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Hepcidin and iron metabolism associated with cardiometabolic risk factors in children: A case–control study

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Abstract *Background and aims:* Iron metabolism plays a crucial role in the development of cardiometabolic disease; however, the association between cardiometabolic risk factors (CMRFs) and hepcidin as well as other iron parameters remains unclear in children. The aims of this study were to compare the circulating hepcidin levels and iron metabolism between children with and without CMRFs and to investigate the association between those iron parameters and CMRFs.
Methods and results: A case–control study was conducted among 1126 children aged 7–14 years in the case group ($n = 563$) with CMRFs and the healthy control group ($n = 563$). Iron parameters, lipids, and anthropometric characteristics were evaluated. The information on demographics, diet, and physical activities was either children reported or parent reported. Compared with the healthy controls, children with CMRFs had higher levels of hepcidin and lower levels of serum iron, transferrin, and soluble transferrin receptor (sTfR; $P < 0.001$). Besides, the odds ratios (ORs) for low levels of high-density lipoprotein (HDL) were 2.03, 0.21, and 0.33 in children with higher hepcidin, transferrin, and sTfR levels ($P < 0.05$). Furthermore, ORs for cardiometabolic risk were 0.50 (95% confidence interval (CI): 0.30–0.85, $P < 0.05$), 0.22 (95% CI: 0.12, 0.42, $P < 0.01$) and 0.19 (95% CI: 0.10, 0.36, $P < 0.01$) in children with higher serum iron, transferrin, and sTfR levels, respectively.
Conclusion: The levels of hepcidin were higher, while those of iron, transferrin, and sTfR were lower in children with CMRF. Hepcidin was positively associated with the risk of low HDL levels, whereas transferrin and sTfR levels negatively correlated with the risk of low HDL levels. In addition, serum iron, transferrin, and sTfR levels were negatively associated with cardiometabolic risk.

Introduction

A series of studies have clearly documented that metabolic risk factors, such as obesity, hypertension, insulin resistance, and dyslipidemia, are closely associated with the onset of cardiovascular diseases (CVDs). Metabolic syndrome (MetS) was usually applied to describe the clustering of cardiometabolic risk factors and was defined as central adiposity, dyslipidemia, impaired glucose metabolism, and elevated blood pressure [1]. The prevalence of

Abbreviations: BMI, body mass index; *CI*, confidence interval; CVDs, cardiovascular diseases; DBP, diastolic blood pressure; Fe, serum iron; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MetS, metabolic syndrome; *OR*, odds ratio; SBP, systolic blood pressure; sTfR, soluble transferrin receptor; TC, total cholesterol; TG, triglyceride; WHR, waist-to-hip ratio.

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MetS in adolescents had sharply increased from 4.1% to 10% over the past decades according to the National Health and Nutrition Examination Survey data in the USA [2,3]. In China, a survey conducted in six cities showed that the prevalence of MetS in children and adolescents was 2.5% [4]. These two studies revealed that the proportion of children with at least one metabolic risk factor was even higher in the USA (73.2%) and China (25%). MetS and its risk factors in adolescents would accelerate and aggravate early atherosclerotic vascular changes, leading to an increasing risk of CVDs in adulthood [5]. Given the ascending prevalence and known adverse consequences of MetS, the prevention of the syndrome and its related cardiometabolic risk factors in childhood remain urgent public health priorities.

A large number of studies have shown that iron metabolism plays a crucial role in the development of cardiometabolic disorders, such as MetS, type 2 diabetes, atherosclerosis, and consequent CVDs [6]. Previous epidemiological studies reported that the hepcidin levels, the key regulator of iron metabolism, increased in children and adults with obesity and type 2 diabetes [7,8]. Another study conducted in adults with MetS demonstrated that higher hepcidin levels were associated with the increasing number of metabolic risk factors [9]. However, whether the same situation exists in children remains unclear. Other iron metabolic parameters, such as serum iron, ferritin, transferrin, and soluble transferrin receptor (sTfR), have also been reported to be associated with MetS and its components in adults [10–13]. Nevertheless, the relationships between cardiometabolic risk factors and multiple iron metabolic parameters, including hepcidin, transferrin, and sTfR, are less well studied in children, which are necessary to be explored.

Several studies carried out in in vitro cell lines have further indicated that hepcidin might contribute to iron-induced atherosclerosis [14]. It is well known that the atherosclerotic process is closely relevant to dyslipidemia. However, the associations between the lipid profile and hepcidin as well as other iron metabolic parameters are still unclear in children. Considering these factors, this study aimed to investigate the status of hepcidin and other iron parameters, such as serum iron, ferritin, transferrin, and sTfR, in children with and without cardiometabolic risk factors and to explore the associations between these iron parameters and the cardiometabolic risk factors, especially the adverse lipid profile.

