)	< **0.001**
Insulin 2h (mU/L)	35.61 (22.02–53.77)	71.62 (42.38–101.37)	< **0.001**
HOMA-IR	1.34 (0.81–2.29)	3.40 (2.44–5.40)	< **0.001**
HOMA-B	96.70 (60.82–158.97)	187.87 (132.54–278.75)	<**0.001**
ISIM	6.48 (4.38–9.78)	3.29 (2.07–4.01)	< **0.001**
IGI	1.14 (0.78–1.84)	1.25 (0.80–2.02)	0.281
DIO	7.91 (5.08–12.28)	3.93 (2.42–7.48)	< **0.001**
25-hydroxyvitamin D (ng/ml)	14.21 (11.08–19.09)	12.49 (10.34–18.28)	**0.005**
Vitamin D deficiency (%, <20 ng/ml)	77.8%	80.7%	0.539
Severe deficiency (%, <11 ng/ml)	24.7%	28.1%	0.366

Data were expressed as: % for categorical variables, mean ± SEM for normally distributed variables, median (IQR) for Skewed distributions. *P* values are from general linear model (GLM) after adjustment for age and gender. Vitamin D was additionally adjusted for visiting season.
Values in bold are significant at $P < 0.05$.
Abbreviations: MS, metabolic syndrome; BMI, body mass index; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; HOMA-B, homeostasis model assessment for beta cell function; ISIM, Matsuda insulin sensitivity index; IGI, insulinogenesis index; DIO, oral disposition index.

(mean 20.2 ± 2.9 years) from the BCAMS study were included in this analysis. Overall, the mean values of 25(OH)D levels was 15.2 ± 6.0 ng/ml, which was even more tenuous in our young adults (> 18 years, 14.9 ± 5.9 ng/ml) than in the paediatric subjects (≤ 18 years old, 16.1 ± 6.1 ng/ml). The percentage of vitamin D deficiency (< 20 ng/ml) was 78.3%, which was even higher in female (88.9%) compared to male (68.7%).

Over 11% of participants met the criteria for MS. In addition to the parameters of the MS components, participants with MS had significantly higher BMI, neck circumference, percent body fat, total cholesterol, LDL-C, HbA1c and HOMA-IR levels, as well as lower ISIM and DIO relative to participants without MS (all $P < 0.01$). Additionally, compared with participants without MS, 25(OH)D levels were significantly lower (14.60 ng/ml vs. 15.30 ng/ml) in those with MS. While the prevalence of vitamin D deficiency (< 20 ng/ml) (80.7% vs. 77.8%) and severe deficiency (< 11 ng/ml) (28.1% vs. 24.7%) appeared to be higher in participants with MS than those without MS, these differences were not statistically significant.

The partial correlations coefficients between 25(OH)D and metabolic parameters are shown in Table 2. After adjustment for age, gender and season, 25(OH)D level was significantly negatively correlated with percent body fat ($P = 0.043$), neck circumference ($P = 0.001$), LDL-C ($P = 0.039$), FBG ($P = 0.033$), and OGTT 2h-BG ($P = 0.003$). Meanwhile, 25(OH)D level was marginally negatively correlated with HbA1c ($P = 0.054$). However, there was no statistically significant association between vitamin D levels and ISIM, IGI or DIO. After further adjustment for BMI, vitamin D levels showed a significant inverse relationship with 0.5h-insulin levels ($P = 0.048$) and a marginal association with IGI, while the significant association with glucose levels persisted. In addition, 25(OH)D was significantly associated with increased level of physical activity ($r = 0.10$, $P = 0.028$) with adjustment for age, gender, visiting season and BMI.

Comparisons of 25(OH)D levels in relation to various metabolic abnormalities after adjusting for age, gender, and visiting season are shown in Fig. 1. Participants with obesity or high triglycerides groups showed lower 25(OH)D levels than their counterparts, respectively ($P < 0.05$). With respect to glucose status, 25(OH)D was lower in the T2DM group compared with the NGT ($P = 0.004$) or IFG/IGT ($P = 0.008$) groups respectively. Moreover, 25(OH)D levels were significantly lower in participants with more than 3 MS components, compared with those with either no MS component ($P = 0.011$) or 1–2 components ($P = 0.015$). Notably, even after adjusting for BMI (data not shown), the difference among glucose status and MS groups remained significant ($P < 0.05$), while the difference among triglycerides groups was attenuated ($P > 0.05$).

