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Longitudinal association of serum 25-hydroxyvitamin D levels with metabolically healthy body size transition in children and adolescents: A prospective cohort study with 2 years of follow-up

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ABSTRACT

Background and aims: Although the associations of vitamin D with obesity and metabolic abnormalities have been reported, the role of vitamin D in the transition of obesity phenotype remains unclear but is highly desired since it is crucial to identify potential methods for obesity management. Therefore, we aimed to investigate the relationship between vitamin D and the risk for metabolically unhealthy obesity (MUO) or metabolically healthy obesity (MHO) in metabolically healthy children with 2 years of follow-up.

Methods: Data were collected from a population-based cohort consisting of 6424 metabolically healthy children aged 6–16 years at baseline. Metabolic abnormalities including hypertension, high triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), hyperglycemia, and hyperuricemia were assessed both at baseline and follow-up. Baseline serum 25-hydroxyvitamin D (25[OH]D) concentrations were measured as exposure. The obesity phenotype transition was evaluated by weight status with the combination of metabolic health status from baseline to follow-up.

Results: During a 2-year follow-up, 889 (13.8 %) incident MUO cases occurred. For participants with obesity, each 10 nmol/L increment in 25(OH)D concentrations was associated with a 21 % (95%*CI*: 13 %~43 %) and a 7 % (95%CI: 1 %~14 %) decreased risk in high TG and hyperuricemia, respectively. A 51 % (95%CI: 22 %~69 %) lower risk of MUO was observed in participants with sufficient vitamin D levels (≥50 nmol/L) compared to those with vitamin D deficiency (<30 nmol/L). Besides, among children who were MHO at baseline, those with sufficient vitamin D levels (≥50 nmol/L) were more likely to transition to metabolically healthy normal weight (MHNW) than vitamin D deficient individuals (<30 nmol/L).

Conclusions: Vitamin D may prevent the development of MUO and help increase the transition from MHO to MHNW. The findings highlight that vitamin D might be an effective nutrient for obesity management.

1. Introduction

Obesity continues to rise at an alarming rate worldwide, with the prevalence increasing 8-fold in the past four decades among children and adolescents globally [1]. In particular, China had over twice the global average increase in age-standardized summary exposure value of high BMI after 2010 [2]. This pandemic poses a substantial threat to public health due to the numerous health consequences related to obesity, including cardiovascular disease (CVD), musculoskeletal disorders, cancer, dementia, and pain [2,3]. Also of interest is that metabolically unhealthy obesity (MUO) is commonly defined by metabolic involvement leading to related diabetic and cardiorespiratory diseases [4]. In contrast, obesity without the presence of elevated metabolic risk factors, termed metabolically healthy obesity (MHO), entails a lower risk for multiple diseases compared to MUO [5]. Thus, MHO has raised a series of scientific questions regarding the biological basis and

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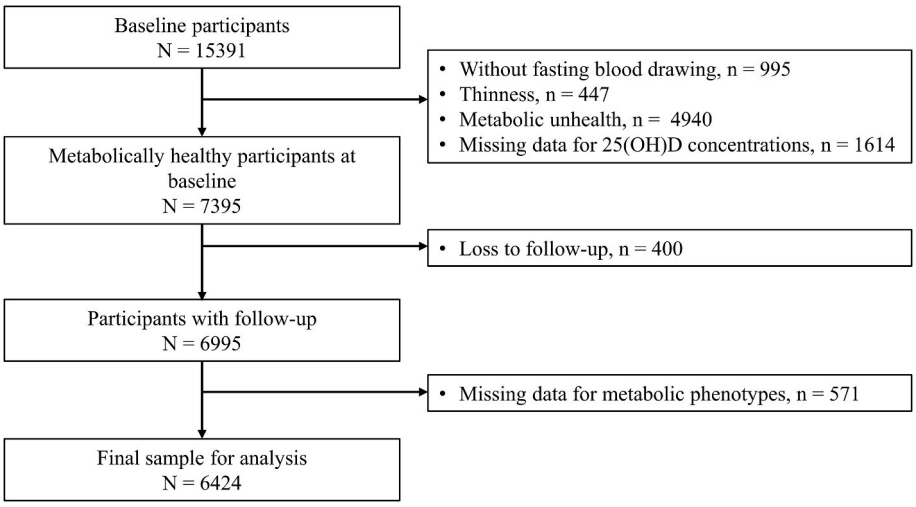

Fig. 1. The flow chart of the study population.
25(OH)D, 25-hydroxyvitamin D.

influencing factors of the transition between metabolic phenotypes of obesity [4,5].

Vitamin D, a fat-soluble micronutrient, is generally considered to benefit skeletal health [6]. Despite the presence of vitamin D-related components in various organ systems, there is ongoing debate on the non-skeletal benefits of this nutrient [7]. Several observational studies indicate that increased vitamin D levels are linked to a lower risk of obesity as well as obesity-associated metabolic risk factors [8,9]. However, vitamin D deficiency may be the consequence of obesity, rather than the cause, due to the sequestration of this fat-soluble vitamin in adipose tissue [10]. Additionally, the impact of vitamin D on the transition of body size metabolic phenotype is poorly understood. As excess body fat compartments reduce vitamin D bioavailability [11], the potential effects of vitamin D on metabolic health may vary based on weight status.

At present, vitamin D is still a research hotspot in the field of obesity prevention. However, there is still a large gap in our understanding of how vitamin D affects metabolically healthy body size transition. Here, using data from a large prospective cohort in China, we aimed to investigate the relationship between vitamin D and the risk for MUO or MHO in metabolically healthy children with 2 years of follow-up.

2. Material and methods

2.1. Study population

The current study utilized data from the school-based cardiovascular and bone health program (SCVBH), which is a prospective study to investigate risk factors for cardiovascular and bone health in school-aged children. The protocol and baseline characteristics of the study population have been reported elsewhere [12]. Briefly, a stratified cluster sampling method was used to select students in 30 schools (8 primary schools, 21 middle schools, and a 12-year education school) from Dongcheng, Tongzhou, Fangshan, and Miyun districts of Beijing. All the students in Grades 1 to 4 from primary schools, and Grade 1 from junior and senior high schools were invited to participate in the baseline survey from November to September 2017. A total of 15391 children in Beijing aged 6–16 years completed a self-administered questionnaire, underwent a physical examination, and provided biological samples at baseline. Then, 12984 participants were successfully followed up at the end of 2019, completing the same survey content as the baseline.

In the present analysis, we initially selected 7395 participants, applying exclusion criteria at baseline, which conducted: (1) hypertension, dyslipidemia, hyperglycemia, or hyperuricemia; (2) being underweight; (3) lacking data for vitamin D measurements. Of these, 400 participants were lost to follow-up and 571 participants were missing data on metabolic phenotypes. Ultimately, the study included a total of 6424 children (as shown in Fig. 1).

Ethical approval of SCVBH was granted by the Institutional Review Boards of Capital Institute of Pediatrics (approval number: SHERLL2016026), and informed consent was obtained from participants aged ≥12 years and parents of participants aged <12 years.

2.2. Questionnaire

A validated questionnaire was used to collect socio-demographic (age, sex, etc.) and lifestyle information (dietary and physical activity). Smoking behavior was defined as having smoked at least one entire cigarette in the previous month [13]. Alcohol drinking was defined as consumption of a standard amount of alcoholic beverage (e.g., 120 ml wine, 50 ml liquor, or a bottle of beer) in the past month [14]. The frequency (per week), duration (minutes), and intensity (vigorous or moderate) of physical activity in a typical week were collected by questionnaire, and individuals with a daily frequency of moderate or vigorous physical activity ≥60 min were considered to achieve an ideal physical activity [15]. The questionnaire also collected information on the use of vitamin D supplements in the past 6 months. A validated food frequency questionnaire was used to collect the frequency of different food intakes in the past half-year. Ideal dietary behaviors were defined as achieving at least 4 out of 5 following items: (1) fruits and vegetables (≥1 time/day); (2) aquatic foods (≥1 time/week); (3) whole-grain foods (≥1 time/day); (4) sugar-sweetened beverage (<1 time/week); and (5) bean-curd or dairy products (≥1 time/day) [15]. Parental height and weight were collected by questionnaire, and then parental weight status was classified as normal (<24 kg/m^2), overweight (24 -< 28 kg/m^2), and obesity (≥28 kg/m^2). Self-reported questions were used to collect information about family history of hypertension, dyslipidemia, and diabetes.

2.3. Anthropometric and laboratory analysis

Anthropometric measurements included weight measurement using the electronic scale without shoes and height using the stadiometer. Body mass index (BMI) was calculated as weight (kilograms)/(height (meters))^2. Resting blood pressure (BP) was measured three times with 1–2 min intervals (OMRON HBP-1300, Omron, Kyoto, Japan) in a seated position, and the average of the last two readings was used.

Fasting venous blood samples (5 ml) were drawn after an overnight

Table 1
Characteristics of study population by vitamin D status.