Methods

Study population

The present study included children aged 7–14 years, who were enrolled from a large epidemiological study conducted in Guangzhou, South China, in 2014. Firstly, five elementary schools and four secondary schools were selected via multistage cluster sampling. Secondly, we chose subjects with the available anthropometric, lipid profile, and fasting serum glucose data, and then divided them into case and control groups according to the inclusive and exclusive criteria. The case group involved individuals with at least one MetS component according to the criteria published by Cook et al. [15] The control group included individuals without any MetS component, who were randomly matched by age and gender (1:1 pair-wise matching). Both groups excluded individuals with genetic syndromes, endocrine diseases, or psychiatric disorders. In addition, individuals who would graduate within a year (in grades 6 and 9) were not enrolled due to their stressful courses. Eventually 1126 adolescents were included in the present study.

This study was approved by the Ethical Committee of the Peking University. Signed informed consents were given by parents or other legal guardians of the participants.

Anthropometric measurement

All the participants were subjected to anthropometric measurements, namely height, weight, waist circumference, hip circumference, and blood pressure, which were performed by the same group of experienced clinicians and nurses (no more than four observers for each item). Height was measured to the nearest 0.1 cm using a fixed stadiometer (Yilian TZG, Jiangsu, PRC). Weight was measured to the nearest 0.1 kg using a lever scale (Hengxing RGT-140, Jiangsu, PRC). Waist circumference and hip circumference were measured to the nearest 0.1 cm using a flexible tape in the standing position at the end of a gentle respiration, taking the umbilical scar and the largest point of outer hip as the reference, respectively. Blood pressure was measured on the upper right arm in the seated position using a mercury sphygmomanometer (Yutu XJ1ID, Shanghai, PRC) with at least a 10-min rest before the measurement. The first and the fifth Korotkoff sounds were used for representing the systolic and diastolic blood pressure. These anthropometric measurements were digitally measured twice for each subject and the average values were calculated. Inter- and intra-observer reliability were >0.94 and > 0.96, respectively. The body mass index (BMI) was calculated as weight (kg)/(height (m)) [2], and the waist-to-hip ratio (WHR) was calculated as waist circumference (cm)/hip circumference (cm).

Questionnaire assessment

The self-reported questionnaires were developed on the basis of previously tested and validated questions, including questions of demography, sleep duration, physical activities (vigorous-intensity activities, moderate-intensity activities, and walking and sedentary behaviors) and diet (sugar-sweetened beverage consumption and snacking habits). For sleep duration, participants were asked, “How many hours do you sleep per day?” Sleep duration per day was categorized into four groups (<7.0, 7–9, 9–11, and >11 h/day). For physical activities, the participants were asked the following questions: “How

many days and how many hours per day did you perform vigorous-intensity activities (running, basketball, football, physical fitness activities, etc.), moderate-intensity activities (table tennis, moving something light, dancing, etc.), and walking last week?" Children were also asked questions regarding sedentary behaviors: "How many hours do you spend in sedentary behaviors (sitting or lying still at school and home, not including sleeping) each day?" To investigate sugar-sweetened beverage consumption and snacking habits, the following questions were put forth: "How many days and how many cups did you have sugary drinks last week? (One cup of sugar-sweetened beverage is approximately equal to 250 mL.)" and "How many days did you have snacks last week?"

Laboratory assays

Venous blood samples were collected from the children after an overnight fast. The serum and plasma were collected after centrifugation at 3000 r/min for 10 min at 4 °C within 2 h and were stored at −80 °C until analysis. The fasting serum glucose (FSG), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol (TC) levels were measured using routine laboratory methods, which were performed by specialty laboratories accredited by Peking University. The levels of serum iron, ferritin, transferrin, and sTfR were measured using an automated chemistry analyzer (HITACHI 7060, Hitachi Koki Co. Ltd., Hitachinaka, Japan). The serum iron level was determined by the ferrozine method (SI 7967, Randox Laboratories Co. Ltd., Crumlin, UK). The immunoturbidimetric assay kits were applied to test the levels of serum ferritin (Fer0060, Jingyuan medical instrument Co. Ltd., Shanghai, PRC), transferrin (Transferrin Reagent No.67758, Orion Diagnostica Oy Co. Ltd., Espoo, Finland), and sTfR (12148315, Roche Diagnostics Co. Ltd., Indianapolis, US). The serum hepcidin level was determined by enzyme-linked immune sorbent assay (ELISA) kits (SEB979Hu, Uscn Life Science Inc. Wuhan, Hubei, PRC) according to the manufacturer's instructions. For all laboratory methods, the intra- and inter-assay coefficients of variation were below 10% and 12%, respectively.

Definitions of metabolic risk factors and dyslipidemia

In detail, adolescents were classified as having metabolic risk factors and were recruited in the case group if they met one or more of the following criteria: (1) waist circumference ≥90th percentile for their age and sex according to the Chinese children percentiles [16]; (2) either systolic blood pressure (SBP) or diastolic blood pressure (DBP) ≥90th percentile for their height, age, and gender [17]; (3) triglyceride ≥1.7 mmol/L; (4) HDL ≤1.03 mmol/L; and (5) fasting serum glucose ≥5.6 mmol/L [18]. A combination of at least three of the abovementioned criteria constitutes a diagnosis of MetS. Definitions of high LDL and TC levels in this study were according to the high cutoff values of the US National Institutes of Health Heart, Lung and Blood Institute [19]. The definition of iron deficiency was considered with serum iron concentrations <45 μg/dL [20].