In the analysis with multiple logistic regression, shown in Table 3, lower 25(OH)D levels were correlated with higher odds of having MS. In comparison with participants in the highest tertile of

Table 2
Partial correlations between 25-hydroxyvitamin D and metabolic traits.

Variables	Adjusted 1		Adjusted 1 + BMI	
	r	P	r	P
Adiposity-related traits				
BMI (kg/m^2)	−0.073	0.092	/	/
Waist circumference (cm)	−0.059	0.176	0.058	0.186
Neck circumference (cm)	−0.140	**0.001**	−0.131	**0.003**
Percent body fat	−0.088	**0.043**	−0.058	0.186
Blood pressures (mmHg)				
Systolic	−0.061	0.160	−0.028	0.516
Diastolic	−0.048	0.270	−0.017	0.695
Lipids (mmol/L)				
Total cholesterol	−0.021	0.638	−0.006	0.882
Triglycerides[a]	−0.051	0.238	−0.026	0.556
LDL-C	−0.090	**0.039**	−0.069	0.111
HDL-C	0.060	0.166	0.036	0.405
Glucose and insulin-related traits				
Glucose-0h (mmol/L)	−0.093	**0.033**	−0.089	**0.041**
Glucose-0.5h (mmol/L)	−0.045	0.309	−0.039	0.381
Glucose-2h (mmol/L)	−0.129	**0.003**	−0.123	**0.005**
HbA1c (%)	−0.084	0.054	−0.078	0.076
Insulin-0h (mU/L)[a]	−0.066	0.134	−0.026	0.554
Insulin-0.5h ((mU/L)[a]	0.058	0.193	0.088	**0.048**
Insulin-2h ((mU/L)[a]	−0.040	0.368	−0.015	0.734
HOMA-IR[a]	−0.076	0.083	−0.038	0.389
HOMA-B[a]	−0.043	0.360	0.003	0.938
ISIM[a]	0.020	0.623	−0.024	0.596
IGI[a]	0.058	0.193	0.077	0.084
DIO[a]	0.071	0.116	0.056	0.217

Notes: Adjusted 1 was analyzed after controlling for gender, age and visiting season; r: partial correlation coefficients.
Values in bold are significant at $P < 0.05$.
Abbreviations: BMI, body mass index; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; HOMA-B, homeostasis model assessment for beta cell function; ISIM, Matsuda insulin sensitivity index; IGI, insulinogenesis index; DIO, oral disposition index.
[a] Skewed distributions including 25-hydroxyvitamin D were logarithmically transformed.

25(OH)D levels (> 17.1 ng/ml), participants in the lowest tertile of 25(OH)D levels (< 11.9 ng/ml) were 2.8 times more likely to have MS (OR: 2.76; 95% CI: 1.39–5.50; $P = 0.005$). The association did not significantly change (OR: 2.48, 95% CI: 1.13–5.45; $P = 0.022$) after adjusting for lifestyle factors and BMI.

4. Discussion

In this cross-sectional sample of Chinese youths with high risk for MS, we found that vitamin D deficiency (< 20 ng/ml) was very common. Furthermore, we demonstrate that 25(OH)D levels are significantly lower in participants with obesity, elevated triglycerides, T2DM and MS, compared to their respective counterparts. Moreover, participants in the lowest vs. highest tertile of 25(OH)D were nearly 2.5 times more likely to exhibit MS.

Vitamin D deficiency has emerged as a worldwide public health concern [7]. For example, the prevalence of vitamin D deficiency was over 53% among the 15,000 children and adolescent participants from the 2010–2012 Chinese National Nutrition and Health Survey (CNNHS), 50% for males and 57% for females [18]. In a 2007–2010 National Survey of the US population, the prevalence of vitamin D deficiency in adolescents aged 12–19 years was 25% [19], while in the 2008–2011 Korean National Health and Nutrition Examination Survey, 73.3% of the participants were vitamin D deficient [20]. While vitamin D deficiency appears to be more common among Asian youth, with a slight female predominance, there is less of a disparity than in the Middle East. In a study of Turkish adolescents, vitamin D deficiency in female students was nearly twice as common as in males [21]. Similarly, a study of 216 girls aged 14–17 years from Iran showed a 96% prevalence of vitamin D deficiency [22]. In the present study, the prevalence of vitamin D deficiency was 78% in the overall population and as high as 89% in females. The higher prevalence in our study (compared with CNNHS 2010–2012) is likely to be due to the relative risk for MS and the reduced sunlight exposure of our subjects, who were all from Beijing, the northernmost major city in China. The higher prevalence in females from different countries may be attributed to reduced sunlight exposure from the use of sunscreen or shrouding due to religious customs. Therefore, vitamin D supplementation or increased sunlight exposure should be recommended in young populations, especially females.

