



Association of Serum Retinol Concentrations With Metabolic Syndrome Components in Iranian Children and Adolescents: The CASPIAN-V Study

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Specialty section:

This article was submitted to
Nutritional Epidemiology,
a section of the journal
Frontiers in Nutrition

Received: 02 November 2021

Accepted: 19 April 2022

Published: 13 May 2022

Citation:

Qorbani M, Seif E, Heshmat R,
Ghonbalani ZN, Basiry P, Kazemian E
and Kelishadi R (2022) Association of
Serum Retinol Concentrations With
Metabolic Syndrome Components in
Iranian Children and Adolescents: The
CASPIAN-V Study.
Front. Nutr. 9:807634.
doi: 10.3389/fnut.2022.807634

Background: As a fat-soluble vitamin, vitamin A plays a crucial role in adipogenesis, lipolysis, insulin resistance, and obesity. However, it is still unclear whether they are associated with cardiometabolic risk factors in children and adolescents. The current study aimed to determine the association between serum retinol concentration and the cluster of metabolic syndrome components among children and adolescents.

Methods: This nationwide cross-sectional study was performed on 2,518 students aged 7–18 years from the Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable disease (CASPIAN-V) study. Students were selected via multistage cluster sampling method from 30 provinces of Iran in 2015. Multivariable logistic regression was used to assess the association of serum retinol concentration with metabolic syndrome (MetS) components.

Results: Overall, the mean (SD) age of study participants was 12.16 (3.04) years, and 44.9% ($n = 1,166$) of them were girls. The mean serum retinol concentration was $1.48 \pm 1.55 \mu\text{mol/L}$ and vitamin A deficiency was observed among 19.7% (95% CI: 18.2–21.3) of study subjects. The results of the logistic regression analysis showed that increasing serum retinol concentrations were associated with an increased likelihood of developing obesity (OR: 1.12, 95% CI: 1.04, 1.20), abdominal obesity (OR: 1.07, 95% CI: 1.01, 1.14), low high-density lipoprotein cholesterol (HDL-C) (OR: 1.10, 95% CI: 1.04, 1.16) and high fasting blood glucose (FBG) (OR: 1.21, 95% CI: 1.10, 1.35), whereas it was associated with a decreased odds of developing high blood pressure (OR: 0.82, 95% CI: 0.73, 0.93). Nevertheless, there was no statistically significant association between metabolic syndrome itself and retinol concentration (OR: 1.02, 95% CI: 0.88, 1.18).

Conclusion: We found that serum retinol concentration was positively associated with metabolic syndrome components such as obesity, low HDL-C, and high FBG, but not with metabolic syndrome itself.

Keywords: metabolic syndrome, obesity, cardiometabolic risk factor, retinol, children, adolescents

INTRODUCTION

Vitamin A functions as an essential fat-soluble vitamin necessary for cell development, metabolism, immunity, vision, and reproduction (1, 2). Vitamin A deficiency (VAD) is endemic worldwide among young children in developing countries with a high morbidity and mortality rate (1, 2). Two national surveys indicated an increase in VAD prevalence among Iranian children aged 15–23 months (18.3% in 2012 vs. 2.1% in 2001) (3). Globally, 250 million preschool children suffer from VAD, a condition that is influenced by several factors, including economic constraints, socio-cultural challenges, insufficient dietary intake, and poor absorption of vitamin A (4). VAD is diagnosed clinically by identifying specific visual symptoms and assessing plasma retinol levels (1, 5).

Vitamin A is involved in several physiological processes in the body and functions at two levels: first, it contributes to the visual cycle; second, it maintains growth, development, immune function, and energy metabolism (6). Furthermore, vitamin A has been suggested to be linked with several metabolic diseases, including obesity, non-alcoholic fatty liver disease, and atherosclerosis (7). Eighty percent of vitamin A is stored in the form of retinyl palmitate in hepatic stellate cells (HSCs) in lipid droplets in the cytoplasm, similar to those found in adipose cells (8–10). Additionally, white adipose tissue (WAT) plays an important role in lipid metabolism, acting as a lipid storage site, as well as a site where vitamin A is stored and metabolized (11). Vitamin A is metabolized into retinoic acid (RA) in WAT, which then regulates genome expression through signaling pathways and cellular equipment (11). RA, the transcriptionally active form of vitamin A, regulates the expression of more than 700 genes through the activation of transcription factors, including retinoic acid receptors (RARs) and retinoid receptors (RXRs) which bound to the RA-responsive elements in the promoters of RA-targeted genes (12, 13). RA contributes to the regulation of several genes which are involved in glucose, lipid, and energy homeostasis (13).

The combination of abdominal obesity along with hyperglycemia, hypertension, reduced high-density lipoprotein cholesterol (HDL-C), and elevated triglyceride (TGs) and low-density lipoprotein cholesterol (LDL-C) levels dramatically increase the risk of developing diabetes type 2 (T2D) and cardiovascular disease (CVD) (14–17). Thus, metabolic syndrome (MetS) is considered as an extremely serious public health concern, resulting in increased disability and all-cause mortality rates (17, 18). There is an also increasing prevalence of metabolic syndrome among children and adolescents, along with an increase in obesity rates. Furthermore, some individuals, who have high cardiovascular risk in adulthood, have been presenting clusters of MetS risk factors in childhood (19, 20). In the past decade, modifiable risk factors which could minimize MetS burdens have gained increasing attention, particularly those associated with diet and circulating nutritional biomarkers (21–24). In particular, vitamin A and its derivatives have been implicated in adipogenesis, lipolysis, insulin resistance, and the pathophysiology of MetS (24). Several case-control and cross-sectional studies have demonstrated that a high plasma

carotenoid concentration may reduce the risk of atherosclerotic cardiovascular disease (ASCVD) (25, 26) as well as type 2 diabetes (27–30). Additionally, prospective cohort studies indicate that individuals with higher baseline serum carotenoid levels were less likely to develop ASCVD (31, 32). Accordingly, epidemiologic studies noted that higher serum carotenoid levels have a beneficial effect in regulating cardiometabolic risk factors associated with MetS (33). There is, however, substantial controversy about the role of retinol in this context, and further investigation is warranted (33).