Statistical methods

We calculated the sample size for the case−control study on the basis of differences seen in the children with and without obesity [8]. In the previous study, the hepcidin level differed by 2 ng/L, with the standard deviation value (SD) of 8.4 ng/mL. Assuming a significance level of 0.05 and 90% power, the number of participants required in each group for obtaining a hepcidin level difference of 2 ng/L is 379. At least 445 participants should be enrolled in each group for a 20% dropout rate.

The data bank was established by EpiData 3.0 software (The EpiData Association, Odense, Denmark). The collected data were analyzed using the Statistical Package for the Social Science (SPSS) (version 19.0, SPSS Inc. Chicago, IL, USA). Categorical data were presented as cases with frequencies and percentages. Quantitative data were presented as means with SDs and medians with interquartile ranges. Paired sample *t*-test and Wilcoxon signed-rank test were used for the comparison of quantitative variables between the case and the control group, while the *chi*-squared test was used for categorical variables. For comparison among the subjects with different amounts of MetS components, one-way analysis of variance (ANOVA) and Kruskal−Wallis *H* test were used. Spearman's correlation analysis was applied to examine the correlation coefficients between iron parameters and lipids. Binary logistic regression was used for calculating the odds ratios (ORs) of individual cardiometabolic risk factors and general cardiometabolic risk factors in both crude model and adjusted model controlling for age, gender, physical activities, and dietary behaviors. ORs and 95% confidence intervals (CIs) were obtained as measures of association and precision. All *P*-values are two sided and all the statistical significance levels were set at $P = 0.05$.

Results

Baseline clinical and biochemical characteristics of the participants

The baseline characteristics of 1126 participants, all by case and control classification (case: $n = 563$, children with MetS components, control: $n = 563$, healthy children), are summarized in Table 1, including demographic and anthropometric characteristics, lipid levels, iron parameters, sleep duration, diet, and physical activities. The waist circumference, BMI, and WHR values as well as the TG and fasting serum glucose levels and blood pressure in children with MetS components were significantly higher compared with those of the healthy controls (all $P < 0.001$). By contrast, compared with their healthy counterparts, children in the case group had decreased levels of TC, HDL, and LDL, thus suggesting significant differences in the blood glucose and lipid levels between the two groups (all $P < 0.05$). Regarding the iron metabolic

Table 1 Baseline characteristics of the study participants segregated by case and control.