Characteristics	Overall (n = 6424)	Vitamin D status			P value
		Deficiency (n = 1566)	Insufficiency (n = 3198)	Sufficiency (n = 1660)	
Demographic and lifestyle indicators					
age, mean (SD), year	11.0 (3.3)	11.9 (3.2)	11.0 (3.3)	10.1 (3.2)	<0.001
boys, n(%)	2878 (44.8)	461 (29.4)	1366 (42.7)	1051 (63.3)	<0.001
smoking, n(%)	57 (0.9)	9 (0.6)	26 (0.8)	22 (1.3)	0.062
drinking, n(%)	405 (6.3)	118 (7.5)	194 (6.1)	93 (5.6)	0.058
ideal physical activity, n(%)	354 (5.5)	86 (5.5)	157 (4.9)	111 (6.7)	0.036
parental obesity, n(%)	1648 (25.7)	376 (24.0)	862 (27.0)	410 (24.7)	0.054
family history of metabolic abnormalities, n(%)	1856 (28.9)	498 (31.8)	927 (29.0)	431 (26.0)	0.001
Baseline metabolic parameters					
ideal dietary behaviors, n(%)	1234 (19.2)	297 (19.0)	592 (18.5)	345 (20.8)	0.156
usage of vitamin D supplements, n(%)	1326 (20.6)	307 (19.6)	643 (20.1)	376 (22.7)	0.058
BMI, mean (SD), kg/m^2	19.3 (3.8)	19.5 (3.5)	19.3 (3.8)	18.8 (3.8)	<0.001
weight status, n(%)					<0.001
normal weight	4404 (68.6)	1160 (74.1)	2156 (67.4)	1088 (65.5)	
overweight	1088 (16.9)	228 (14.6)	567 (17.7)	293 (17.7)	
obesity	932 (14.5)	178 (11.4)	475 (14.9)	279 (16.8)	
SBP, mean (SD), mmHg	106.4 (9.1)	106.8 (8.9)	106.4 (9.0)	105.9 (9.4)	0.018
DBP, mean (SD), mmHg	58.8 (6.5)	59.8 (6.2)	58.9 (6.5)	57.7 (6.7)	<0.001
TG, mean (SD), mmol/L	0.70 (0.30)	0.76 (0.29)	0.70 (0.29)	0.64 (0.30)	<0.001
HDL-C, mean (SD), mmol/L	1.47 (0.28)	1.47 (0.28)	1.47 (0.28)	1.48 (0.29)	0.393
FBG, mean (SD), mmol/L	5.06 (0.31)	5.11 (0.28)	5.06 (0.31)	5.03 (0.31)	<0.001
UA, mean (SD), μmol/L	256.3 (73.7)	250.6 (75.2)	255.1 (73.7)	264.1 (71.7)	<0.001
Follow-up metabolic parameters					
ideal dietary behaviors, n(%)	1359 (21.2)	322 (20.6)	668 (20.9)	369 (22.2)	0.653
usage of vitamin D supplements, n(%)	1440 (22.4)	300 (19.2)	675 (21.1)	465 (28.0)	<0.001
BMI, mean (SD), kg/m^2	20.3 (4.1)	20.5 (3.9)	20.4 (4.2)	19.8 (4.1)	<0.001
weight status, n(%)					<0.001
normal weight	4424 (68.9)	1156 (73.8)	2149 (67.2)	1119 (67.4)	
overweight	1111 (17.3)	234 (14.9)	583 (18.2)	294 (17.7)	
obesity	889 (13.8)	176 (11.2)	466 (14.6)	247 (14.9)	
SBP, mean (SD), mmHg	109.9 (10.7)	110.2 (10.3)	109.7 (10.7)	110.3 (11.2)	0.177
DBP, mean (SD), mmHg	61.3 (7.2)	62.4 (6.9)	61.3 (7.1)	60.4 (7.6)	<0.001
Hypertension, n(%)	610 (9.5)	127 (8.1)	287 (9.0)	196 (11.8)	0.001
TG, mean (SD), mmol/L	0.69 (0.36)	0.74 (0.37)	0.69 (0.37)	0.63 (0.33)	<0.001
High TG, n(%)	115 (1.8)	31 (2.0)	63 (2.0)	21 (1.3)	0.173
HDL-C, mean (SD), mmol/L	1.47 (0.27)	1.46 (0.26)	1.47 (0.27)	1.50 (0.28)	<0.001
Low HDL-C, n(%)	207 (3.2)	57 (3.6)	105 (3.3)	45 (2.7)	0.316
FBG, mean (SD), mmol/L	5.10 (0.38)	5.02 (0.44)	5.12 (0.36)	5.15 (0.36)	<0.001
Hyperglycemia, n(%)	552 (8.6)	131 (8.4)	277 (8.7)	144 (8.7)	0.934
UA, mean (SD), μmol/L	348.2 (80.1)	350.4 (77.1)	346.7 (80.6)	349.0 (81.7)	0.299
Hyperuricemia, n(%)	1155 (18.0)	285 (18.2)	556 (17.4)	314 (18.9)	0.406

SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; UA, uric acid.
Data was presented as mean (SD) or percentage.

fast and centrifuged for 10 min at 1509.3×*g*. Fasting blood glucose (FBG), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and uric acid (UA) were measured using the Hitachi 7080 biochemistry autoanalyzer (Hitachi, Tokyo, Japan) at both the baseline and follow-up survey. The enzymatic method (Sekisui Medical Incorporation, Tokyo, Japan) was allowed to assess on the spot values for TC and TG while HDL-C and LDL-C were analyzed by the direct method (Sekisui Medical Incorporation, Tokyo, Japan). Fasting glucose was measured using a hexokinase method (Biosino Bio-Technology and Science Incorporation, Beijing, China). UA was detected with commercial detecting Kits (Biosino Bio-Technology and Science Incorporation, Beijing, China) according to the manufacturer's protocols. Serum concentrations of 25-hydroxyvitamin D [25(OH)D] were measured using DiaSorin 25OH Vitamin D total assay (DiaSorin, Stillwater, MN, United States) on an automated chemiluminescent platform at baseline.

2.4. Study variables

According to the Institute of Medicine recommendations, vitamin D status was classified as deficiency (<30 nmol/L), insufficiency (30 ~ <50 nmol/L), and sufficiency (≥50 nmol/L) based on the baseline serum 25(OH)D concentrations [16].

Childhood weight status was classified as normal weight (<85th), overweight (85th −95th), and obesity (>95th) according to the age-and-sex-specific cut-offs proposed by the World Group on Obesity in China [17]. As suggested in the expert consensus on screening metabolically unhealthy obesity in children [18], participants were defined as being metabolically unhealthy if they met at least one of the following criteria: (1) systolic BP and/or diastolic BP > 95th percentile for sex- and age-specific group [19]; (2) HDL-C ≤1.03 mmol/L; (3) TG ≥ 1.70 mmol/L; (4) fasting glucose ≥5.6 mmol/L; (5) UA >420 μmol/L. In the present study, we classified the metabolic phenotypes of weight status at follow-up to six classes as the primary outcome: metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), metabolically healthy overweight (MHOW), metabolically unhealthy overweight (MUOW), metabolically healthy obesity (MHO), and metabolically unhealthy obesity (MUO).

2.5. Statistical analysis

For the present study, we initially limited our sample to metabolically healthy individuals at baseline. Study population characteristics were presented as frequency (%) for categorical variables, and mean (*SD*) for continuous variables. Differences across the vitamin D status categories were examined using analysis of variance for continuous variables, and chi-squared tests for categorical variables. The

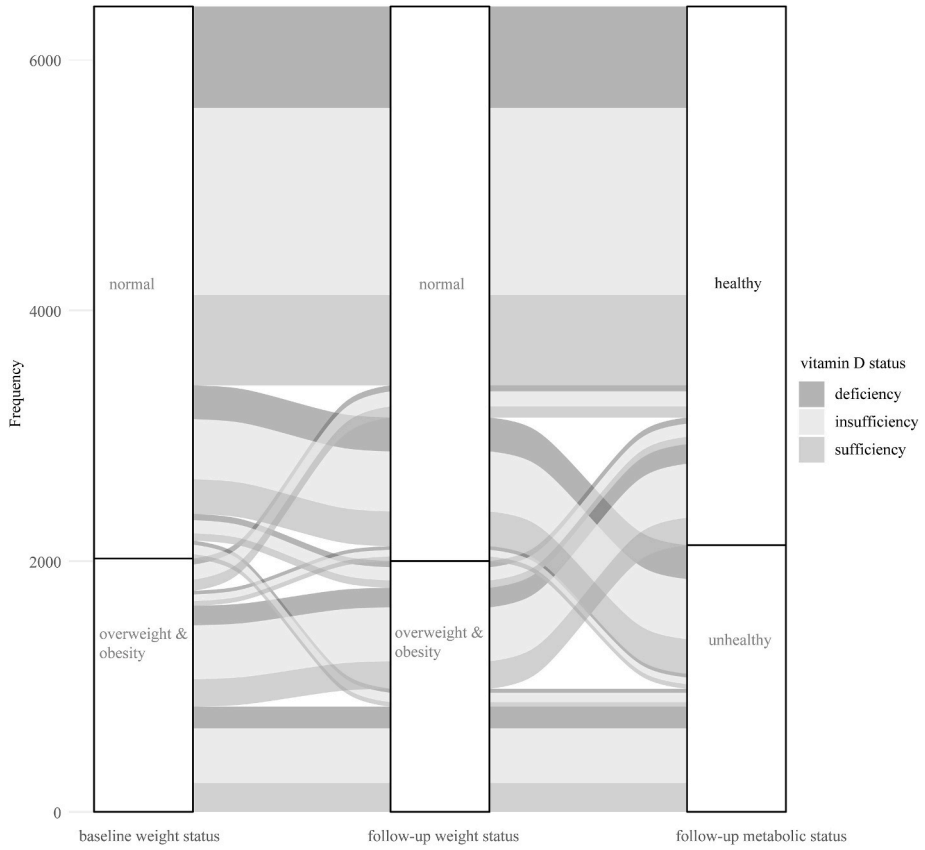

Fig. 2. The alluvial plot of condition frequencies by weight and metabolically healthy status.