Childhood and adolescence are important stages of life when adequate dietary intake of macronutrients and micronutrients is required to ensure optimal growth and development, which then determines overall health during adulthood (34–36). Despite that to our knowledge, only a few nationally representative studies have examined the association of serum retinol, as a marker of vitamin A status with MetS biomarker among children and adolescents. To illuminate this uncharted area, we examined the association between serum retinol concentration and the cluster of metabolic syndrome components among children and adolescents aged 7–18 years. Furthermore, we examined the relation between socio-demographic and dietary determinants and serum retinol concentration in this vulnerable population.

METHODS

Study Design and Participants

This national cross-sectional study was conducted as part of the fifth survey of Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable Disease (CASPIAN)-V in Iran (2014–2015) (37). Shortly, in CASPIAN-V, 14,400 students were sampled from both urban and rural areas of thirty provinces of Iran in winter month. Multi-stage stratified cluster sampling was employed to select study participants proportionally by sex, primary and secondary education level, and location based on rural or urban residence. The inclusion criteria were as follows: (1) Children and adolescents attending primary and secondary education in Iran with Iranian nationality; (2) Without a history of chronic diseases, such as cardiovascular disease, diabetes, and cancers. Fourteen clusters, each including 10 subjects, were randomly picked for biochemical measurements in each province, and 2,518 blood samples were collected to evaluate serum retinol concentrations for the current study. The study objectives and procedure were explained to the students and their parents, and then verbal and written informed consents were obtained from all participants and their guardian. The study protocol was approved by the Ethics Committee of Alborz University of Medical Sciences and was conducted according to the declaration of Helsinki.

Assessments

Baseline characteristics of study participants, including demographics, socioeconomic status (SES), screen time (ST), and physical activity, were gathered through interview or self-administered questionnaire (37).

Basal Characteristics

Students were interviewed about their schools, dietary habits, health behaviors, physical activity, leisure time activities, academic performance, and exposure to green space and environmental pollution. Parents were also administered a questionnaire that asked about their family characteristics (e.g., household size, order of students, and socioeconomic variables), past medical history of the student, medical history, dietary habits and leisure time activities of the family, parents' sleep pattern, and anthropometric measures (37). Health behaviors and protective parameters related to the leading causes of morbidity and mortality of children and adolescents were assessed using the questionnaire implemented by the World Health Organization-Global School Student Health Survey (WHO-GSHS) (38). The Farsi version of the questionnaire was tested previously and found to have satisfactory reliability and validity (39).

Dietary Behavior

Students were asked to report frequency of fruit, vegetables, milk, sugar sweetened beverages, fast foods, sweets and salty snacks consumption. Using principal component analysis (PCA) method, the first factor which was loaded was defined as dietary eating behaviors.

Socio-Economic Status

SES was determined using an index constructed from variables based on five criteria: parents' education and occupation, school type, i.e., public or private, home ownership, and family possessions (e.g., having personal computers or cars). These characteristics were combined using PCA method. The SES score was then calculated and categorized into three groups: low, medium, and high (37).

Screen Time

In order to measure ST, participants were asked how many hours a day they spent watching TV and playing video games.

Physical Activity

The physical activity levels were determined using a self-administrated physical activity questionnaire (PAQ-A), validated for this target population (40).

Anthropometric Measurements

Weight measurement was performed using a digital scale while participants were wearing a light cloth, and height was measured without shoes to the nearest 0.1 cm. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Waist circumference (WC) was measured at the midpoint between the lower border of the rib cage and the iliac crest after normal expiration using non-elastic tape. Hip circumference (HC) was measured at the widest part of the hip at the level of the greater trochanter. A tape meter was used to measure the wrist circumference (WrC) on the dominant arm to the nearest 0.1 cm. Neck circumference (NC) was measured at a prominent portion of the thyroid cartilage (37).

Blood Pressure Measurement

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured on the right arm with a mercury sphygmomanometer and an appropriate cuff size in the sitting position. It was measured twice at 5-min intervals, and the average was recorded (37).

Biochemical Assessments

After 12 h of overnight fasting, venous blood samples were collected from participants. Serum retinol concentration was measured using the reversed-phase high-performance liquid chromatography (HPLC). Two-hundred microliter of serum and 50 μ L of the internal standard solution (retinyl acetate) were transferred into a 2 mL polypropylene microtube. Next, 200 μ L of ethanol and 200 μ L of methanol solution were added to the sample. Following vortexing for 10 s, 500 μ L of hexane was added and vortexed again and centrifuged for 5 min at 1,500 rpm to facilitate phase separation and pellet precipitated protein. Non-polar retinoids were removed from the top phase. Further extraction was carried out with a 500 μ L aliquot of hexane. Hexane was completely evaporated from top phases (organic phase) by heating at 45–50°C. After evaporation, the sample was dissolved again in 200 μ L of methanol. A reversed-phase high-performance liquid chromatography (HPLC) with multi-wavelength detection and super Pac Pep-S column (Pharmacia LKB) was then used to determine the retinol concentration. Biochemical variables, including fasting blood glucose (FBG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) were measured by enzymatic methods using an auto-analyzer by Hitachi (Tokyo, Japan).

Definition of Terms

Cardiometabolic risk factors were defined as follows: High TG: serum TG concentration of >150 mg/dL; High LDL-C: serum LDL-C concentration of >110 mg/dL; High TC: serum TC concentration of >200 mg/dL; Low HDL-C: serum HDL-C concentration of <40 mg/dL (boys 15–19 years <35 mg/dL); High FBG: serum FBG concentration of ≥ 100 mg/dL; High SBP: SBP ≥ 90 th for sex, age and height; High DBP: DBP ≥ 90 th for sex, age and height; and High BP: either SBP or DBP ≥ 90 th for age, sex and height (41).