	All subjects (n = 1126)	Control (n = 563)	Children with any MetS component (n = 563)	P	Number of MetS components			P
					1 (n = 388)	2 (n = 135)	≥3 (n = 40)	
Demographic								
Gender, n (%)				–				0.228
Male	524 (46.5)	262 (46.5)	262 (46.5)		173 (44.6)	62 (45.9)	27 (67.5)	
Female	602 (53.5)	301 (53.5)	301 (53.5)		215 (55.4)	73 (54.1)	13 (22.5)	
Age (years)	9.59 ± 2.09	9.52 ± 2.08	9.52 ± 2.08	–	9.35 ± 2.08	10.11 ± 2.08	10.15 ± 1.67	–
Household income, *n* (%)				0.006				0.055
≤5000 CNY/month	118 (10.5)	67 (11.9)	51 (9.1)		34 (8.8)	14 (10.4)	3 (7.5)	
~12,000 CNY/month	269 (23.9)	139 (24.7)	130 (23.1)		86 (22.2)	31 (23.0)	13 (32.5)	
~15,000 CNY/month	86 (7.6)	30 (5.3)	56 (9.9)		41 (10.6)	14 (10.4)	1 (2.5)	
>15,000 CNY/month	143 (12.7)	61 (10.8)	82 (14.6)		60 (15.5)	18 (13.3)	4 (10.0)	
Unknown	510 (45.3)	266 (47.2)	244 (43.3)		167 (43.0)	58 (43.0)	19 (47.5)	
Anthropometry								
Height (cm)	141.45 ± 13.20	138.75 ± 12.10	144.15 ± 13.72	<0.001	142.02 ± 13.46	148.30 ± 13.39	150.88 ± 12.18	<0.001
Weight (kg)	36.91 ± 12.81	31.43 ± 8.78	42.40 ± 13.82	<0.001	39.17 ± 12.30	48.04 ± 14.23	54.64 ± 13.67	<0.001
BMI (kg/m^2)	17.95 ± 3.74	16.01 ± 2.23	19.90 ± 3.95	<0.001	18.98 ± 3.66	21.41 ± 3.69	23.68 ± 3.77	<0.001
WC (cm)	64.12 ± 10.95	58.23 ± 6.22	70.00 ± 11.48	<0.001	67.32 ± 11.17	74.56 ± 9.59	80.64 ± 9.20	<0.001
HC (cm)	73.30 ± 10.94	68.55 ± 8.45	78.04 ± 11.08	<0.001	75.60 ± 10.37	82.63 ± 10.33	86.29 ± 11.55	<0.001
WHR	0.88 ± 0.09	0.85 ± 0.05	0.90 ± 0.11	<0.001	0.89 ± 0.11	0.90 ± 0.07	0.95 ± 0.13	<0.001
SBP (mmHg)	97.15 ± 9.66	94.38 ± 7.83	99.94 ± 10.48	<0.001	98.51 ± 9.93	102.17 ± 10.84	106.18 ± 11.17	<0.001
DBP (mmHg)	61.98 ± 7.87	59.60 ± 6.45	64.38 ± 8.43	<0.001	63.02 ± 7.72	67.04 ± 8.76	68.58 ± 10.35	<0.001
Biochemistry								
TC (mmol/L)	4.33 ± 0.82	4.44 ± 0.76	4.23 ± 0.86	<0.001	4.23 ± 0.86	4.24 ± 0.89	4.22 ± 0.86	<0.001
TG (mmol/L)	0.95 ± 0.51	0.77 ± 0.27	1.11 ± 0.63	<0.001	0.95 ± 0.43	1.32 ± 0.67	2.08 ± 0.93	<0.001
HDL (mmol/L)	1.36 ± 0.34	1.50 ± 0.30	1.21 ± 0.31	<0.001	1.28 ± 0.31	1.11 ± 0.29	0.93 ± 0.12	<0.001
LDL (mmol/L)	2.42 ± 0.69	2.47 ± 0.68	2.38 ± 0.71	0.049	2.39 ± 0.69	2.39 ± 0.74	2.29 ± 0.63	0.194
FSG (mmol/L)	4.66 ± 0.71	4.61 ± 0.41	4.71 ± 0.91	0.025	4.70 ± 1.01	4.74 ± 0.70	4.93 ± 0.49	0.026
Fe (μmol/L)	15.87 ± 5.62	16.89 ± 5.65	15.04 ± 5.48	<0.001	15.04 ± 5.50	15.19 ± 5.38	14.48 ± 5.62	<0.001
Ferritin (μg/L)	56.00 (41.00−75.00)	60.00 (41.00−80.50)	54.00 (42.50−71.50)	0.517	55.00 (43.00−69.00)	52.00 (38.00−73.00)	61.00 (44.50−73.00)	0.051
Transferrin (g/L)	2.40 ± 0.43	2.50 ± 0.41	2.32 ± 0.43	<0.001	2.31 ± 0.41	2.30 ± 0.48	2.48 ± 0.46	<0.001
sTfR (mg/L)	3.35 ± 0.88	3.58 ± 0.84	3.16 ± 0.86	<0.001	3.16 ± 0.84	3.06 ± 0.93	3.48 ± 0.76	<0.001
Hepcidin (μg/L)	33.77 ± 12.64	32.70 ± 9.77	34.84 ± 14.91	0.004	34.74 ± 15.10	34.35 ± 15.46	37.50 ± 10.49	0.018
Ratio of sTfR/ferritin	58.10 (39.73−78.95)	61.66 (42.30−82.21)	54.52 (39.29−78.19)	0.012	56.52 (39.29−76.36)	54.72 (38.46−88.57)	59.02 (42.47−70.27)	0.225
Iron deficiency, n (%)	74(6.6)	20(3.6)	54(9.6)	<0.001	39(10.1)	13(9.6)	2(5.9)	<0.001
Sleep duration, *n* (%)				0.730				0.072
<7 h/day	80 (7.1)	39 (6.9)	41 (7.3)		25 (6.4)	11 (8.1)	5 (12.5)	
~9 h/day	611 (54.3)	284 (50.4)	327 (58.1)		228 (58.8)	80 (59.3)	19 (47.5)	
~11 h/day	216 (19.2)	92 (16.3)	124 (22.0)		92 (23.7)	22 (16.3)	10 (25.0)	
>11 h/day	9 (0.8)	4 (0.7)	5 (0.9)		1 (0.3)	4 (3.0)	0 (0.0)	
Unknown	210 (18.7)	144 (25.6)	66 (11.7)		42 (10.8)	18 (13.3)	6 (15.0)	
Physical activities								
Vigorous intensity (h/week)	2.00 (0.50−4.50)	2.00 (0.29−4.00)	2.00 (0.66−4.50)	0.358	2.00 (0.58−4.50)	2.00 (1.00−4.50)	2.00 (0.75−5.37)	0.828
Moderate intensity (h/week)	2.00 (0.67−4.00)	2.00 (0.67−4.18)	2.00 (0.75−4.00)	0.985	1.67 (0.92−3.75)	2.00 (0.67−3.50)	2.00 (0.83−4.00)	0.974
Walking (h/week)	3.50 (1.75−7.00)	3.50 (1.29−7.00)	3.50 (1.88−7.00)	0.552	3.50 (1.75−7.00)	5.25 (2.33−10.15)	4.00 (1.38−6.83)	0.028
Sedentary behavior (h/day)	4.50 (2.00−7.83)	4.50 (2.00−7.18)	4.50 (2.00−8.00)	0.946	4.50 (1.98−7.75)	5.00 (3.00−8.00)	2.02 (0.91−5.25)	0.066
Diet								
Sugary beverages consumption (ml/week)	250 (0.00−625.00)	250.00 (0.00−500.00)	250 (0.00−750.00)	0.174	250.00 (0.00−500.00)	250.00 (0.00−750.00)	500.00 (0.00−1000.00)	0.027
Snacking habits (day/week)	1.00 (0.00−2.00)	1.00 (0.00−2.00)	1.00 (0.00−2.00)	0.115	1.00 (0.00−2.00)	1.00 (0.00−2.00)	1.00 (0.00−2.00)	0.298