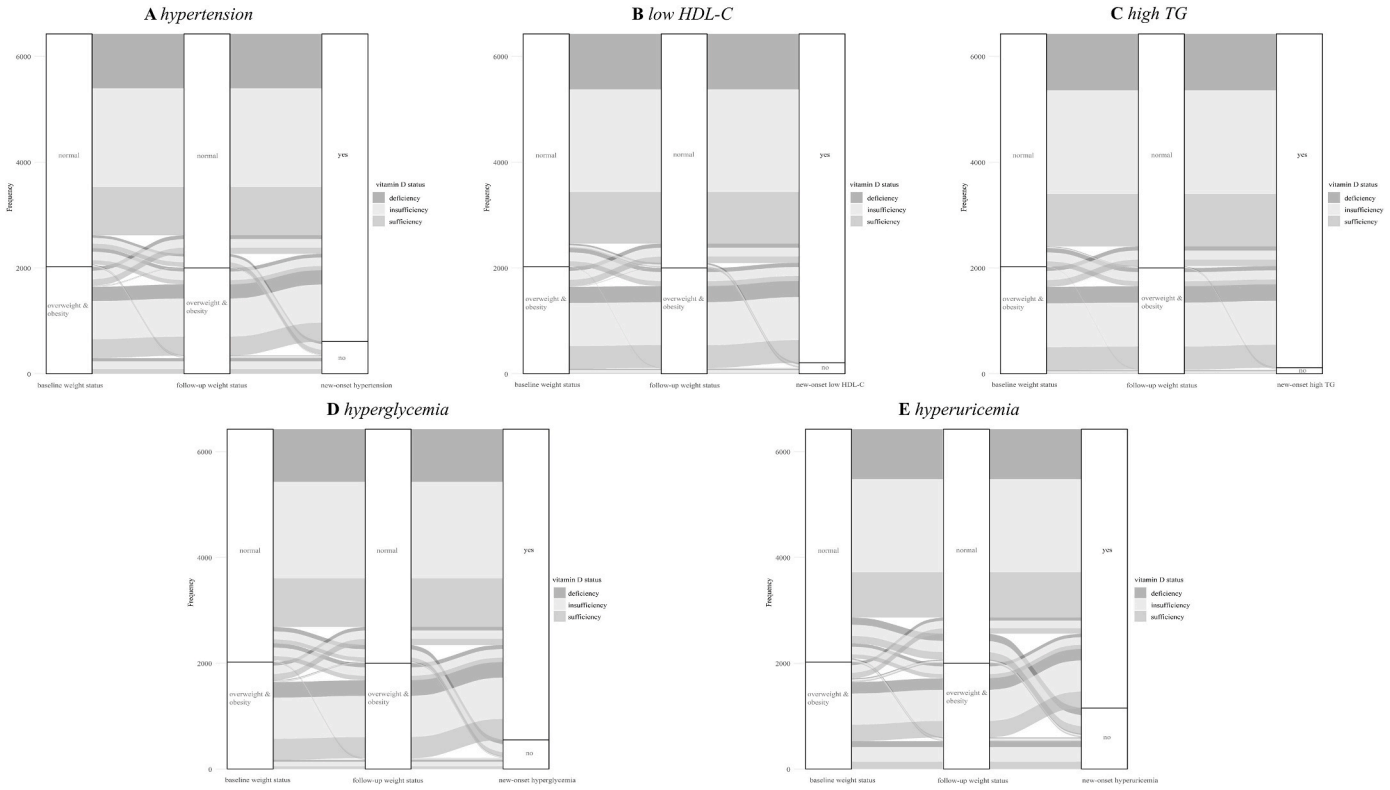

Fig. 3. The alluvial plot of condition frequencies by weight status and incident of metabolic abnormalities. A, B, C, D, and E stand for hypertension, low HDL-C, high TG, hyperglycemia, and hyperuricemia, respectively.
HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

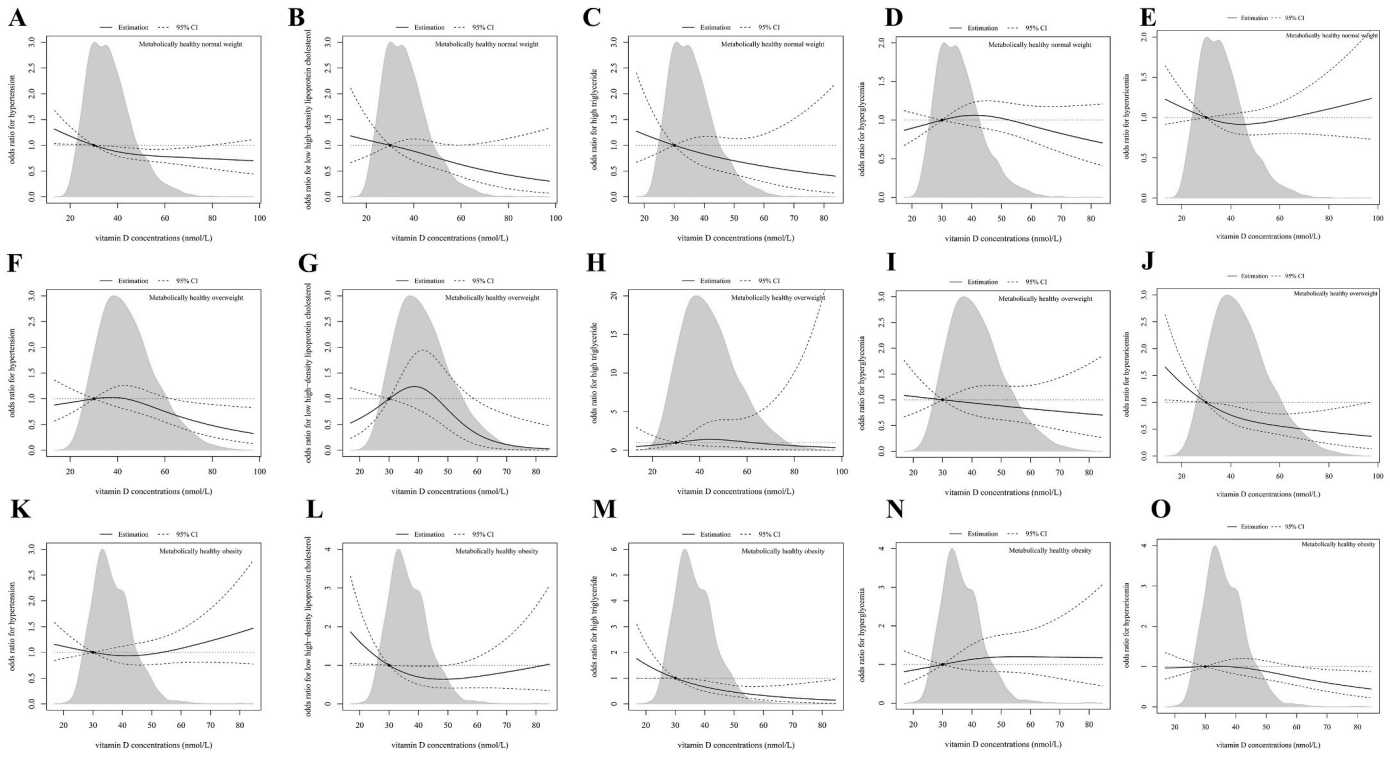

Fig. 4. Restricted cubic spline analysis for the associations of 25(OH)D concentrations and risk of metabolic abnormalities. A, B, C, D, and E stand for the associations of 25(OH)D levels with the risk for hypertension, low HDL-C, high TG, hyperglycemia, and hyperuricemia, respectively, in baseline metabolically healthy normal weight children. F, G, H, I, and J stand for the associations of 25(OH)D levels with the risk for hypertension, low HDL-C, high TG, hyperglycemia, and hyperuricemia, respectively, in baseline metabolically healthy overweight children. K, L, M, N, and O stand for the associations of 25(OH)D levels with the risk for hypertension, low HDL-C, high TG, hyperglycemia, and hyperuricemia, respectively, in baseline metabolically healthy obese children.
HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.
The gray shaded area indicates the density of participants according to 25(OH)D levels.
Models were adjusted for age, sex, smoking, drinking, physical activity, dietary behaviors, vitamin D supplementation, parental obesity, family history of metabolic abnormalities, and baseline metabolic parameters (including BMI, SBP, DBP, HDL-C, TG, FBG, and UA).

cumulative incidence rates (*CIRs*) for each outcome in different vitamin D status groups were calculated as the number of new cases within a 2-year follow-up divided by the number of participants who were free of the corresponding outcome at baseline. An alluvial plot was used to demonstrate the transitions of metabolic status from baseline to follow-up by weight status.