Several studies have demonstrated that obesity is associated with vitamin D deficiency [2,8], while the CNNHS failed to demonstrate a significant difference between 25(OH)D levels in different BMI strata [18]. Consistent with several previous studies [2,8,23], our data established a negative correlation between vitamin D levels and several measures of adiposity, including neck circumference and percent body fat, establishing a relationship between low vitamin D status and obesity, even after adjustment for age and gender. Several pathogenic mechanisms have been implicated in the association between vitamin D deficiency and obesity. Experimental evidence suggests that vitamin D deficiency may augment adipogenesis by contributing to excess differentiation of preadipocytes to adipocytes [24], whereas a number of clinical investigations have suggested that obesity may in turn result in low vitamin D status [8,25]. The negative correlation between body fat and 25(OH)D has also been attributed to decreased bioavailability of vitamin D_3 from cutaneous and dietary sources due to vitamin D deposition in expanded body fat compartments [26]. Furthermore, decreased outdoor activity in obese subjects, resulting in reduced sunlight exposure and decreased cutaneous vitamin D synthesis has been considered another factor [27].

The association between vitamin D and glucose homeostasis remains somewhat controversial [28]. A recent study in youth with diabetes showed that while vitamin D deficiency is rather common, it is no more so than in youth without diabetes [29]. This has led to speculation that vitamin D's association with obesity is primary, and may confound the perceived relationship between decreased vitamin D levels and related metabolic conditions. However, in our study, we found vitamin D concentrations were significantly lower among those with T2DM, and negatively correlated with both fasting and 2-h OGTT glucose levels, irrespective of adiposity. Our findings are consistent with several previous studies in young populations. A study in 1,745 French-Canadian children and adolescents showed a modest but significant negative association between fasting glucose and vitamin D levels after adjusting for BMI [30]. Similarly, a study of 216 Iran adolescent girls showed that after adjusting for BMI, exercise and energy intake, vitamin D levels were inversely correlated to fasting glucose [22]. The precise mechanism(s) linking vitamin D deficiency with hyperglycemia are not completely understood. Studies have shown that vitamin D possesses anti-inflammatory properties [31,32], which may benefit islet-cell function and insulin sensitivity [33]. Moreover, several clinical studies have reported that supplementation with vitamin D can augment insulin release, improve insulin sensitivity, and reduce inflammation in patients with T2DM [34–36]. While other studies have failed to demonstrate the ability of vitamin D supplementation to improve β cell function, insulin sensitivity or glucose homeostasis [37,38]. These inconsistent results may be largely explained by the fact that these studies may not have been large enough, of long enough duration or conducted in appropriate subject populations to adequately elucidate the impact of vitamin D supplementation on β cell