We defined general obesity as a BMI greater than the 95th percentile for age and sex and overweight as age and sex-specific BMI between the 85th and 95th percentile. Abdominal obesity was also defined as waist to height ratio > 0.5 (41). In accordance with the Adult Treatment Panel III (ATP III) criteria modified for the children, MetS was defined as the presence of three or more of the following factors: (1) serum TG concentration of >150 mg/dL; (2) serum HDL-C concentration of <40 mg/dL; (3) serum FBG concentration of ≥ 100 mg/dL; (4) waist to height ratio of > 0.5 ; (5) either SBP or DBP ≥ 90 th for age, sex and height.

Serum retinol concentrations below 0.7 μ mol/L were defined as vitamin A deficiency (42).

Having physical activity levels of <30 min/day was considered low, and engaging in physical activity for equal to or more than 30

min/day was regarded as high physical activity. Individuals with $ST \leq 2$ h/day were classified as having low ST; otherwise, they were considered to have high ST (37).

Statistical Analysis

Continuous and categorical variables were presented as mean (SD) and number (%), respectively. As Vitamin A distribution was skewed, results are reported as medians (IQRs) instead of means (SDs). Bivariate association between continuous and categorical variables with vitamin A deficiency was assessed using the T-test and Chi-square test. Linear regression models

were used to determine the crude and adjusted association of serum retinol concentration as well as vitamin A deficiency with cardiometabolic risk factors. Three models were defined. Model I was adjusted for age, gender, and living area; model II for physical activity, socioeconomic status, screen time, and dietary behavior; and the final model (Model III) was additionally adjusted for BMI (except for anthropometric measures). Results of linear regression model was presented as beta coefficient (β) and 95% confidence interval (CI). Binary logistic regression analysis was also performed for evaluating the association of serum retinol concentration with different cardiometabolic risk factors after

TABLE 1 | Socio-demographic, socioeconomic and life style according to vitamin A status in Iranian children and adolescents.

Variable		Total (N = 2,518)	Vitamin A status		P-value
			Deficient (N = 497)	Sufficient (N = 2,021)	
Region	Urban	1,787 (70.9%)	358 (20.0%)	1,429 (80.0%)	0.582
	Rural	731 (29.1%)	139 (19.0%)	592 (81.0%)	
Sex	Female	1,133 (44.9%)	231 (20.4%)	902 (79.6%)	0.481
	Male	1,385 (55.1%)	266 (19.2%)	1,119 (80.8%)	
Age (year) mean \pm SD		12.16 \pm 3.04	12.07 \pm 2.98	12.18 \pm 3.05	0.42
Age category	7–10 year	850 (33.7%)	168 (19.8%)	682 (80.2%)	0.847
	11–14 year	1,057 (42.0%)	213 (20.2%)	844 (79.8%)	
	15–18 year	611 (24.3%)	116 (19.0%)	495 (81.0%)	
Vitamin/mineral supplement	No	1,662 (66.3%)	328 (19.7%)	1,334 (80.3%)	0.958
	Yes	843 (33.7%)	165 (19.6%)	678 (80.4%)	
Type of supplement	Multivitamin	223 (26.5%)	49 (22.0%)	174 (78.0%)	0.094
	B Complex	67 (7.9%)	13 (19.4%)	54 (80.6%)	
	Vitamin D	79 (9.3%)	11 (13.9%)	68 (86.1%)	
	Calcium	52 (6.2%)	7 (13.5%)	45 (86.5%)	
	Iron	315 (37.4%)	55 (17.5%)	260 (82.5%)	
	Others	107 (12.7%)	30 (28.0%)	77 (72.0%)	
Fresh fruit consumption	Daily	1,363 (60.5%)	272 (20.0%)	1,091 (80.0%)	0.300
	Non-daily	891 (39.5%)	162 (18.2%)	729 (81.8%)	
Vegetable consumption	Daily	729 (29.3%)	133 (18.2%)	596 (81.8%)	0.245
	Non-daily	1,754 (70.7%)	357 (20.4%)	1,397 (79.6%)	
Milk consumption	Daily	940 (37.3%)	190 (20.2%)	750 (79.8%)	0.679
	Non-daily	1,576 (62.7%)	307 (19.5%)	1,269 (80.5%)	
	Yes	65 (2.6%)	19 (29.2%)	46 (70.8%)	
	Yes	96 (4.0%)	11 (11.5%)	85 (88.5%)	
SES	Low	786 (32.6%)	147 (18.7%)	639 (81.3%)	0.421
	Moderate	803 (33.4%)	155 (19.3%)	648 (80.7%)	
	High	816 (34%)	173 (21.2%)	643 (78.8%)	
Physical activity	Low	791 (33.3%)	162 (20.5%)	629 (79.5%)	0.357
	Moderate	771 (32.4%)	155 (20.1%)	616 (79.9%)	
	High	812 (34.3%)	145 (17.9%)	667 (82.1%)	
ST category	Low	2,098 (85.4%)	412 (19.6%)	1,686 (80.4%)	0.99
	High	358 (14.6%)	70 (19.6%)	288 (80.4%)	

BMI, Body mass index; FBG, Fasting blood glucose; DBP, Diastolic blood pressure; HDL-C, High-density lipoprotein cholesterol; HC, Hip circumference; LDL-C, Low-density lipoprotein cholesterol; NK, Neck circumference; SBP, Systolic blood pressure; SES, Socioeconomic state; ST, Screen time; TC, Total cholesterol; TG, Triglycerides; WC, Waist circumference; WrC, Wrist circumference. High TG, serum TG concentration > 150 mg/dL; High LDL, serum LDL-C concentration > 110 mg/dL; High TC, serum TC concentration > 200 mg/dL; Low HDL-C, serum HDL concentration < 40 mg/dL (boys 15–19 years < 35 mg/dL); High FBG, serum FBG concentration \geq 100 mg/dL; High SBP, SBP \geq 90th for sex, age and height; High DBP, DBP \geq 90th for sex, age and height; High BP, either SBP or DBP \geq 90th for age, sex and height; Physical Activity, <30 min/day as low, \geq 30 min/day as high; ST Category, <2 h/day as low, \geq 2 h/day as high. Serum retinol concentrations below 0.7 μ mol/L were defined as vitamin A deficiency.