The estimated marginal means of 25(OH)D concentrations in different metabolic phenotypes were calculated using analysis of covariance, and the Tukey-Kramer test was used to compare the mean between groups in the post-hoc analysis. By assigning numeric values to the categorical variables, the trend of 25(OH)D concentrations across groups was tested in the linear regression models. To examine the dose-response relationship between 25(OH)D concentrations as a continuous variable and the incidence of MUO and metabolic abnormalities by baseline weight status group, we used restricted cubic spline curves with three knots based on logistic models. The associations between baseline vitamin D and metabolic phenotypes of weight status at follow-up were determined by the multinomial logistic regression after adjustment for demographic, parental, lifestyle, and baseline metabolic indicators. We further used multivariable log-binomial regressions to examine the associations of vitamin D with each metabolic abnormality. Also, stratified analyses were performed by sex and weight status. The potential effect modification of stratified variables was examined using a two-way product term in the models.

The sample size calculation was performed using an online sample size calculator (https://sample-size.net/). A 2-tailed $P \leq 0.05$ was considered statistically significant, and all analyses were performed by *R* software (version 3.4.0, www.cran.r-project.org).

3. Results

The mean age of 6424 participants was 11.1 ± 3.3 years at baseline, and 2878 (44.8 %) of them were boys. Overall, the mean of serum 25(OH)D concentrations was 41.5 ± 15.3 nmol/L, and the prevalence of vitamin D deficiency was 24.3 %. As compared to those with vitamin D deficiency or insufficiency, participants who had sufficient vitamin D had the lowest level of BMI, DBP, and TG at both the baseline and follow-up (Table 1). Fig. 2 illustrates the frequencies of weight and metabolic status from baseline to follow-up by vitamin D status. By the end of follow-up, we found that 8.1 % of the initial 4048 normal weight children became overweight and obese. Of these, 40.2 % developed at least one metabolic abnormality, and 22.8 % had vitamin D deficiency. 82.2 % of the initial 2020 children with overweight/obesity maintained their weight status at follow-up. Among them, 839 (51.0 %) became metabolically unhealthy. Similarly, the frequencies of the transition for each metabolic phenotype are depicted in Fig. 3.

During a 2-year follow-up, the cumulative incidence of hypertension, low HDL-C, high TG, hyperglycemia, and hyperuricemia were 9.5 %, 3.2 %, 1.8 %, 8.6 %, and 18.0 %, respectively. Fig. 4 shows the nonlinear associations between the risk of metabolic abnormalities and 25(OH)D concentrations by baseline weight status. We mainly found that the risk for high TG (*P* for linearity = 0.005) and hyperuricemia (*P* for linearity = 0.050) decreased approximately linearly with increasing 25(OH)D levels in the baseline obesity group. The associations of vitamin D both as continuous and categorical variables with the risk for metabolic abnormalities derived from multivariate logistic regressions were given in Table 2. The results demonstrated that a 10 nmol/L increment for 25(OH)D concentrations in children with obesity at baseline would yield

Table 2
Associations of vitamin D with risk for metabolic abnormalities by baseline weight status.

Baseline weight status	Metabolic abnormalities	Continuous 25(OH)D concentrations per 10 nmol/L		Vitamin D status						P_{trend}
				Deficiency		Insufficiency		Sufficiency		
		RR (95%CI)	P value	CIR (%, 95% CI)	RR (95% CI)	CIR (%, 95% CI)	RR (95%CI)	CIR (%, 95% CI)	RR (95%CI)	
Normal										
	hypertension	0.99 (0.97, 1.01)	0.497	9.1 (7.4, 10.9)	Reference	6.0 (5.1, 7.1)	0.99 (0.92, 1.07)	5.3 (4.1, 6.8)	0.96 (0.87, 1.05)	0.441
	low HDL-C	0.86 (0.75, 1.01)	0.052	2.7 (1.9, 3.9)	Reference	2.1 (1.6, 2.8)	0.79 (0.50, 1.23)	1.9 (1.2, 2.9)	0.67 (0.37, 1.21)	0.176
	high TG	0.83 (0.66, 1.05)	0.107	1.0 (0.5, 1.8)	Reference	1.3 (0.8, 1.8)	1.13 (0.56, 2.29)	0.6 (0.2, 1.2)	0.49 (0.17, 1.37)	0.175
	hyperglycemia	0.98 (0.91, 1.05)	0.515	7.3 (5.9, 8.9)	Reference	8.1 (6.9, 9.3)	1.11 (0.85, 1.44)	7.7 (6.2, 9.5)	1.04 (0.75, 1.43)	0.825
	hyperuricemia	0.99 (0.94, 1.05)	0.972	13.3 (11.4, 15.4)	Reference	11.5 (10.2, 12.9)	0.83 (0.67, 1.02)	14.2 (12.2, 16.5)	0.90 (0.71, 1.14)	0.421
Overweight										
	hypertension	0.99 (0.95, 1.05)	0.960	10.9 (7.2, 15.7)	Reference	10.6 (8.2, 13.4)	1.00 (0.85, 1.18)	12.3 (8.7, 16.6)	0.99 (0.82, 1.21)	0.949
	low HDL-C	0.82 (0.65, 1.04)	0.090	3.5 (1.5, 6.8)	Reference	5.1 (3.5, 7.3)	1.31 (0.60, 2.83)	2.3 (1.0, 4.9)	0.55 (0.19, 1.57)	0.263
	high TG	1.02 (0.68, 1.52)	0.922	0.9 (0.1, 3.0)	Reference	1.6 (0.7, 3.0)	2.11 (0.43, 10.29)	1.0 (0.2, 2.9)	1.29 (0.19, 8.88)	0.849
	hyperglycemia	0.98 (0.91, 1.05)	0.571	11.8 (7.9, 16.7)	Reference	9.3 (7.1, 12.0)	0.79 (0.49, 1.27)	9.2 (6.2, 13.1)	0.76 (0.43, 1.33)	0.338
	hyperuricemia	0.89 (0.81, 0.97)	0.009	31.1 (25.2, 37.6)	Reference	22.0 (18.7, 25.7)	0.66 (0.49, 0.89)**	24.6 (19.8, 30.0)	0.60 (0.42, 0.85)**	0.006
Obesity										
	hypertension	1.02 (0.92, 1.13)	0.768	22.5 (16.6, 29.3)	Reference	20.4 (16.9, 24.3)	0.88 (0.61, 1.28)	21.9(17.2, 27.2)	1.01 (0.67, 1.55)	0.841
	low HDL-C	0.91 (0.75, 1.10)	0.307	9.5 (5.7, 14.8)	Reference	6.3 (4.3, 8.9)	0.52 (0.28, 0.96)*	6.1 (3.6, 9.6)	0.58 (0.28, 1.18)	0.187
	high TG	0.71 (0.57, 0.87)	<0.001	9.6 (5.7, 14.8)	Reference	5.7 (3.8, 8.2)	0.56 (0.29, 1.01)	4.3 (2.2, 7.4)	0.38 (0.17, 0.81)*	0.012
	hyperglycemia	1.04 (0.91, 1.19)	0.571	10.7 (6.5, 16.2)	Reference	10.5 (7.9, 13.6)	1.09 (0.64, 1.88)	11.8 (8.3, 16.2)	1.26 (0.69, 2.29)	0.414
	hyperuricemia	0.93 (0.86, 0.99)	0.049	33.7 (26.8, 41.1)	Reference	38.3 (33.9, 42.8)	1.02 (0.75, 1.37)	31.2 (25.8, 36.9)	0.80 (0.57, 1.14)	0.168

RR, risk ratio; CIR, cumulative incidence rate; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol. *$0.01 \leq P < 0.05$; **$0.001 \leq P < 0.01$.
Multivariable logistic regression models were used to examine the association between vitamin D both as continuous and categorical variables and risk of metabolic abnormalities.
RRs were adjusted for age, sex, smoking, drinking, physical activity, dietary behaviors, vitamin D supplementation, parental obesity, family history of metabolic abnormalities, and baseline metabolic parameters (including BMI, SBP, DBP, HDL-C, TG, FBG, and UA).

21 % (95%*CI*: 13 %~43 %) and 7 % (95%*CI*: 1 %~14 %) risk reduction for high TG and hyperuricemia, respectively. In this subgroup, we also found that children with sufficient and insufficient vitamin D levels had 62 % (95%*CI*: 19 %~83 %) and 48 % (95%*CI*: 4 %~72 %) decreased risk for high TG and low HDL-C, respectively, compared to those who had vitamin D deficiency status.

The adjusted means across different metabolic phenotypes by baseline weight status are presented in the bar plot (Fig. 5). From MHNW to MUO at follow-up, a significantly decreased trend ($P = 0.005$) in 25(OH)D concentrations was observed only in the children with obesity at baseline. Likewise, the adjusted mean of 25(OH)D concentrations decreased linearly with the clustering of metabolic abnormalities at follow-up only in children with baseline obesity($P = 0.017$) (Fig. 6).

Fig. 7 illustrates the dose-response associations between baseline 25(OH)D concentration and the risk of MUO and metabolically unhealthy status by baseline weight status. A linear inverse association (*P* for linearity = 0.018) between vitamin D and the risk of MUO was observed in the baseline metabolically healthy obesity group. Besides, in this study group, the risk for metabolically unhealthy status decreased approximately linearly with increasing 25(OH)D concentrations from 50 nmol/L. Adjusted ORs from multivariate multinomial logistic regressions are given in Table 3 to show the associations between vitamin D and risk for each metabolic phenotype in the overall population. Compared to vitamin D deficient children, those with sufficient vitamin D levels had 51 % (95%*CI*: 22 %~69 %) decreased risk for MUO. In addition, each 10 nmol/L higher of baseline 25(OH)D concentrations were associated with a 13 % (95%*CI*: 3 %~22 %) reduction in the risk for MHO during follow-up.