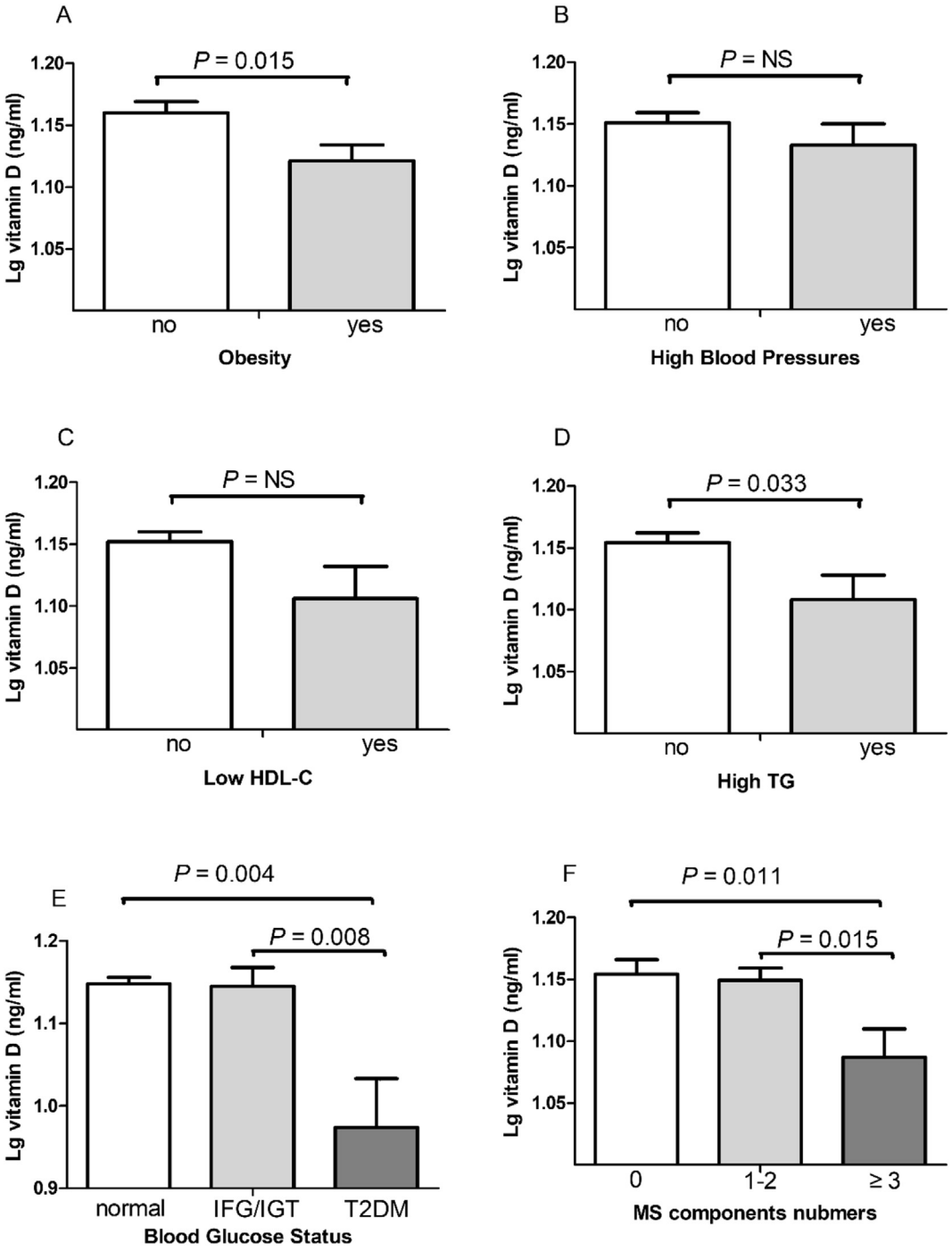

Fig. 1. Comparison of vitamin D levels in relation to various metabolic abnormalities. 25-hydroxyvitamin D levels were logarithmically (lg-) transformed. Data were analyzed using a multiple regression model after adjusting for gender, age and visiting season, and expressed as mean ± SEM. Abbreviations: MS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; T2DM: type 2 diabetes mellitus; NS: nonsignificant.

function and insulin sensitivity. We observed no significant correlation between vitamin D levels and various indices of insulin sensitivity other than a marginal association with HOMA-IR. However, the relatively strong relationship between vitamin D and fasting and 2 h OGTT glucose (which remains even after adjustment for BMI), suggests that it is dysglycemia rather than insulin resistance which is associated with low vitamin D levels. Larger, prospectively designed studies in adolescents and young adults will be needed to confirm these findings.

The present study demonstrated negative correlations between vitamin D levels and LDL-C and triglycerides, which were attenuated after adjustment for BMI. Previous studies have described this inverse relationship between vitamin D and hyperlipidemia, even after adjusting for potential confounders, such as BMI [39,40]. A systematic review of the pediatric literature found that 15 such studies have evaluated the relationship between vitamin D status and dyslipidemia [2]. No less than 10 of these studies concluded that low vitamin D levels might be associated with dyslipidemia;

Table 3
Odds ratio (95% confidence interval) for metabolic syndrome according to 25-hydroxyvitamin D levels.