status, the levels of serum iron and transferrin, sTfR concentration, and the ratio of sTfR/ferritin were lower, while the hepcidin concentration was significantly higher in the case group, compared with those concentrations of the control group ($P < 0.05$). Meanwhile, the prevalence of iron deficiency was higher in children with MetS components. There were no significant differences in the serum ferritin levels, sleep duration, physical activities, sedentary behaviors, sugary beverage consumption, and snacking habits between the case and control groups.

In order to observe the status of the baseline characteristics in various degrees of metabolic dysfunction, we analyzed these variables by different numbers of MetS components in the case group (Table 1). Evidently, all anthropometric characteristics and the TG, fasting serum glucose, hepcidin, and ferritin levels exhibited an ascending trend, while the HDL level showed a descending trend with an increasing number of MetS components.

Relationship between iron parameters and cardiometabolic risk factors in the participants

Spearman's correlation coefficients were applied to examine the relationship between the iron parameters and the cardiometabolic risk factors (Table 2). The serum iron level was positively associated with the levels of TC, HDL, and LDL and negatively associated with waist circumference (all $P < 0.05$). The serum ferritin level was positively related to TC and LDL concentrations in children. The transferrin level positively correlated with TC and HDL and fasting serum glucose concentrations in children (all $P < 0.05$). The sTfR level was positively associated with the levels of TC, LDL, and HDL, while it was negatively associated with TG concentration and waist circumference (all $P < 0.05$). However, no significant correlations were found between the hepcidin level and these cardiometabolic risk factors.

We further examined the associations between the iron metabolic parameters and the risks of individual cardiometabolic risk factors in children using logistic regression analysis (Table 3). After adjustment, the *OR* for low HDL levels in the highest quartile of hepcidin was 2.03 (95% confidence interval (CI): 1.10–3.74, $P < 0.05$) compared with the lowest quartile, which indicated that the higher hepcidin concentration was associated with the higher risk of low HDL level. The adjusted OR for high TC level was 2.90 (95% CI: 1.14–7.40, $P < 0.05$) in the highest quartile in contrast with the lowest quartile of ferritin. Meanwhile, the adjusted ORs for low HDL and high waist circumference in the highest quartile versus the lowest quartile of serum iron were 0.39 (95% CI: 0.25–0.61, $P < 0.01$) and 0.48 (95% CI: 0.23–0.69, $P < 0.01$), respectively. The adjusted OR for the low HDL level was 0.21 (95% CI: 0.10–0.43, $P < 0.01$) in the highest quartile in contrast with the lowest quartile of transferrin. In the highest quartile of sTfR, the adjusted OR of low HDL level was 0.33 (95% CI: 0.18–0.60, $P < 0.01$) and that of high waist circumference was 0.46 (95% CI: 0.28–0.73, $P < 0.01$) when compared with the lowest quartile.

The associations between the iron metabolic parameter levels and the general cardiometabolic risks in children are shown in Table 4. In contrast with the lowest quartile, the adjusted ORs of having more than one MetS component in the highest quartile of serum iron, transferrin, and sTfR were 0.50 (95% CI: 0.30–0.85, $P < 0.05$), 0.22 (95% CI: 0.12–0.42, $P < 0.01$) and 0.19 (95% CI: 0.10–0.36, $P < 0.01$), respectively, indicating that a higher level of serum iron, transferrin, and sTfR would contribute to reduced cardiometabolic risk in children.

Table 2 Spearman's correlation coefficients between iron parameters and cardiometabolic risk factors.