We also examined the associations of vitamin D with risk for MUO (Table 4) or MHO (Table 5) by sex and baseline weight status. The risk for MUO was significantly lower in vitamin D insufficient and sufficient boys compared to vitamin D deficient boys. However, the association was not statistically significant in girls. The weight status stratified analyses found a significantly lower risk of MUO in vitamin D sufficient children for baseline normal weight (OR[95%*CI*]: 0.13 [0.03–0.61]) and obesity groups (OR[95%*CI*]: 0.20 [0.05–0.85]), but not for the baseline overweight group. Furthermore, children with vitamin D sufficiency had a significantly lower risk of maintaining the MHO status compared to vitamin D deficient children in the baseline obesity group. Further, sensitivity analyses were performed to analyze the associations between vitamin D and the risk for metabolically unhealthy obesity and overweight (MUOO) (Table 6). Similarly, an inverse association between the risk of MUOO and vitamin D levels was found in boys as well as overweight and obese individuals. However, the association was not statistically significant in girls and normal weight individuals.

4. Discussion

Leveraging this large, school-based prospective cohort study involving more than 6000 children who were free of metabolic

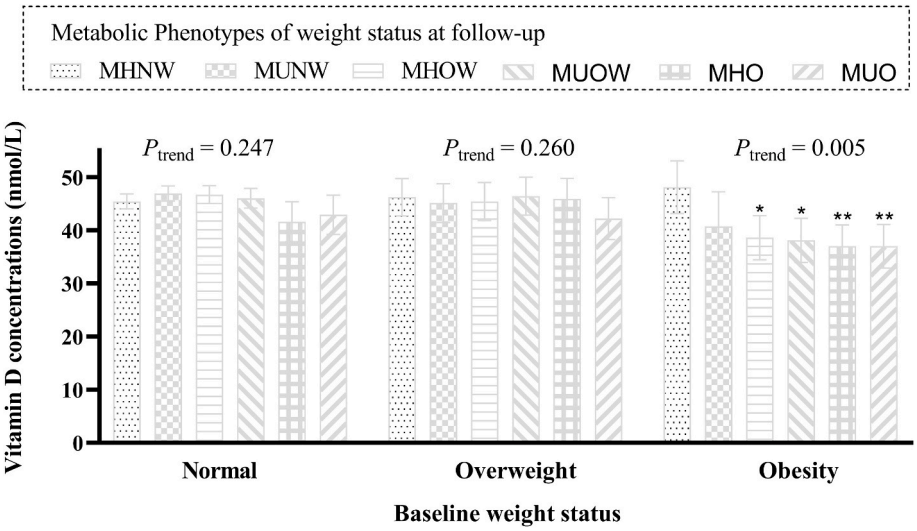

Fig. 5. The estimated marginal mean of 25(OH)D concentrations in different metabolic phenotypes at follow-up by baseline weight status. MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOW, metabolically healthy overweight; MUOW, metabolically unhealthy overweight; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity. Error bar represents standard error of the mean. The means were adjusted for age, sex, smoking, drinking, physical activity, dietary behaviors, vitamin D supplementation, parental obesity, family history of metabolic abnormalities, and baseline metabolic parameters (including BMI, SBP, DBP, HDL-C, TG, FBG, and UA). *$0.01 \leq P < 0.05$, **$0.001 \leq P < 0.01$ compared to the metabolically healthy normal weight group (reference group).

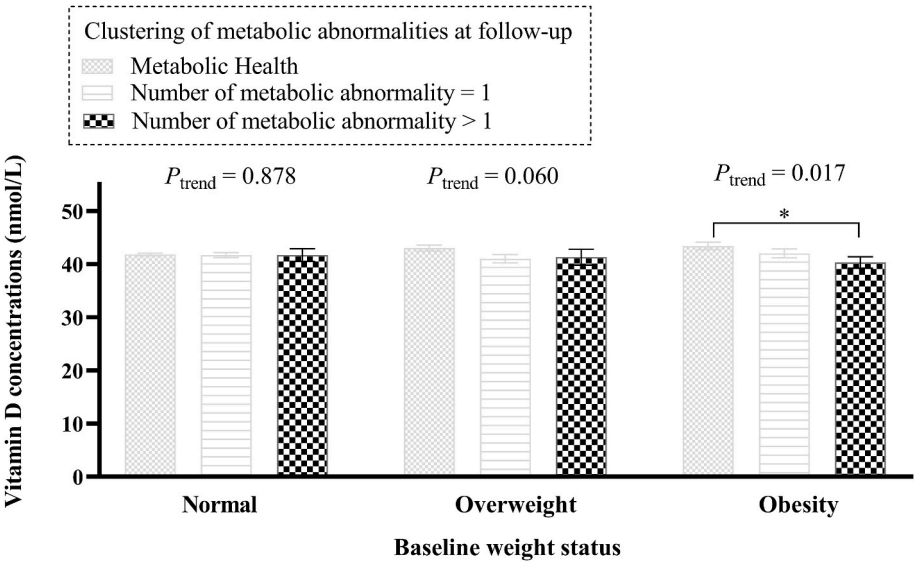

Fig. 6. The estimated marginal mean of 25(OH)D concentrations according to the clustering of metabolic abnormalities at follow-up by baseline weight status. Error bar represents standard error of the mean.
The means were adjusted for age, sex, smoking, drinking, physical activity, dietary behaviors, vitamin D supplementation, parental obesity, family history of metabolic abnormalities, and baseline metabolic parameters (including BMI, SBP, DBP, HDL-C, TG, FBG, and UA). *$P < 0.05$ compared to the metabolic health group (reference group).

abnormalities at baseline, we found that vitamin D was inversely associated with the incidence of MUO over a 2-year follow-up period. Besides, our results showed that the risk of high TG and hyperuricemia decreased with increasing levels of serum 25(OH)D concentrations only in children with overweight/obesity at baseline. As a result, public health and clinical strategies based on vitamin D supplementation may have significant implications for preventing potential health hazards caused by obesity. Additionally, our participants with higher vitamin D levels at baseline were more likely to transition from MHO to MHNW at follow-up. In light of these findings, we speculate that vitamin D might be an effective nutrient for obesity management in children.

It is well documented that obesity poses substantial health issues for both individuals and society [20]. Specifically, several obesity-related metabolic abnormalities including hypertension, dyslipidemia, and diabetes, are increasing with the obesity epidemic [21]. Despite the mechanisms that link obesity to metabolic disease have been elucidated in detail, individuals with obesity but apparently free of metabolic disorders, the so-termed MHO, have been extensively debated [22]. Currently, metabolically unhealthy obesity is generally considered at a high risk of progressing to the metabolically unhealthy phenotype, and therefore should not be regarded as a benign condition [23]. In our analysis, 76 % of 932 MHO children at baseline transitioned into MUO phenotype after a 2-year follow-up. Similar to our results, another study comprised of 59957 Korean adults reported that about 70 % of MHO