adjusting for potential confounders, including age, gender, living area, physical activity, socioeconomic status, screen time and dietary behavior. Results are displayed as odds ratios (OR) with a 95% confidence interval (CI). A p -value <0.05 was considered as statistically significant. All statistical analysis was performed using Stata version 13 (StataCorp. 2013. College Station, TX: StataCorp LP).

RESULTS

The final analysis was conducted on 2,518 subjects, including 1,133 (44.9%) girls and 1,385 (55.1%) boys, respectively. The mean age of the study participants was 12.16 ± 3.04 years, and the median (interquartile range) of serum retinol concentration was 0.84 (0.58) $\mu\text{mol/L}$. Vitamin A deficiency was observed among 19.7% (95% CI: 18.2–21.3) of study subjects. Demographic, dietary, and lifestyle determinants based on serum retinol status are depicted in **Table 1**. No significant differences were found in vitamin A status according to sex (p -value = 0.48), age (p -value = 0.84), region of residence (p -value = 0.58), vitamin/mineral supplement (p -value = 0.95), fruits (p -value = 0.30), vegetables (p -value = 0.24), and milk consumption (p -value = 0.67), SES (p -value = 0.42), physical activity (p -value = 0.35), and screen time (p -value = 0.99).

Table 2 summarizes the demographic, metabolic, and anthropometric characteristics of study participants based on their retinol levels categorized as sufficient or deficient. We found significant differences in anthropometric indices including BMI Z-score (0.01 in the sufficient vs. -0.13 in the deficient group, p -value = <0.001), WC (66.94 in the sufficient vs. 64.81 cm in the deficient group, p -value = 0.001), WrC (14.78 in the sufficient vs. 14.52 cm in the deficient group, p -value = 0.005), HC (79.54 in the sufficient vs. 77.99 cm in the deficient group, p -value = 0.03), and NC (29.90 in the sufficient vs. 29.49 cm in the deficient group, p -value = 0.03) between individuals with adequate and inadequate serum retinol concentration. Moreover, subjects with sufficient levels of vitamin A had lower HDL-C concentration than those with insufficient levels (46.38 vs. 47.88 mg/dL, p -value = 0.03). There were no significant differences across the retinol concentration groups in SBP, DBP, serum FBG, TG, TC, and LDL-C concentration (p -value > 0.05).

The results of linear regression models on the association between serum retinol levels and cardiometabolic risk factors are presented in **Table 3**. We found a negative association between serum retinol and HDL-C concentration both in the crude model (β : -0.503 , 95% CI: -0.80 , -0.205) and after controlling for potential confounders including age, gender and living area (Model I; β : -0.498 , 95% CI: -0.796 , -0.200); age, gender, living area, physical activity, SES, screen time, and dietary pattern (Model II; β : -0.506 , 95% CI: -0.805 , -0.207); and age, gender, living area, physical activity, SES, screen time, dietary pattern and BMI (Model III; β : -0.508 , 95% CI: -0.807 , -0.209). Our analysis also revealed a negative correlation between DBP and serum retinol levels after adjusting for age, gender, living area, physical activity, SES, screen time, dietary pattern and BMI (β : -0.298 , 95% CI: -0.577 , -0.020). According to the linear

TABLE 2 | Baseline characteristics of study participants.

Variable	Vitamin A status		P-value
	Deficient	Sufficient	
BMI z-score	-0.13 ± 0.78	0.01 ± 0.96	<0.001
WC (cm)	64.81 ± 11.85	66.94 ± 12.37	0.001
WrC (cm)	14.52 ± 1.81	14.78 ± 1.80	0.005
HC (cm)	77.99 ± 13.87	79.54 ± 14.74	0.034
NC (cm)	29.49 ± 3.85	29.90 ± 3.93	0.035
SBP (mmHg)	99.00 ± 13.51	98.18 ± 12.84	0.209
DBP (mmHg)	63.67 ± 10.37	63.25 ± 10.10	0.412
FBG (mg/dL)	91.24 ± 9.45	92.07 ± 13.07	0.187
TG (mg/dL)	85.62 ± 44.68	85.93 ± 47.04	0.894
TC (mg/dL)	155.01 ± 27.61	152.65 ± 27.53	0.325
HDL-C (mg/dL)	47.88 ± 11.11	46.38 ± 9.82	0.003
LDL-C (mg/dL)	90.30 ± 22.86	90.18 ± 22.11	0.918

Values are presented as mean \pm standard deviation. BMI, Body mass index; FBG, Fasting blood glucose; DBP, Diastolic blood pressure; HDL-C, High-density lipoprotein cholesterol; HC, Hip circumference; LDL-C, Low-density lipoprotein cholesterol; NK, Neck circumference; SBP, Systolic blood pressure; TC, Total cholesterol; TG, Triglycerides; WC, Waist circumference; WrC, Wrist circumference. Serum retinol concentrations below $0.7 \mu\text{mol/L}$ were defined as vitamin A deficiency.

regression analysis, serum retinol levels did not correlate with anthropometric indices or metabolic syndrome biomarkers.