	25-hydroxyvitamin D			*P* for trend
	T1: <11.9 ng/ml (n = 186)	T2: 11.9 to <17.1 ng/ml (n = 187)	T3: ≥17.1 ng/ml (n = 186)	
Model 1	2.76 (1.39–5.50)	1.53 (0.75–3.12)	1[a]	**0.004**
Model 2	2.66 (1.33–5.31)	1.52 (0.74–3.10)	1[a]	**0.005**
Model 3	2.48 (1.13–5.45)	1.01 (0.44–2.29)	1[a]	**0.022**

Notes: Tertile values of 25-hydroxyvitamin D are expressed as T1, T2, and T3. Model 1 was adjusted for age, gender and season.
Values in bold are significant at $P < 0.05$.
Model 2 was adjusted as for model 1 plus smoking status, alcohol intake, and physical activities.
Model 3 was adjusted as for model 2 plus BMI.
[a] Referent category.

including high levels of triglycerides and LDL-C, as well as low HDL-C. In addition, an interventional study exploring the impact of vitamin D supplementation on serum lipids found that triglyceride levels decreased significantly after weekly supplementation with 300,000 IU of vitamin D for 12 weeks [41]. However, numerous other studies, consistent with our findings, have failed to demonstrate an association between vitamin D and dyslipidemia after adjustment for BMI [4,42,43]. Additional studies will be necessary to elucidate a specific mechanism.

Limited studies, with inconsistent results, have explored the relationship between vitamin D status and individual components of the MS [10,11,23,44,45] as we have done here. A recent study including 2,880 Korean children and adolescents aged 10–18 years found that the prevalence of MS was significantly higher in subjects with vitamin D deficiency than in those with vitamin D levels above 21 ng/ml [44]. Reiset al. also found that the incidence of MS among US adolescents decreased as serum 25(OH)D increased and that participants without MS had higher levels of vitamin D than those exhibiting MS [45]. Similarly, compared with subjects with MS, vitamin D levels were significantly higher in subjects without MS in our study. Meanwhile, in accordance with prior studies [44,45], our data demonstrated that participants in the lowest vs. highest tertile of 25(OH)D levels (i.e. < 12 ng/ml vs. > 17 ng/ml) were 2.8 times more likely to exhibit MS. The association did not change even after adjusting for potential confounders such as physical activity, gender and BMI. In contrast, studies in Asian adults fail to reveal an association between vitamin D status and MS [10,11]. Kim et al. [10] reported the overall risk of MS was not related to vitamin D levels in South Korean adults. Similarly, a study of 441 Asian Indians with a mean age of 39.7 years found that vitamin D deficiency was not associated with MS in either sex [11]. These inconsistent findings may result from differences in age, gender, race, diet, and skin pigmentation in the various study populations. The relationship between vitamin D levels and MS, and its underling mechanism(s), await further elucidation from well-designed, large-scale prospective studies.

To our knowledge, this is the first study to explicate the relationship between vitamin D levels and MS in a well-characterized young Chinese cohort. The inclusion of data regarding seasonal and lifestyle factors as potential confounders, as well as the large sample size lend considerable credence to our results. However, this study has several limitations. These results may not be readily generalized to other races or age groups, since our sample represented northern Chinese adolescents and young adults with an increased high risk of MS. Further large, prospective studies in youths of different races will be needed to clarify the relationship between vitamin D status and cardiometabolic risk. In addition, although most young people in China do not receive supplementation with vitamin D, we did not obtain data on subjects' vitamin D intake from diet or supplements.

In summary, our study demonstrated a very high prevalence of vitamin D deficiency among youth at increased risk for MS, as well as an inverse relationship between vitamin D levels and various components of the MS. Our finding suggested that effective sun exposure and vitamin D supplementation should be encouraged in young people, particular those with increased cardiometabolic risk.

Author contributions

Junling Fu and Lanwen Han contributed to the data collection and drafted the manuscript; Yanglu Zhao contributed to the data analysis and revised the manuscript; Ge Li, Yingna Zhu and Yu Li contributed to follow-up study and data collection; Steven. M. Willi contributed to the data interpretation and reviewed/edited the manuscript. Ming Li was responsible for the concept, design of the study, and contributed to the data analysis and interpretation, and revised the manuscript. Shan Gao was responsible for the BCAMS follow-up study, and contributed to acquisition and interpretation of the data, and revised the manuscript.

Conflicts of interest

The authors declared there was no conflict of interests.

Acknowledgments

Fundings: National Key R&D Program of China, 2016YFC1304801; Beijing Municipal Science and Technology Commission, D111100000611001 and D111100000611002; Beijing Natural Science Foundation, 7172169; National Key Program of Clinical Science of China, WBYZ2011-873; Novo Nordisk Union Diabetes Research Talent Fund, 2011A002; Beijing Science & Technology Star Program, 2004A027; and Jingxi Scientific Program of Beijing Chaoyang Hospital, JXPY201606.