	Hepcidin	Fe	Ferritin	Transferrin	sTfR
TC (mmol/L)	0.024	**0.102**[b]	**0.112**[b]	**0.073**[a]	**0.111**[b]
LDL (mmol/L)	0.049	**0.075**[a]	**0.147**[b]	0.059	**0.114**[a]
TG (mmol/L)	−0.002	0.010	−0.042	−0.027	**−0.071**[a]
HDL (mmol/L)	−0.033	**0.146**[b]	−0.018	**0.161**[b]	**0.168**[b]
WC (cm)	0.023	**−0.085**[b]	−0.013	0.054	**−0.094**[a]
SBP (mmHg)	0.011	−0.035	0.000	0.062	0.015
DBP (mmHg)	−0.017	−0.034	0.027	0.025	−0.007
FSG (mmol/L)	−0.043	0.027	0.003	**0.105**[b]	0.035

Bold text: Significant correlations was revealed at both 0.05 and 0.01 level.
[a] The correlation coefficient is significant at the 0.05 level.
[b] The correlation coefficient is significant at the 0.01 level.

Discussion

Several studies have demonstrated that iron metabolic disorder plays an important role in the initiation and progression of atherosclerosis and the relevant cardiometabolic disease in adults. However, few studies explored the status of circulating hepcidin and iron metabolic parameters and their association with cardiometabolic risk factors in children. In the present study, children with cardiometabolic risk factors had higher levels of hepcidin and lower levels of serum iron, transferrin, and sTfR. Hepcidin levels elevated with an increasing number of MetS components. Meanwhile, higher serum hepcidin level was related to a higher risk of low HDL level, while the higher levels of transferrin and sTfR were associated with a lower risk of lower HDL levels. Higher levels of serum iron and sTfR were associated with a lower risk of abdominal obesity. Furthermore, higher levels of serum iron, transferrin, and sTfR were significantly associated with a lower cardiometabolic risk in children.

The status of hepcidin and its association with HDL

The results of our study have shown higher hepcidin levels in children with MetS components, compared with their healthy counterparts. In addition, the hepcidin levels increased with an increasing number of MetS components. An epidemiological study has also reported high levels of hepcidin in MetS adults [9]. The underlying mechanism of high hepcidin levels in the individuals with MetS

Table 3 Associations of individual cardiometabolic risk factors[a] and iron parameters.[a].