Linear regression analyses on the relationship between vitamin A deficiency and cardiometabolic risk factors are presented in **Table 4**. Vitamin A deficiency was negatively associated with anthropometric indices including BMI z-score (β : -0.13 , 95% CI: -0.23 , -0.03), WC (β : -2.06 , 95% CI: -3.34 , -0.77), and WrC (β : -0.23 , 95% CI: -0.42 , -0.04) while positively associated with HDL-C (β : 1.90 , 95% CI: 0.85 , 2.95). The observed association remained significant even after adjustment for potential confounders.

Table 5 shows the adjusted OR for the effect of serum retinol levels on obesity and abnormal cardiometabolic factors. Logistic regression analysis showed that increases in serum retinol concentrations were associated with higher odds of obesity (OR: 1.12, 95% CI: 1.04, 1.20), abdominal obesity (OR: 1.07, 95% CI: 1.01, 1.14), low HDL-C (OR: 1.10, 95% CI: 1.04, 1.16) and high FBG (OR: 1.21, 95% CI: 1.10, 1.35), but decreased odds of high blood pressure development (OR: 0.82, 95% CI: 0.73, 0.93).

DISCUSSION

We found that serum retinol concentration in children and adolescents has been linked with some metabolic syndrome components, such as FBG, DBP, HDL-C, obesity, and abdominal obesity, but not with the metabolic syndrome itself. Based on our findings, the likelihood of developing obesity, abdominal obesity, low HDL-C levels, and high FBG levels increased with increasing retinol concentration after controlling for possible confounders.

The majority of prior research on the association of obesity and metabolic syndrome components with blood carotenoid concentration has been conclusive, suggesting that carotenoid

TABLE 3 | Association between serum retinol concentration ($\mu\text{mol/l}$) with cardiometabolic risk factors in linear regression analysis.

Serum retinol concentration ($\mu\text{mol/L}$)		B (95% CI)*	P-value
WC (cm)	Crude model	0.193 (−0.163, 0.554)	0.293
	Model I	0.170 (−0.143, 0.488)	0.293
	Model II	0.179 (−0.136, 0.494)	0.265
WrC (cm)	Crude model	0.030 (−0.024, 0.084)	0.282
	Model I	0.025 (−0.020, 0.070)	0.270
	Model II	0.027 (−0.018, 0.071)	0.238
HC (cm)	Crude model	0.006 (−0.415, 0.426)	0.979
	Model I	−0.042 (−0.383, 0.299)	0.810
	Model II	0.024 (−0.363, 0.316)	0.891
NC (cm)	Crude model	0.032 (−0.080, 0.144)	0.573
	Model I	0.023 (−0.068, 0.114)	0.615
	Model II	0.030 (−0.060, 0.120)	0.516
SBP (mmHg)	Crude model	−0.211 (−0.585, 0.164)	0.270
	Model I	−0.223 (−0.571, 0.125)	0.209
	Model II	−0.220 (−0.567, 0.128)	0.215
	Model III	−0.302 (−0.639, 0.305)	0.079
DBP (mmHg)	Crude model	−0.256 (−0.553, 0.041)	0.091
	Model I	−0.269 (−0.552, 0.015)	0.063
	Model II	−0.246 (−0.529, 0.038)	0.089
	Model III	−0.298 (−0.577, 0.020)	0.036
FBG (mg/dL)	Crude model	0.188 (−0.200, 0.576)	0.343
	Model I	0.194 (−0.194, 0.582)	0.327
	Model II	0.191 (−0.198, 0.581)	0.336
	Model III	0.204 (−0.186, 0.593)	0.305
TG (mg/dL)	Crude model	−0.176 (−1.488, 1.136)	0.793
	Model I	−0.218 (−1.526, 1.090)	0.744
	Model II	−0.152 (−1.462, 1.158)	0.820
	Model III	−0.125 (−1.437, 1.186)	0.852
TC (mg/dL)	Crude model	−0.135 (−0.947, 0.677)	0.745
	Model I	−0.148 (−0.960, 0.664)	0.720
	Model II	−0.131 (−0.945, 0.684)	0.753
	Model III	−0.127 (−0.943, 0.688)	0.759
HDL-C (mg/dL)	Crude model	−0.503 (−0.801, −0.205)	0.001
	Model I	−0.498 (−0.796, −0.200)	0.001
	Model II	−0.506 (−0.805, −0.207)	0.001
	Model III	−0.508 (−0.807, −0.209)	0.001
LDL-C (mg/dL)	Crude model	0.357 (−0.300, 1.014)	0.287
	Model I	0.347 (−0.309, 1.004)	0.300
	Model II	0.357 (−0.302, 1.016)	0.288
	Model III	0.355 (−0.304, 1.015)	0.291
Z-score for BMI	Crude model	0.31 (0.003, 0.059)	0.30
	Model I	0.31 (0.003, 0.059)	0.30
	Model II	0.32 (0.004, 0.060)	0.28

BMI, Body mass index; FBG, Fasting blood glucose; DBP, Diastolic blood pressure; HDL-C, High-density lipoprotein cholesterol; HC, Hip circumference; LDL-C, Low-density lipoprotein cholesterol; NC, Neck circumference; SBP, Systolic blood pressure; TC, Total cholesterol; TG, Triglycerides; WC, Waist circumference; WrC, Wrist circumference.
 Model 1: Adjusted for age, gender and living area.
 Model 2: Additionally, adjusted for physical activity, socioeconomic status, screen time and dietary behavior.
 Model 3: Additionally, adjusted for BMI except for anthropometric measures.
 *Are calculated per each $\mu\text{mol/L}$ increment.

TABLE 4 | Association between vitamin A deficiency with cardiometabolic risk factors in linear regression analysis.