References

[1] Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014;2014:943162.
[2] Murni IK, Sulistyoningrum DC, Oktaria V. Association of vitamin D deficiency with cardiovascular disease risk in children: implications for the Asia Pacific Region. Asia Pac J Clin Nutr 2016;25:S8–19.
[3] Bener A, Al-Hamaq AO, Kurtulus EM, Abdullatef WK, Zirie M. The role of vitamin D, obesity and physical exercise in regulation of glycemia in Type 2 Diabetes Mellitus patients. Diabetes Metab Syndr 2016;10:198–204.
[4] Gannage-Yared MH, Chedid R, Khalife S, Azzi E, Zoghbi F, Halaby G. Vitamin D in relation to metabolic risk factors, insulin sensitivity and adiponectin in a young Middle-Eastern population. Eur J Endocrinol 2009;160:965–71.
[5] Wimalawansa SJ. Non-musculoskeletal benefits of vitamin D. J Steroid Biochem Mol Biol 2018;175:60–81.
[6] Eggemoen AR, Knutsen KV, Dalen I, Jenum AK. Vitamin D status in recently arrived immigrants from Africa and Asia: a cross-sectional study from Norway of children, adolescents and adults. BMJ Open 2013;3, e003293.
[7] van Schoor NM, Lips P. Worldwide vitamin D status. Best Pract Res Clin Endocrinol Metabol 2011;25:671–80.
[8] Turer CB, Lin H, Flores G. Prevalence of vitamin D deficiency among overweight and obese US children. Pediatrics 2013;131:e152–61.