	Hepcidin		Fe		Ferritin		Transferrin		sTfR	
	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
High TC										
Q1	1	1	1	1	1	1	1	1	1	1
Q2	1.14 (0.70,1.83)	1.64 (0.78,3.47)	1.08 (0.62,1.89)	0.63 (0.28,1.44)	1.14 (0.62,2.11)	1.64 (0.61,4.40)	0.78 (0.44,1.39)	0.90 (0.39,2.08)	1.65 (0.94,2.90)	1.08 (0.49,2.36)
Q3	0.81 (0.49,1.33)	0.96 (0.44,2.10)	1.03 (0.59,1.80)	0.83 (0.38,1.84)	1.32 (0.71,2.45)	1.33 (0.46,3.86)	1.07 (0.62,1.85)	0.77 (0.32,1.83)	1.57 (0.87,2.83)	0.81 (0.34,1.95)
Q4	0.66 (0.38,1.11)	0.89 (0.41,1.94)	1.25 (0.73,2.14)	0.63 (0.28,1.41)	**2.28 (1.31,3.97)**[d]	**2.90 (1.14,7.40)**[c]	1.28 (0.76,2.17)	1.28 (0.57,2.84)	**1.79 (1.01,3.19)**[c]	1.35 (0.59,3.10)
High LDL										
Q1	1	1	1	1	1	1	1	1	1	1
Q2	1.27 (0.73,2.20)	1.52 (0.65,3.55)	1.01 (0.52,1.98)	0.91 (0.34,2.46)	1.42 (0.71,2.82)	1.46 (0.54,4.00)	0.88 (0.47,1.68)	1.12 (0.45,2.78)	**2.09 (1.06,4.12)**[c]	1.13 (0.45,2.86)
Q3	0.54 (0.28,1.03)	0.72 (0.28,1.87)	1.04 (0.54,2.01)	1.19 (0.46,3.13)	1.06 (0.50,2.24)	0.48 (0.12,1.92)	0.91 (0.48,1.72)	0.36 (0.11,1.21)	1.92 (0.94,3.91)	1.00 (0.37,2.71)
Q4	0.87 (0.49,1.55)	0.98 (0.41,2.35)	1.35 (0.72,2.52)	1.07 (0.42,2.76)	**2.25 (1.19,4.28)**[d]	1.95 (0.73,5.22)	1.05 (0.57,1.94)	1.13 (0.45,2.81)	1.74 (0.85,3.56)	1.25 (0.47,3.36)
High TG										
Q1	1	1	1	1	1	1	1		1	1
Q2	0.64 (0.35,1.15)	1.33 (0.60,2.96)	1.33 (0.72,2.45)	1.27 (0.56,2.90)	0.66 (0.37,1.19)	0.71 (0.30,1.68)	0.68 (0.39,1.18)	0.61 (0.27,1.35)	**0.53 (0.30,0.94)**[c]	0.49 (0.22,1.11)
Q3	**0.54 (0.30,0.99)**[c]	0.56 (0.22,1.45)	1.07 (0.58,2.00)	1.17 (0.48,2.86)	0.61 (0.33,1.14)	0.68 (0.27,1.73)	**0.34 (0.17,0.67)**[d]	**0.19 (0.06,0.58)**[d]	0.69 (0.39,1.23)	0.58 (0.25,1.37)
Q4	0.86 (0.50,1.47)	1.21 (0.56,2.62)	1.01 (0.54,1.89)	0.83 (0.35,1.99)	0.83 (0.48,1.45)	1.04 (0.45,2.39)	0.60 (0.34,1.06)	0.57 (0.25,1.27)	**0.53 (0.29,0.97)**[c]	0.47 (0.19,1.16)
Low HDL										
Q1	1	1	1	1	1	1	1	1	1	1
Q2	0.94 (0.61,1.53)	1.64 (0.85,3.17)	**0.55 (0.36,0.85)**[d]	0.61 (0.36,1.01)	1.44 (0.91,2.27)	1.37 (0.72,2.64)	**0.61 (0.41,0.92)**[c]	**0.47 (0.25,0.87)**[c]	**0.47 (0.31,0.70)**[d]	**0.56 (0.34,0.92)**[c]
Q3	0.84 (0.53,1.32)	1.05 (0.54,2.07)	**0.41 (0.31,0.73)**[d]	**0.57 (0.34,0.96)**[c]	1.27 (0.78,2.05)	1.34 (0.67,2.66)	**0.34 (0.21,0.53)**[d]	**0.42 (0.22,0.79)**[d]	**0.36 (0.23,0.57)**[d]	**0.44 (0.25,0.77)**[d]
Q4	**1.58 (1.05,2.40)**[c]	**2.03 (1.10,3.74)**[c]	**0.39 (0.25,0.61)**[d]	**0.50 (0.30,0.84)**[d]	1.32 (0.83,2.10)	0.86 (0.43,1.74)	**0.33 (0.21,0.52)**[d]	**0.21 (0.10,0.43)**[d]	**0.31 (0.19,0.49)**[d]	**0.33 (0.18,0.60)**[d]
High WC										
Q1	1	1	1	1	1	1	1	1	1	1
Q2	0.86 (0.60,1.25)	1.07 (0.62,1.86)	**0.61 (0.42,0.90)**[c]	0.67 (0.40,1.14)	1.16 (0.80,1.70)	1.43 (0.82,2.48)	1.07 (0.74,1.54)	1.10 (0.65,2.88)	**0.48 (0.34,0.70)**[d]	**0.53 (0.34,0.82)**[d]
Q3	0.92 (0.64,1.31)	1.04 (0.62,1.75)	0.84 (0.58,1.20)	1.10 (0.64,1.88)	1.38 (0.93,2.03)	1.75 (0.98,3.12)	**0.61 (0.41,0.89)**[c]	0.63 (0.36,1.10)	**0.52 (0.36,0.76)**[d]	**0.40 (0.25,0.64)**[d]
Q4	1.33 (0.94,1.88)	1.41 (0.86,2.33)	**0.48 (0.33,0.70)**[d]	**0.40 (0.23,0.69)**[d]	1.09 (0.74,1.59)	0.78 (0.44,1.40)	0.83 (0.57,1.20)	0.82 (0.48,1.41)	**0.56 (0.39,0.81)**[d]	**0.46 (0.28,0.73)**[d]
High SBP										
Q1	1	1	1	1	1	1	1	1	1	1
Q2	1.71 (0.76,3.88)	2.49 (0.56,11.04)	0.73 (0.31,1.69)	0.35 (0.09,1.39)	1.23 (0.58,2.62)	0.26 (0.05,1.29)	1.24 (0.59,2.62)	1.07 (0.23,4.96)	0.72 (0.36,1.47)	0.63 (0.23,1.78)
Q3	1.54 (0.68,3.50)	2.56 (0.59,11.16)	1.10 (0.52,2.33)	0.70 (0.21,2.31)	1.23 (0.56,2.67)	0.98 (0.30,3.14)	0.88 (0.39,1.97)	1.06 (0.23,4.99)	0.52 (0.23,1.18)	0.57 (0.19,1.78)
Q4	1.80 (0.81,4.01)	2.59 (0.63,10.65)	1.23 (0.59,2.56)	0.59 (0.18,1.88)	0.98 (0.44,2.16)	0.66 (0.19,2.21)	0.99 (0.45,2.14)	2.63 (0.68,10.12)	0.80 (0.39,1.64)	0.94 (0.34,2.59)
High DBP										
Q1	1	1	1	1	1	1	1	1	1	1
Q2	1.32 (0.60,2.90)	1.22 (0.41,3.66)	0.87 (0.36,2.08)	0.38 (0.10,1.54)	0.45 (0.19,1.06)	0.62 (0.18,2.16)	1.71 (0.74,3.95)	0.79 (0.18,3.42)	0.72 (0.35,1.48)	1.04 (0.42,2.62)
Q3	**0.25 (0.07,0.88)**[c]	0.14 (0.02,1.16)	0.80 (0.33,1.92)	0.67 (0.19,2.37)	0.45 (0.23,1.22)	0.66 (0.18,2.46)	0.74 (0.27,2.02)	1.34 (0.34,5.35)	**0.24 (0.08,0.73)**[c]	0.27 (0.06,1.29)
Q4	1.21 (0.55,2.67)	0.71 (0.22,2.31)	0.87 (0.37,2.05)	0.70 (0.23,2.16)	0.54 (0.24,1.24)	0.70 (0.21,2.40)	1.02 (0.41,2.55)	1.93 (0.54,6.91)	0.42 (0.18,1.01)	0.66 (0.21,2.06)
High FSG										
Q1	1	1	1	1	1	1	1	1	1	1
Q2	0.61 (0.20,1.85)	0.44 (0.08,2.37)	1.33 (0.53,3.38)	3.51 (0.76,16.15)	2.09 (0.78,5.58)	1.66 (0.31,8.96)	1.71 (0.71,4.17)	4.72 (0.85,26.21)	0.60 (0.25,1.43)	1.13 (0.36,3.50)
Q3	0.44 (0.13,1.45)	0.24 (0.03,2.14)	0.55 (0.18,1.70)	0.55 (0.05,5.96)	1.29 (0.44,3.77)	2.75 (0.54,14.06)	0.60 (0.19,1.85)	2.36 (0.39,14.50)	**0.24 (0.07,0.85)**[c]	0.54 (0.13,2.32)