Vitamin A deficiency		B (95% CI)	P-value
BMI z-score	Crude model	−0.13 (−0.23, −0.03)	0.008
	Model I	−0.13 (−0.22, −0.04)	0.006
	Model II	−0.13 (−0.22, −0.04)	0.005
WC (cm)	Crude model	−2.06 (−3.34, −0.77)	0.002
	Model I	−1.94 (−3.06, −0.82)	0.001
	Model II	−1.95 (−3.06, −0.83)	0.001
WrC (cm)	Crude model	−0.23 (−0.42, −0.04)	0.017
	Model I	−0.20 (−0.36, −0.043)	0.013
	Model II	−0.20 (−0.35, −0.04)	0.014
HC (cm)	Crude model	−1.34 (−2.87, 0.20)	0.088
	Model I	−1.19 (−2.43, 0.06)	0.061
	Model II	−1.18 (−2.43, 0.06)	0.061
NC (cm)	Crude model	−0.37 (−0.79, 0.04)	0.074
	Model I	−0.31 (−0.65, 0.02)	0.069
	Model II	−0.31 (−0.65, 0.02)	0.069
SBP (mmHg)	Crude model	0.63 (−0.71, 1.97)	0.356
	Model I	0.74 (−0.51, 1.99)	0.247
	Model II	0.70 (−0.55, 1.95)	0.271
	Model III	1.13 (−0.08, 2.34)	0.068
DBP (mmHg)	Crude model	0.29 (−0.77, 1.36)	0.586
	Model I	0.36 (−0.66, 1.38)	0.489
	Model II	0.37 (−0.65, 1.39)	0.475
	Model III	0.63 (−0.37, 1.63)	0.219
FBG (mg/dL)	Crude model	−0.83 (−2.21, 0.48)	0.208
	Model I	−0.85 (−2.20, 0.49)	0.212
	Model II	−0.86 (−2.20, 0.48)	0.210
	Model III	−0.91 (−2.26, 0.44)	0.185
TG (mg/dL)	Crude model	−1.15 (−5.92, 3.61)	0.635
	Model I	−1.27 (−6.03, 3.48)	0.599
	Model II	−1.24 (−6.00, 3.52)	0.61
	Model III	−1.28 (−6.05, 3.48)	0.598
TC (mg/dL)	Crude model	1.93 (−0.98, 4.83)	0.193
	Model I	1.85 (−1.05, 4.76)	0.211
	Model II	1.85 (−1.06, 4.75)	0.212
	Model III	1.90 (−1.01, 4.81)	0.202
HDL-C (mg/dL)	Crude model	1.90 (0.85, 2.95)	<0.001
	Model I	1.90 (0.84, 2.95)	<0.001
	Model II	1.88 (0.83, 2.93)	<0.001
	Model III	1.88 (0.82, 2.93)	<0.001
LDL-C (mg/dL)	Crude model	0.50 (−1.86, 2.86)	0.68
	Model I	0.45 (−1.91, 2.81)	0.707
	Model II	0.45 (−1.91, 2.82)	0.706
	Model III	0.52 (−1.85, 2.89)	0.667

BMI, Body mass index; FBG, Fasting blood glucose; DBP, Diastolic blood pressure; HDL-C, High-density lipoprotein cholesterol; HC, Hip circumference; LDL-C, Low-density lipoprotein cholesterol; NC, Neck circumference; SBP, Systolic blood pressure; TC, Total cholesterol; TG, Triglycerides; WC, Waist circumference; WrC, Wrist circumference.
 Model 1: Adjusted for age, gender and living area.
 Model 2: Additionally, adjusted for physical activity, socioeconomic status, screen time, and dietary behavior.
 Model 3: Additionally, adjusted for BMI except for anthropometric measures.
 Serum retinol concentrations below $0.7 \mu\text{mol/L}$ were defined as vitamin A deficiency.

TABLE 5 | Adjusted odds ratio (OR) for the effect of serum retinol levels on the development of obesity and abnormal cardiometabolic factors.

Serum retinol concentration ($\mu\text{mol/L}$)	Odds Ratio (CI 95%)*	P-value
High TG (mg/dL)	1.026 (0.966, 1.090)	0.406
High LDL (mg/dL)	0.980 (0.913, 1.053)	0.585
High TC (mg/dL)	0.999 (0.886, 1.125)	0.982
Low HDL (mg/dL)	1.101 (1.040, 1.165)	0.001
High BP (mmHg)	0.825 (0.727, 0.935)	0.003
High FBG (mg/dL)	1.214 (1.093, 1.348)	<0.001
Overweight	0.932 (0.839, 1.034)	0.184
Obesity	1.116 (1.038, 1.200)	0.003
Abdominal obesity	1.070 (1.006, 1.139)	0.03
MetS	1.019 (0.877, 1.184)	0.80

Estimates are adjusted for age, gender, living area, physical activity, socioeconomic status, screen time, and dietary behavior.

BMI, Body mass index; FBG, Fasting blood glucose; DBP, Diastolic blood pressure; HDL-C, High-density lipoprotein cholesterol; HC, Hip circumference; LDL-C, Low-density lipoprotein cholesterol; MetS, metabolic syndrome; NC, Neck circumference; SBP, Systolic blood pressure; TC, Total cholesterol; TG, Triglycerides; WC, Waist circumference; Wc, Wrist circumference. High TG, serum TG concentration > 150 mg/dL; High LDL, serum LDL-C concentration > 110 mg/dL; High TC, serum TC concentration > 200 mg/dL; Low HDL-C, serum HDL concentration < 40 mg/dL (boys 15–19 years < 35 mg/dL); High FBG, serum FBG concentration \geq 100 mg/dL; High BP, either SBP or DBP \geq 90th for age, sex and height.