[9] Khan H, Kunutsor S, Franco OH, Chowdhury R. Vitamin D, type 2 diabetes and other metabolic outcomes: a systematic review and meta-analysis of prospective studies. Proc Nutr Soc 2013;72:89–97.
[10] 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 Res Clin Pract 2012;96:230–6.
[11] Majumdar V, Nagaraja D, Christopher R. Vitamin D status and metabolic syndrome in Asian Indians. Int J Obes 2011;35:1131–4.
[12] Li M, Fisette A, Zhao XY, Deng JY, Mi J, Cianflone K. Serum resistin correlates with central obesity but weakly with insulin resistance in Chinese children and adolescents. Int J Obes 2009;33:424–39.
[13] Standards of medical care in diabetes–2013. Diabetes Care 2013;36(Suppl. 1): S11–66.
[14] Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462–70.
[15] Billings LK, Jablonski KA, Ackerman RJ, Taylor A, Fanelli RR, McAteer JB, et al. The influence of rare genetic variation in SLC30A8 on diabetes incidence and beta-cell function. J Clin Endocrinol Metabol 2014;99:E926–30.
[16] Gonzalez-Gross M, Valtuena J, Breidenassel C, Moreno LA, Ferrari M, Kersting M, et al. Vitamin D status among adolescents in Europe: the healthy lifestyle in Europe by nutrition in adolescence study. Br J Nutr 2012;107: 755–64.
[17] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation 2009;120:1640–5.
[18] Hu Y, Chen J, Wang R, Li M, Yun C, Li W, et al. Vitamin D nutritional status and its related factors for Chinese children and adolescents in 2010-2012. Nutrients 2017;9.
[19] Schleicher RL, Sternberg MR, Looker AC, Yetley EA, Lacher DA, Sempos CT, et al. National estimates of serum total 25-hydroxyvitamin D and metabolite concentrations measured by liquid chromatography-tandem mass spectrometry in the US population during 2007-2010. J Nutr 2016;146:1051–61.
[20] Byun EJ, Heo J, Cho SH, Lee JD, Kim HS. Suboptimal vitamin D status in Korean adolescents: a nationwide study on its prevalence, risk factors including cotinine-verified smoking status and association with atopic dermatitis and asthma. BMJ Open 2017;7, e016409.
[21] Cizmecioglu FM, Etiler N, Gormus U, Hamzaoglu O, Hatun S. Hypovitaminosis D in obese and overweight schoolchildren. J Clin Res Pediatr Endocrinol 2008;1:89–96.
[22] 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 Nutr 2014;17:803–9.
[23] Huang CY, Chang HH, Lu CW, Tseng FY, Lee LT, Huang KC. Vitamin D status and risk of metabolic syndrome among non-diabetic young adults. Clin Nutr 2015;34:484–9.
[24] Wood RJ. Vitamin D and adipogenesis: new molecular insights. Nutr Rev 2008;66:40–6.
[25] Oliveira RM, Novaes JF, Azeredo LM, Candido AP, Leite IC. Association of vitamin D insufficiency with adiposity and metabolic disorders in Brazilian adolescents. Public Health Nutr 2014;17:787–94.
[26] Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690–3.
[27] Harel Z, Flanagan P, Forcier M, Harel D. Low vitamin D status among obese adolescents: prevalence and response to treatment. J Adolesc Health 2011;48: 448–52.
[28] Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metabol 2007;92:2017–29.
[29] Wood JR, Connor CG, Cheng P, Ruedy KJ, Tamborlane WV, Klingensmith G, et al. Vitamin D status in youth with type 1 and type 2 diabetes enrolled in the Pediatric Diabetes Consortium (PDC) is not worse than in youth without diabetes. Pediatr Diabetes 2016;17:584–91.
[30] Delvin EE, Lambert M, Levy E, O'Loughlin J, Mark S, Gray-Donald K, et al. Vitamin D status is modestly associated with glycemia and indicators of lipid metabolism in French-Canadian children and adolescents. J Nutr 2010;140: 987–91.
[31] Neyestani TR, Nikooyeh B, Alavi-Majd H, Shariatzadeh N, Kalayi A, Tayebinejad N, et al. Improvement of vitamin D status via daily intake of fortified yogurt drink either with or without extra calcium ameliorates systemic inflammatory biomarkers, including adipokines, in the subjects with type 2 diabetes. J Clin Endocrinol Metabol 2012;97:2005–11.
[32] Chagas CE, Borges MC, Martini LA, Rogero MM. Focus on vitamin D, inflammation and type 2 diabetes. Nutrients 2012;4:52–67.
[33] Pilz S, Kienreich K, Rutters F, de Jongh R, van Ballegooijen AJ, Grubler M, et al. Role of vitamin D in the development of insulin resistance and type 2 diabetes. Curr Diabetes Rep 2013;13:261–70.
[34] Belenchia AM, Tosh AK, Hillman LS, Peterson CA. Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. Am J Clin Nutr 2013;97:774–81.
[35] Nigil Haroon N, Anton A, John J, Mittal M. Effect of vitamin D supplementation on glycemic control in patients with type 2 diabetes: a systematic review of interventional studies. J Diabetes Metab Disord 2015;14:3.
[36] Takiishi T, Gysemans C, Bouillon R, Mathieu C. Vitamin D and diabetes. Endocrinol Metab Clin N Am 2010;39:419–46. table of contents.
[37] Moreira-Lucas TS, Duncan AM, Rabasa-Lhoret R, Vieth R, Gibbs AL, Badawi A, et al. Effect of vitamin D supplementation on oral glucose tolerance in individuals with low vitamin D status and increased risk for developing type 2 diabetes (EVIDENCE): a double-blind, randomized, placebo-controlled clinical trial. Diabetes Obes Metabol 2017;19:133–41.
[38] Mousa A, Naderpoor N, de Courten MP. Vitamin D supplementation has no effect on insulin sensitivity or secretion in vitamin D-deficient, overweight or obese adults: a randomized placebo-controlled trial 2017;105:1372–81.
[39] Guasch A, Bullo M, Rabassa A, Bonada A, Del Castillo D, Sabench F, et al. Plasma vitamin D and parathormone are associated with obesity and atherogenic dyslipidemia: a cross-sectional study. Cardiovasc Diabetol 2012;11:149.
[40] Kim MK, Il Kang M, Won Oh K, Kwon HS, Lee JH, Lee WC, et al. The association of serum vitamin D level with presence of metabolic syndrome and hypertension in middle-aged Korean subjects. Clin Endocrinol 2010;73:330–8.
[41] 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.
[42] 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.
[43] Atabek ME, Eklioglu BS, Akyurek N, Alp H. Association between vitamin D level and cardiovascular risk in obese children and adolescents. J Pediatr Endocrinol Metabol JPEM 2014;27:661–6.
[44] 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 Metabol 2015;20:46–52.
[45] Reis JP, von Muhlen D, Miller 3rd ER, Michos ED, Appel LJ. Vitamin D status and cardiometabolic risk factors in the United States adolescent population. Pediatrics 2009;124:e371–9.