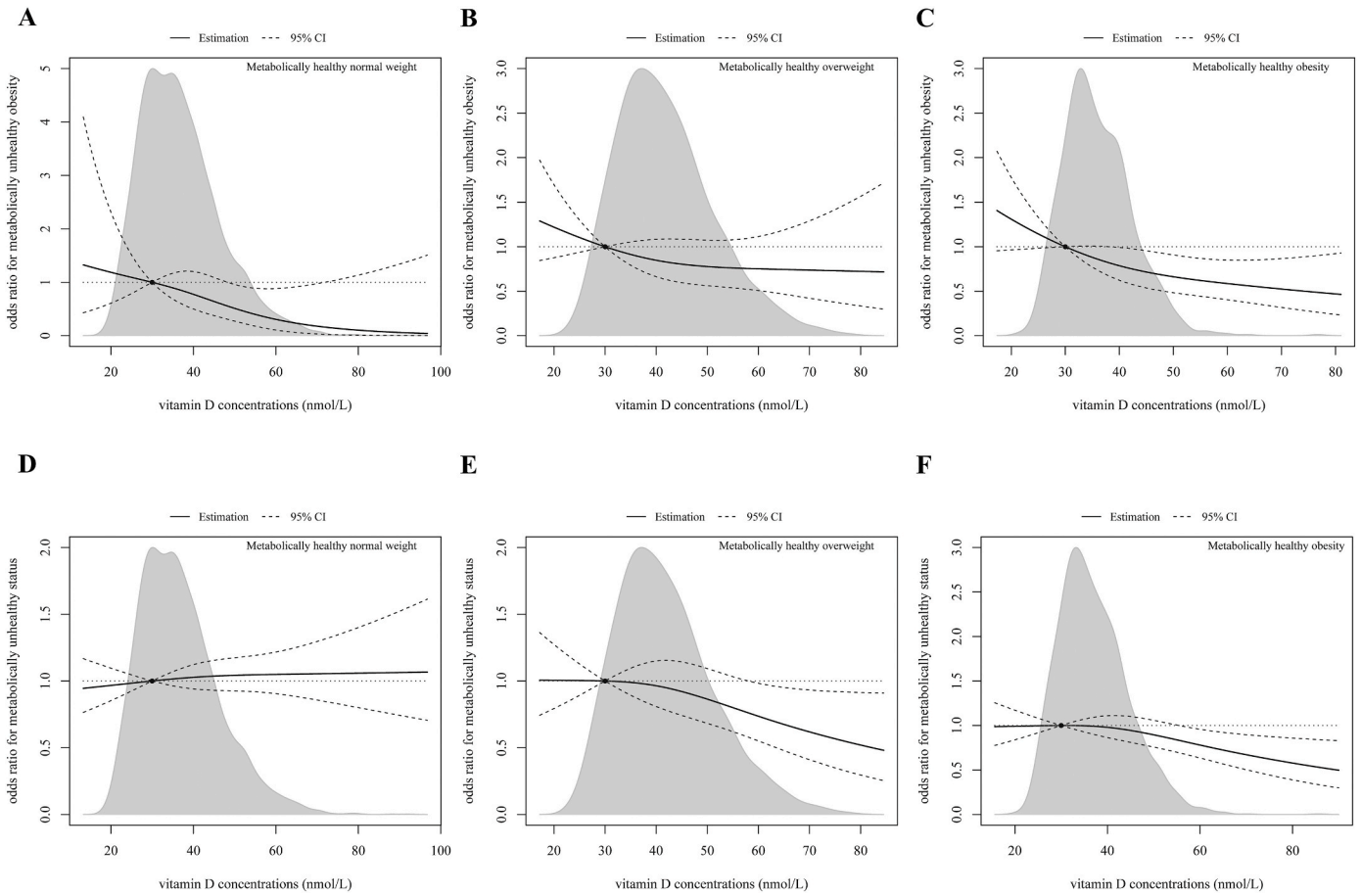

Fig. 7. Restricted cubic spline analysis for the associations of 25(OH)D concentrations and risk of metabolically unhealthy obesity and metabolically unhealthy status. A, B, and C stand for the associations of 25(OH)D levels with the risk for metabolically unhealthy obesity in baseline metabolically healthy normal weight, overweight, and obesity group, respectively. D, E, and F stand for the associations of 25(OH)D levels with the risk for metabolically unhealthy status in baseline metabolically healthy normal weight, overweight, and obesity group, respectively.
The gray shaded area indicates the density of participants according to 25(OH)D levels.
Models were adjusted for age, sex, smoking, drinking, physical activity, dietary behaviors, vitamin D supplementation, parental obesity, family history of metabolic abnormalities, and baseline metabolic parameters (including BMI, SBP, DBP, HDL-C, TG, FBG, and UA).

Table 3
Associations between vitamin D and risk of metabolic phenotypes of weight status.

Metabolic Phenotypes	Continuous 25(OH)D concentrations per 10 nmol/L		Vitamin D status						P_{trend}
			Deficiency		Insufficiency		Sufficiency		
	RR (95%CI)	P	CIR (%, 95% CI)	RR (95% CI)	CIR (%, 95% CI)	RR (95%CI)	CIR (%, 95% CI)	RR (95%CI)	
MUO	0.81 (0.73, 0.90) ***	<0.001	6.8 (5.7, 8.1)	Reference	8.5 (7.6, 9.5)	0.86 (0.58,1.28)	9.5 (8.2, 11.0)	0.49 (0.31, 0.78) **	<0.001
MHO	0.87 (0.78, 0.97) **	0.005	4.8 (3.8, 5.9)	Reference	6.4 (5.6, 7.3)	1.10 (0.73,1.65)	6.0 (4.9, 7.2)	0.66 (0.41, 1.05)	0.022
MUOW	0.91 (0.84, 0.99)*	0.015	18.7 (16.8, 20.7)	Reference	17.2 (15.9, 18.5)	1.12 (0.83,1.53)	18.6 (16.8, 20.5)	0.82 (0.57, 1.17)	0.104
MHOW	0.98 (0.91, 1.05)	0.307	9.3 (7.9, 10.8)	Reference	10.9 (9.9, 12.1)	1.14 (0.87,1.49)	11.0 (9.6, 12.6)	0.97 (0.71, 1.33)	0.422
MUNW	1.00 (0.95, 1.05)	0.443	18.7 (16.8, 20.7)	Reference	17.2 (15.9, 18.5)	0.96 (0.81,1.15)	18.6 (16.8, 20.5)	1.01 (0.82, 1.25)	0.550

RR, risk ratio; CIR, cumulative incidence rate; MUO, metabolically unhealthy obesity; MHO, metabolically healthy obesity; MUOW, metabolically unhealthy overweight; MHOW, metabolically healthy overweight; MUNW, metabolically unhealthy normal weight. *$0.01 \leq P < 0.05$; **$0.001 \leq P < 0.01$; ***$P < 0.001$.
Multivariable multinomial logistic regression models were used to examine the association between vitamin D both as continuous and categorical variables and risk of metabolic phenotypes.
RRs were calculated by taking metabolically healthy normal weight as reference group, and adjusted for age, sex, smoking, drinking, physical activity, dietary behaviors, vitamin D supplementation, parental obesity, family history of metabolic abnormalities, and baseline metabolic parameters (including BMI, SBP, DBP, HDL-C, TG, FBG, and UA).

Table 4
Associations of vitamin D and risk for metabolically unhealthy obesity by sex and baseline weight status.

Subgroup	Continuous 25(OH)D concentrations per 10 nmol/L		Vitamin D status						P_{trend}
			Deficiency		Insufficiency		Sufficiency		
	RR (95%CI)	$P_{interaction}$	CIR (%, 95%CI)	RR (95%CI)	CIR (%, 95%CI)	RR (95%CI)	CIR (%, 95%CI)	RR (95%CI)	
Sex		0.861							
boy	0.84 (0.73, 0.95)**		13.3 (10.4, 16.6)	Reference	11.5 (9.9, 13.2)	0.49 (0.28, 0.88)*	11.2 (9.4, 13.2)	0.37 (0.20, 0.68)**	<0.001
girl	0.90 (0.75, 1.07)		4.1 (3.0, 5.4)	Reference	6.2 (5.1, 7.3)	1.35 (0.78, 2.35)	6.6 (4.7, 8.8)	0.95 (0.47, 1.91)	0.497
Weight status		0.635							
normal	0.62 (0.42, 0.91)*		0.8 (0.3, 1.4)	Reference	0.5 (0.2, 0.9)	0.40 (0.14, 1.11)	0.3 (0.1, 0.8)	0.13 (0.03, 0.61)**	0.002
overweight	0.81 (0.67, 0.99)*		8.0 (4.9, 12.2)	Reference	6.4 (4.6, 8.7)	1.13 (0.56, 2.26)	6.2 (3.8, 9.5)	0.71 (0.32, 1.59)	0.164
obesity	0.69 (0.53, 0.89)**		43.7 (36.5, 51.1)	Reference	45.7 (41.3, 50.1)	0.91 (0.22, 3.82)	47.1 (41.4, 52.8)	0.20 (0.05, 0.85)*	0.004

RR, risk ratio; CIR, cumulative incidence rate. *$0.01 \le P < 0.05$; **$0.001 \le P < 0.01$.
Multivariable multinomial logistic regression models were used to examine the association between vitamin D both as continuous and categorical variables and risk of metabolic phenotypes.
RRs were calculated by taking metabolically healthy normal weight as reference group, and adjusted for age, sex (except for stratified analyses by sex), smoking, drinking, physical activity, dietary behaviors, vitamin D supplementation, parental obesity, family history of metabolic abnormalities, and baseline metabolic parameters (including BMI, SBP, DBP, HDL-C, TG, FBG, and UA).

Table 5
Associations of vitamin D and risk for metabolically healthy obesity by sex and baseline weight status.

Subgroup	Continuous 25(OH)D concentrations per 10 nmol/L		Vitamin D status						P_{trend}
			Deficiency		Insufficiency		Sufficiency		
	RR (95%CI)	$P_{interaction}$	CIR (%, 95%CI)	RR (95%CI)	CIR (%, 95%CI)	RR (95%CI)	CIR (%, 95%CI)	RR (95%CI)	
Sex		0.331							
boy	0.83 (0.72, 0.95)**		5.5 (3.7, 7.9)	Reference	8.3 (7.0, 9.9)	1.00 (0.53, 1.90)	6.7 (5.4, 8.4)	0.50 (0.25, 0.99)*	0.003
girl	0.78 (0.65, 0.93)**		4.5 (3.4, 5.9)	Reference	4.9 (4.0, 6.0)	0.92 (0.54, 1.55)	4.6 (3.1, 6.6)	0.53 (0.27, 1.00)*	0.048
Weight status		0.038							
normal	1.00 (0.69, 1.47)		0.2 (0.1, 0.6)	Reference	0.4 (0.2, 0.7)	1.53 (0.33, 7.05)	0.3 (0.1, 0.9)	1.22 (0.22, 6.89)	0.539
overweight	0.91 (0.75, 1.10)		5.9 (3.3, 9.7)	Reference	7.6 (5.6, 10.1)	1.69 (0.80, 3.55)	5.3 (3.1, 8.3)	0.84 (0.36, 2.01)	0.263
obesity	0.62 (0.48, 0.80)***		32.6 (26.0, 39.8)	Reference	31.5 (27.5, 35.7)	0.89 (0.21, 3.72)	27.5 (22.5, 32.8)	0.14 (0.03, 0.59)**	0.001

RR, risk ratio; CIR, cumulative incidence rate. *$0{\cdot}01 \le P < 0{\cdot}05$; **$0{\cdot}001 \le P < 0{\cdot}01$; ***$P < 0{\cdot}001$.
Multivariable multinomial logistic regression models were used to examine the association between vitamin D both as continuous and categorical variables and risk of metabolic phenotypes.
RRs were calculated by taking metabolically healthy normal weight as reference group, and adjusted for age, sex (except for stratified analyses by sex), smoking, drinking, physical activity, dietary behaviors, vitamin D supplementation, parental obesity, family history of metabolic abnormalities, and baseline metabolic parameters (including BMI, SBP, DBP, HDL-C, TG, FBG, and UA).

patients progress to MUO over a 7.7-year follow-up [24]. In addition, the associations between MHO and atherosclerotic diseases have been investigated in several epidemiological studies. The China Kadoorie Biobank (CKB) cohort involving >450000 Chinese adults found that MHO patients had an 8 % higher risk for atherosclerotic vascular events compared to the MHNW individuals over a 10-year follow-up [25]. Current evidence points to high conversion rates from metabolically healthy to unhealthy obesity and indicates that effective means are needed to prevent this unfavorable transition.