*Are calculated per each $\mu\text{mol/L}$ increment.

may play a protective role against obesity and metabolic syndrome (35, 43–53). In contrast, the relationship between serum retinol levels and markers of metabolic syndrome has been sparsely addressed in the literature, and the available studies also yield inconsistent conclusions (35, 43, 46, 49–51, 54–57) (Table 6). For example, Gunanti et al. found an increased risk of overweight and obesity with higher serum retinol concentration in Mexican-American children aged 8–15 years of age, which is in agreement with our results (46). Rupérez et al. also observed that prepubertal overweight/obese children had higher plasma retinol concentration than normal-weight children (50). Our observation was also in line with Beydoun et al., which reported an inverse correlation between the combined serum level of retinol + retinyl esters and low HDL-C among adolescents aged 12–19 years from the NHANES 2001–2006 (35). Contrary to Beydoun et al., we did not observe any significant correlation between serum retinol concentration and hypertriglyceridemia (35). Similarly in a case-control study of 118 Japanese children aged 6–15 years, circulating retinol levels were positively correlated with plasma total lipids (49). In another study by Wei et al., metabolic syndrome components such as BMI, WC, HDL-C, and glucose levels were significantly correlated with vitamin A status, as obese participants had a significantly higher risk of vitamin A deficiency which is in contrast with what we observed (57). However, some studies showed no relation between circulating retinol levels and metabolic syndrome components (43, 51). In a randomized clinical trial conducted in prepubertal boys, baseline β -carotene concentrations were inversely associated with

homeostatic model assessment for insulin resistance (HOMA-IR) and abdominal fat mass; supplementation with fruit and vegetable concentrate for 6 months in this population led to a considerable improvement in HOMA-IR and abdominal fat mass following improved β -carotene and reduced retinol levels (58). Furthermore, another intervention trial in Filipino school-aged children showed that an improvement in serum beta-carotene and alpha-carotene concentrations following dietary intervention was inversely related to BMI in both boys and girls, but BMI was unrelated to the changes in serum retinol (59). However, it should be mentioned that impaired vitamin A metabolism rather than VAD *per se* may also contribute to obesity and obesity-related metabolic disorders, as suggested by Saeed et al. (5).

Many possible reasons may be accounted for the paradoxical findings on the association between serum retinol concentration and obesity or metabolic health during childhood or adolescence. First, it seems that circulating vitamin A level and its role in vitamin A metabolic response is influenced by some genetic variations (44, 60). For instance, genetic variants in genes such as *SCARB1*, *UCP2*, and *UCP1* have been shown to modulate the effect of vitamin A intake on metabolism and energy balance and, consequently, adiposity measure, i.e., insufficient vitamin A intake is associated with a greater risk of body fat accumulation in genetically predisposed individuals (44). Observed controversies may also have resulted from very different definitions of retinol used in different studies. Accordingly, studies that looked at retinol as a quantitative trait were more likely to find a positive correlation between retinol levels and markers of metabolic syndrome (46, 49), whereas those considered retinol as a dichotomous variable, i.e., sufficient vs. insufficient status, showed a negative correlation (57). One may conclude that both lower and higher retinol levels than sufficient values could play a role in explaining the metabolic impact of vitamin A. Last but not least, a variety of host factors explaining interindividual differences and retinol bioavailability in humans (44, 61), as well as study design and quality, may also be responsible for these discrepancies.

Retinol, the predominant circulating form of vitamin A, plays a significant role in regulating metabolic homeostasis (11). The main chemical form of vitamin A storage is retinal palmitate, which is found in HSCs in the liver and WATs. Along with the liver, WAT, as the body's major energy storage, also contributes to the regulation of energy homeostasis, lipid metabolism, and secretion of endocrine mediators, which are linked to metabolic disorders, such as obesity and MetS (11). It contains all the intracellular tools to metabolize vitamin A into retinoic acid, which controls genomic expression within WAT (11). Indeed, HSCs and adipocytes express key transcription factors such as PPAR- γ and RXR associated with perilipin expression, which are essential to lipid droplet metabolism (11). Furthermore, both cells produce important endocrine signals that influence these transcription factors' expression (11). In fact, a complex interaction between lipid and vitamin A metabolism, along with the complex communication between HSCs and WAT, plays a key role in manifesting MetS (11).

TABLE 6 | Studies that evaluated associations of circulating retinol and carotenoid concentration with obesity and metabolic syndrome components in children and adolescents aged 7–18 years.

References	Population	Age, years	Country	Design	Study measurement	Retinol	Carotenoid
Decsi et al. (54)	17 obese children	13.9 ± 0.3 [†]	Hungary	Cross-sectional	Anthropometric indices, body fat content and fasting plasma insulin	Positively associated with weights and heights	No report
Kuno et al. (47)	24 girls	10.7 ± 2.7 [†]	Japan	Case-control	Weight and height	No report	Negatively associated with obesity
Strauss (52)	6,139 children & adolescents	6–19	USA	Case-control	TC, TG, and BMI	No report	Negatively associated with obesity
Neuhouser et al. (56)	285 adolescents	12–17	USA	Cross-sectional	TC and BMI	Positively associated with TC	Positively associated with TC
Ford et al. (45)	4,231 children & adolescents	6–16	USA	Cross-sectional	BMI, HDL-C, non HDL-C and CRP	No report	Positively associated with HDL-c and non HDL-c Negatively associated with BMI
Morinobu et al. (49)	118 children	6–15	Japan	Case-control	Anthropometric indices, lipid profile	Positively associated with total lipids	Negatively associated with body weight
Molnár et al. (48)	38 children	14.7 ± 1.8 [†]	Hungary	Case-control	Anthropometric indices, FBG, insulin and lipid profile	No report	Negatively associated with MTS
Sarni et al. (51)	46 preschool children	5.7 [‡]	Brazil	Case-control	weight/height z-score, TG, TC, VLDL-C, HDL-C, and LDL-C	No correlation	Negatively associated with obesity and hyperlipidemia
de Souza Valente da Silva et al. (43)	471 children & adolescents	7–17	Brazil	Cross-sectional	Sex- and age-specific BMI	No correlation	Negatively associated with BMI
Beydoun et al. (35)	782–4,285 adolescents	12–19	USA	Cross-sectional	MTS components	Positively associated with HOMA-IR and MTS	Negatively associated with HOMA-IR and MTS
García et al. (55)	197 school-aged children	6–10.5	Mexico	Cross-sectional	Anthropometric indices, lipid profile, insulin resistance and chronic inflammation	Positively associated with measures of obesity, TG and TC	No report
Gunanti et al. (46)	1,131 children & adolescents	8–15	USA	Cross-sectional	BMI, TrFM, and TBFM	Positively associated with obesity	Negatively associated with obesity and fat mass
Wei et al. (57)	1,928 children	7–11	China	Cross-sectional	Anthropometric indices, FBG, lipid profile and BP	Negatively associated with obesity, hypertriglyceridemia and MTS	No report
Farook et al. (44)	670 children & adolescents	6–17	USA	Cohort	Anthropometric indices, HDL-c TC, TG, TBFM, BP, FBG, fasting insulin, and HOMA-IR	No report	Negatively associated with BMI, WC, FM, and TG Positively associated with HDL-C
Rupérez et al. (50)	1,444 children & adolescents	3–17	Spain	Case-control	FBG, TAG, HDL-C, LDL-C, fasting serum insulin and plasma pro-Inflammatory and endothelial Damage biomarkers	Positively associated with obesity Negatively associated with metabolically unhealthy status	Negatively associated with obesity and metabolically unhealthy status
Mummidi et al. (53)	580 children & adolescents	6–17	USA	Cross-sectional	Anthropometric indices, TBFM, BP, FBG, fasting serum insulin, HOMA-IR, HDL-C and TG	No report	Negatively associated with BMI, WC, TG, TBFM, FBG (–0.09), and positive Positively associated with HDL-C
Present study			Iran	Cross-sectional	Anthropometric indices, TG, TC, LDL-C, HDL-C, FBG, BP	Positively associated with obesity, abdominal obesity and FPG Negatively associated with HDL-C and DBP	No report