Vitamin D, which is mainly responsible for calcium homeostasis and bone metabolism, has been shown to have potential benefits for cardiovascular health [26]. A growing body of evidence has investigated the relationship between vitamin D and obesity as well as obesity-related metabolic abnormalities. However, data from different scales have been confusing and conflicting. A previous cross-sectional analysis of 559 Chinese adolescents found a negative correlation between vitamin D and TG after adjustment for BMI [27]. We have now extended this finding to a more specific population by using a cohort study. After 2 years of follow-up in our study population, the risk of high TG was reduced by 62 % (95%*CI*: 19 %~83 %) in the vitamin D sufficiency individuals compared with vitamin D deficiency individuals only in the baseline obese group. However, no significant association between the risk of cardiometabolic abnormalities and vitamin D was found in our baseline normal weight group. The results of a recent meta-analysis are partially consistent with our findings, where vitamin D supplementation ≥200,000 IU was shown to have a beneficial effect on reducing TG and fasting glucose levels but not HDL-C and blood pressure in children [28]. Unfortunately, the subgroup differences according to weight status were not included in their analyses. A recent randomized clinical trial conducted in 604 racially diverse schoolchildren showed beneficial effects of vitamin D supplementation on HDL-C, LDL-C, and total cholesterol but not on TG in all weight status groups [29]. Another randomized controlled trial conducted in elderly patients with type 2 diabetes observed a significant reduction in TG levels in the vitamin D supplementation group in obese patients, which is consistent with our data [30]. The exact mechanism underlying the protective role of vitamin D in the lipid profile remains elusive and is presumably linked to the peroxisome proliferator-activated receptor (PPAR)-α pathway, which may be activated by vitamin D and is essential for lipid metabolism [31]. In addition to the high TG, an inverse association between 25(OH)D concentrations and the risk of hyperuricemia was found in our population with overweight and obesity. Nevertheless,

Table 6
Associations of vitamin D and risk for metabolically healthy obesity and overweight by sex and baseline weight status.

Subgroup	Continuous 25(OH)D concentrations per 10 nmol/L		Vitamin D status						P_{trend}
			Deficiency		Insufficiency		Sufficiency		
	RR (95%CI)	$P_{interaction}$	CIR (%, 95% CI)	RR (95% CI)	CIR (%, 95% CI)	RR (95%CI)	CIR (%, 95% CI)	RR (95%CI)	
Sex		0.986							
boy	0.86 (0.79, 0.95) **		36.9	Reference	40.4	0.57 (0.37, 0.88)*	36.3	0.51 (0.46, 0.56) **	<0.001
girl	0.92 (0.81, 1.04)		21.7	Reference	27.1	1.24 (0.84, 1.82)	26.1	0.99 (0.59, 1.65)	0.554
Weight status		0.112							
normal	0.90 (0.79, 1.02)		6.9	Reference	8.4	0.98 (0.62, 1.56)	8.5	0.68 (0.39, 1.18)	0.067
overweight and obesity	0.83 (0.74, 0.92) **		81.0	Reference	83.2	1.06 (0.69, 1.62)	78.3	0.61 (0.37, 0.98) *	0.010

RR, risk ratio; CIR, cumulative incidence rate. *0·01 ≤ P < 0·05; **0·001 ≤ P < 0·01; ***P < 0·001.
Multivariable multinomial logistic regression models were used to examine the association between vitamin D both as continuous and categorical variables and risk of metabolic phenotypes.
RRs were calculated by taking metabolically healthy normal weight as reference group, and adjusted for age, sex (except for stratified analyses by sex), smoking, drinking, physical activity, dietary behaviors, vitamin D supplementation, parental obesity, family history of metabolic abnormalities, and baseline metabolic parameters (including BMI, SBP, DBP, HDL-C, TG, FBG, and UA).

the effects of vitamin D supplements on hyperuricemia reported by randomized clinical trials are inconsistent. In a randomized controlled trial among patients with prediabetes and hyperuricemia, a significant reduction in uric acid concentration was found after 12 weeks of vitamin D supplementation [32]. According to Hu et al., the response of serum uric acid to vitamin D supplementation in patients with type 2 diabetes was modified by gender and baseline vitamin D status [30].

There is strong evidence from cross-sectional studies that vitamin D deficiency is related to unfavorable adiposity [27,33,34]. However, there is intense scientific debate as to whether this reflects a causal relationship or instead a reverse causation [35]. According to Thacher TD, vitamin D deficiency may be an indicator rather than a cause of obesity due to the sequestration of vitamin D in adipose tissue [36]. Using the bi-directional genetic approach, a Mendelian randomization study suggested that a higher BMI led to a lower 25(OH)D concentration, while any effects of lower 25(OH)D on increasing BMI were likely to be small [9]. Nonetheless, the effect of weight loss interventions including dietary/lifestyle modification and surgery on vitamin D status is still inconclusive [37]. A meta-analysis conducted by Mallard SR indicated that behavior therapy-induced weight and fat mass reduction was associated with a small increase in serum 25(OH)D levels [38], while another study found no significant changes in 25(OH)D levels after weight loss [39]. As for the studies that examined the effect of vitamin D supplementation on weight loss, most of them did not find statistically significant results [40–42]. However, no further studies have yet assessed the associations of vitamin D with obesity phenotypes. Our study extends the previous findings by providing insight into the role of vitamin D in obesity phenotype transition. Although only 14 % (889 of 6424) of participants with metabolic health at baseline transitioned to MUO, we found that each 10 nmol/L higher serum 25(OH)D concentration was significantly associated with a 19 % decreased risk of transitioning to MUO, and the association persisted in weight status-stratified analysis. Interestingly, in the subgroup analysis of initial MHO children, participants with higher vitamin D levels are more likely to transition to the MHNW phenotype. Hence, strategies to increase vitamin D levels in children with obesity for obesity management are warranted. Although the underlying mechanisms by which vitamin D may play a potential role in weight loss are still unclear, several clues can be deduced from previous experimental studies. Evidence suggests that vitamin D may inhibit preadipocyte differentiation and fatty acid synthesis by regulating adipogenic transcription factor gene expression [43]. Additionally, as a key regulator of calcium metabolism, vitamin D may suppress adipocyte fatty acid synthase expression by increasing calcium levels [44].

Our study has several strengths, including its large sample size, objective measurements of serum 25(OH)D concentration and metabolic indicators, and adjustment for a wide range of potential confounders. In particular, we restricted our sample to initially metabolically healthy individuals in a population-based prospective cohort, which can observe the natural history of the transition of obesity phenotype and minimize reverse causality in the causal inference. In addition, the dose-response and stratified analyses were performed to test the robustness of our findings.

5. Limitations

Nevertheless, there are still limitations in our study when interpreting the results. First, unmeasured time-varying and residual confounding cannot be ruled out due to the nature of observational design. Second, the 2-year follow-up period in our cohort may not be sufficient to observe the full effects of vitamin D on obesity phenotype transition. Another limitation of the study is the lack of follow-up vitamin D data, which may not accurately reflect vitamin D levels during the follow-up period. Finally, the generalizability of the conclusion may be limited due to the lack of other ethnic groups in our study population.

6. Conclusion

The associations between vitamin D and metabolic risk factors in populations with different weight statuses have been reported. However, no studies have used a longitudinal design and took metabolically unhealthy obesity as the outcome. Thus, it remains unclear whether vitamin D itself plays a causal role in the transition from metabolically healthy weight status to metabolically unhealthy obesity or whether vitamin D supplementation can serve as a potential method to prevent metabolically unhealthy obesity. To the best of our knowledge, the present study is the first investigation to evaluate the role of vitamin D in obesity phenotype transition among children, revealing that higher levels of vitamin D may help prevent metabolically healthy individuals from transitioning to metabolically unhealthy status and MUO, especially in children with obesity. Our results suggest that public health and clinical strategies based on vitamin D supplementation may have important implications for the prevention of potential health hazards caused by obesity in children and adolescents. Also, vitamin D has been speculated to be an effective nutrient for obesity management in children.

Author contributions

JM: conceptualization, methodology, supervision, reviewing, editing, and writing— original draft. PX and HC: data curation, formal analysis, and writing— original draft preparation. XZ and DH: investigation, visualization and software. All authors contributed to the article and approved the submitted version.

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Data access, responsibility, and analysis

JM and PX had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability statement

The data set can be released upon reasonable request.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Pei Xiao reports financial support was provided by National Natural Science Foundation of China. Jie Mi reports financial support was provided by National Natural Science Foundation of China.

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References

[1] Liu Z, Gao P, Gao A, Lin Y, Feng X, Zhang F, et al. Effectiveness of a multifaceted intervention for prevention of obesity in primary school children in China: a cluster randomized clinical trial. JAMA Pediatr 2022;176:e214375.
[2] Li J, Shi Q, Gao Q, Pan XF, Zhao L, He Y, et al. Obesity pandemic in China: epidemiology, burden, challenges, and opportunities. Chin Med J 2022;135:1328–30.
[3] Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med 2017;376:1492.
[4] Mathis BJ, Tanaka K, Hiramatsu Y. Metabolically healthy obesity: are interventions useful? Curr Obes Rep 2023;12:36–60.
[5] Stefan N, Häring H-U, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol 2013;1:152–62.
[6] Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. Mayo Clin Proc 2013;88:720–55.
[7] de la Guia-Galipienso F, Martinez-Ferran M, Vallecillo N, Lavie CJ, Sanchis-Gomar F, Pareja-Galeano H. Vitamin D and cardiovascular health. Clin Nutr 2021;40:2946–57.
[8] Palaniswamy S, Gill D, De Silva NM, Lowry E, Jokelainen J, Karhu T, et al. Could vitamin D reduce obesity-associated inflammation? Observational and Mendelian randomization study. Am J Clin Nutr 2020;111:1036–47.
[9] Vimaleswaran KS, Berry DJ, Lu C, Tikkanen E, Pilz S, Hiraki LT, et al. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. PLoS Med 2013;10:e1001383.
[10] Pramyothin P, Biancuzzo RM, Lu Z, Hess DT, Apovian CM, Holick MF. Vitamin D in adipose tissue and serum 25-hydroxyvitamin D after roux-en-Y gastric bypass. Obesity 2011;19:2228–34.
[11] 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.
[12] Hou D, Gao A, Zhu Z, Yu Z, Lin N, Liu J, et al. The baseline characteristics of school-based cardiovascular and bone health promotion program in Beijing. Chin J Prev Med 2018;52:1117–23.
[13] Zhu Y, Guo P, Zou Z, Li X, Cao M, Ma J, et al. Status of cardiovascular health in Chinese children and adolescents. JACC (J Am Coll Cardiol): Asia 2022;2:87–100.
[14] Brener ND, Kann L, Shanklin S, Kinchen S, Eaton DK, Hawkins J, et al. Methodology of the youth risk behavior surveillance system–2013. MMWR Recomm Rep (Morb Mortal Wkly Rep) 2013;62:1–20.
[15] Xiao P, Cheng H, Yan Y, Hou D, Dong H, Zhao X, et al. Temporal trends in cardiovascular health among Chinese urban children and adolescents, 2004-2019 pre-pandemic COVID-19. Front Public Health 2022;10:1023717.
[16] Institute of Medicine (US). Committee to Review dietary reference intakes for vitamin D and calcium. Dietary reference intakes for calcium and vitamin D. Washington, DC: The National Academies Press; 2011. p. 462–8.
[17] Ji C. Report on childhood obesity in China (1)–body mass index reference for screening overweight and obesity in Chinese school-age children. Biomed Environ Sci : BES. 2005;18:390–400.
[18] Abiri B, Valizadeh M, Amini S, Kelishadi R, Hosseinpanah F. Risk factors, cutoff points, and definition of metabolically healthy/unhealthy obesity in children and adolescents: a scoping review of the literature. Obes Rev 2023;24:e13548.
[19] Fan H, Hou D, Liu J, Yan Y, Mi J. Performance of 4 definitions of childhood elevated blood pressure in predicting subclinical cardiovascular outcomes in adulthood. J Clin Hypertens 2018;20:508–14.
[20] Jebeile H, Kelly AS, O'Malley G, Baur LA. Obesity in children and adolescents: epidemiology, causes, assessment, and management. Lancet Diabetes Endocrinol 2022;10:351–65.
[21] Stefan N, Schulze MB. Metabolic health and cardiometabolic risk clusters: implications for prediction, prevention, and treatment. Lancet Diabetes Endocrinol 2023;11:426–40.
[22] Valenzuela PL, Carrera-Bastos P, Castillo-García A, Lieberman DE, Santos-Lozano A, Lucia A. Obesity and the risk of cardiometabolic diseases. Nat Rev Cardiol 2023;20:475–94.
[23] Copur S, Tanriover C, Yavuz F, Tuttle KR, Kanbay M. Tirzepatide and potential use for metabolically healthy obesity. Eur J Intern Med 2023;113:1–5.
[24] Kim Y, Chang Y, Cho YK, Ahn J, Shin H, Ryu S. Metabolically healthy versus unhealthy obesity and risk of fibrosis progression in non-alcoholic fatty liver disease. Liver Int 2019;39:1884–94.
[25] Gao M, Lv J, Yu C, Guo Y, Bian Z, Yang R, et al. Metabolically healthy obesity, transition to unhealthy metabolic status, and vascular disease in Chinese adults: a cohort study. PLoS Med 2020;17:e1003351.
[26] Pilz S, Verheyen N, Grübler MR, Tomaschitz A, März W. Vitamin D and cardiovascular disease prevention. Nat Rev Cardiol 2016;13:404–17.
[27] 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. Clin Nutr 2019;38:2161–7.
[28] Cai B, Luo X, Zhang P, Luan Y, Cai X, He X. Effect of vitamin D supplementation on markers of cardiometabolic risk in children and adolescents: a meta-analysis of randomized clinical trials. Nutr Metabol Cardiovasc Dis 2021;31:2800–14.
[29] Sacheck JM, Huang Q, Van Rompay MI, Chomitz VR, Economos CD, Eliasziw M, et al. Vitamin D supplementation and cardiometabolic risk factors among diverse schoolchildren: a randomized clinical trial. Am J Clin Nutr 2022;115:73–82.
[30] Hu Z, Zhi X, Li J, Li B, Wang J, Zhu J, et al. Effects of long-term vitamin D supplementation on metabolic profile in middle-aged and elderly patients with type 2 diabetes. J Steroid Biochem Mol Biol 2023;225:106198.
[31] Ning C, Liu L, Lv G, Yang Y, Zhang Y, Yu R, et al. Lipid metabolism and inflammation modulated by Vitamin D in liver of diabetic rats. Lipids Health Dis 2015;14:31.
[32] Nimitphong H, Saetung S, Chailurkit L-O, Chanprasertyothin S, Ongphiphadhanakul B. Vitamin D supplementation is associated with serum uric acid concentration in patients with prediabetes and hyperuricemia. J Clin Transl Endocrinol 2021;24:100255.
[33] Li H, Huang T, Xiao P, Zhao X, Liu J, Cheng H, et al. Widespread vitamin D deficiency and its sex-specific association with adiposity in Chinese children and adolescents. Nutrition 2020;71:110646.
[34] Chiang JM, Stanczyk FZ, Kanaya AM. Vitamin D levels, body composition, and metabolic factors in Asian Indians: results from the metabolic syndrome and atherosclerosis in South Asians living in America pilot study. Ann Nutr Metabol 2018;72:223–30.
[35] Karampela I, Sakelliou A, Vallianou N, Christodoulatos GS, Magkos F, Dalamaga M. Vitamin D and obesity: current evidence and controversies. Curr Obes Rep 2021;10:162–80.
[36] Thacher TD, Clarke BL. Vitamin D insufficiency. Mayo Clin Proc 2011;86:50–60.
[37] Chattranukulchai Shantavasinkul P, Nimitphong H. Vitamin D and visceral obesity in humans: what should clinicians know? Nutrients 2022;14.
[38] Mallard SR, Howe AS, Houghton LA. Vitamin D status and weight loss: a systematic review and meta-analysis of randomized and nonrandomized controlled weight-loss trials. Am J Clin Nutr 2016;104:1151–9.
[39] Pannu PK, Zhao Y, Soares MJ. Reductions in body weight and percent fat mass increase the vitamin D status of obese subjects: a systematic review and metaregression analysis. Nutr Res 2016;36:201–13.
[40] Emadzadeh M, Rashidmayvan M, Sahebi R, Sadeghi R, Ferns GA, Ghayour-Mobarhan M. The effect of vitamin D fortified products on anthropometric indices: a systematic review and meta-analysis. Compl Ther Clin Pract 2020;41:101242.
[41] Duan L, Han L, Liu Q, Zhao Y, Wang L, Wang Y. Effects of vitamin D supplementation on general and central obesity: results from 20 randomized controlled trials involving apparently healthy populations. Ann Nutr Metabol 2020;76:153–64.
[42] Chandler PD, Wang L, Zhang X, Sesso HD, Moorthy MV, Obi O, et al. Effect of vitamin D supplementation alone or with calcium on adiposity measures: a

systematic review and meta-analysis of randomized controlled trials. Nutr Rev 2015;73:577–93.

[43] Earthman CP, Beckman LM, Masodkar K, Sibley SD. The link between obesity and low circulating 25-hydroxyvitamin D concentrations: considerations and implications. Int J Obes 2012;36:387–96.

[44] Zemel MB, Shi H, Greer B, Dirienzo D, Zemel PC. Regulation of adiposity by dietary calcium. Faseb J : official publication of the Federation of American Societies for Experimental Biology 2000;14:1132–8.