[†]Age presented as mean ± SD.

[‡]Age presented as mean.

BMI, Body mass index; BP, Blood pressure; CRP, C-reactive protein; FBG, Fasting blood glucose; HDL-C, High-density lipoprotein cholesterol; HOMA-IR, Homeostasis model assessment of insulin resistance; LDL-C, Low-density lipoprotein cholesterol; MetS, Metabolic syndrome; TAG, Triacylglycerols; TBFM, Total body fat mass; TC, Total cholesterol; TG, Triglycerides; TrFM, Truncal fat mass; VLDL-C, Very-low-density lipoprotein; WC, Waist circumference.

Vitamin A and its precursor could affect metabolic health in different ways. For example, cell-surface signaling receptors activated by RBP-retinol complex may explain how these compounds affect insulin signaling and energy balance (62). When retinol and retinol-binding protein 4 (RBP4) bind to the cell surface signaling receptor STRA6, it triggers JAK2/STAT5 signaling cascade, which leads to the expression of STAT target genes, including suppressor of cytokine signaling 3 (SOCS3). SOCS3 then contributes to inhibiting insulin signaling and PPAR γ , which results in increased lipid accumulation (62). Furthermore, retinoic acid may contribute to inducing adipogenesis and darkening of fat tissue, as well as promoting adipocyte fatty acid oxidation (63). β -Carotene could also suppress adipogenesis by producing β -apo-14'-carotenal and repressing of PPAR α , PPAR γ , and RXR activation, as well as the production of all-trans retinoic acid (64). Additionally, disturbed vitamin A metabolism such as changes in retinol metabolism due to elevated retinol excretion into serum and conversion into retinoic acid may promote disease progression as obese mice showed higher levels of serum retinol, but lower levels of liver retinol (61).

We did find no association between fruits, vegetables, and milk consumption with vitamin A status in our study population. The same results were duplicated in Bangladeshi school children that leafy vegetables consumption was not associated or negatively correlated with serum retinol levels (65). We found no association between serum retinol levels and demographic characteristics of our study population such as age, sex or region of residence, or socioeconomic status as suggested by previous studies (3, 56, 65). This observation might be partly explained by recent developments in Iran regarding nutrition education and support programs for needy families, as well as special attention being paid to child nutrition (65).

The present work has several limitations. First, we did not measure dietary energy, carotene, or vitamin A intake which is usually extracted from a quantitative food frequency questionnaire (FFQ). Second, the cross-sectional observational design does not permit us to determine causality. Third, considering the fat mass of participants rather than BMI could have been helpful and deserves consideration in future research. Fourth, multiple comparisons may account for some of our significant findings. Finally, residual confounding due to unmeasured or poorly measured variables cannot be ruled out. As for strengths, this is one of a few studies to analyze the obesity and cluster of metabolic syndrome components with serum biomarker of vitamin A deficiency in a large sample of Iranian children and adolescents from geographically distant and different centers. The study has the advantage of using nationally representative data and analyzing a large sample of children and adolescents from the major racial and ethnic groups in Iran.

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CONCLUSION

Overall, our study indicates that serum retinol concentration was positively associated with some metabolic syndrome components such as low HDL, high FBG, but not the occurrence of metabolic syndrome *per se*. Our results also support the potential role of serum retinol concentration in overall and abdominal obesity. However, further studies are needed to confirm our findings. In light of the associations between obesity and metabolic syndrome components with serum retinol concentration, future nutritional intervention studies are warranted to determine recommendations on appropriate dietary vitamin A intake to modify serum retinol concentrations with regards to metabolic health.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was approved by the Research and Ethics Council of Alborz University of Medical Sciences. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MQ designed and performed the statistical analysis. ES revised and edited the manuscript and assisted in the analysis. RH contributed to the design study, revised, and edited the manuscript. ZG assisted in the writing of the manuscript. PB revised and edited the manuscript. EK wrote the manuscript with input from all authors. RK aided in interpreting the results and revised the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded financially by Alborz University of Medical Sciences. It has not had any role in designing, interpreting or providing data.

ACKNOWLEDGMENTS

The authors would like to thank working on this National Survey and all participants who cooperated with this study.

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