Table 3 (*continued*)

	Hepcidin		Fe		Ferritin		Transferrin		sTfR	
	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[b]
Q4	1.39 (0.58,3.36)	1.49 (0.45,4.92)	0.65 (0.22,1.90)	2.39 (0.51,11.22)	0.45 (0.11,1.83)	1.34 (0.25,7.17)	0.34 (0.09,1.30)	0.72 (0.09,5.98)	0.39 (0.14,1.10)	0.44 (0.10,1.91)

Bold text: Significant OR was revealed at both 0.05 and 0.01 level.
[a] Hepcidin quartiles were <26.20, 26.20–32.33, 32.33–39.41, and >39.41 μg/L; serum iron quartiles were <11.90, 11.90–15.45, 15.45–18.90, and >18.90 μmol/L; serum ferritin quartiles were <40.00, 40.00–56.00, 56.00–73.00, and >75.00 μg/L; transferrin quartiles were <2.08, 2.08–2.37, 2.37–2.68, and >2.68 g/L; sTfR quartiles were <2.70, 2.70–3.30, 3.30–3.80, and >3.80 mg/L.
[b] Adjusted for age, gender, physical activities, and dietary behaviors.
[c] The *OR* is significant at the 0.05 level.
[d] The *OR* is significant at the 0.01 level.

components needs to be further investigated. As children with different quantities of MetS components have different BMI, we speculate that in individuals with MetS components, systematic inflammatory states exist, leading to the elevated serum hepcidin levels [21]. Alternatively, it is possible that the iron overload, which would interfere with the hepcidin synthesis and secretion as a compensatory mechanism [22], was associated with an inflammatory and oxidative response causing a series of metabolic disorders [23]. However, another study has shown an inconsistent result, wherein no difference in the serum hepcidin levels was observed between the adults with and without MetS and diabetes mellitus [24]; the small sample size of this study might obscure the difference. In addition, our results showed a lower level of serum iron, transferrin, and sTfR in children with MetS components. Therefore, the underlying theory might be that the systematic inflammation directly contributes to a higher level of hepcidin secretion, which would down-regulate the iron metabolism.

First, our study revealed a significant positive correlation between hepcidin and a higher risk of low HDL level in children, thereby indicating a potential relationship between hepcidin and dyslipidemia. It has been

Table 4 Association between general cardio-metabolic risk and iron metabolism biomarkers.

	Control (*n*, %)	Case (*n*, %)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Hepcidin				
Q1[a]	151 (45.2)	183 (54.8)	1	1
Q2[a]	169 (57.5)	125 (42.5)	0.73 (0.53,1.03)	0.96 (0.58,1.60)
Q3[a]	182 (58.7)	128 (41.3)	**0.65 (0.47,0.90)**[c]	0.87 (0.54,1.41)
Q4[a]	123 (39.4)	189 (60.3)	1.27 (0.93,1.73)	1.60 (0.99,2.60)
Fe				
Q1[a]	95 (33.5)	189 (66.5)	1	1
Q2[a]	112 (41.6)	157 (58.4)	**0.69 (0.27,0.99)**[c]	0.86 (0.50,1.49)
Q3[a]	118 (42.4)	160 (57.6)	0.74 (0.51,1.06)	1.17 (0.67,2.07)
Q4[a]	162 (59.3)	111 (40.7)	**0.41 (0.24,0.49)**[d]	**0.50 (0.30,0.85)**[c]
Ferritin				
Q1[a]	121 (44.3)	152 (55.7)	1	1
Q2[a]	100 (38.8)	158 (61.2)	1.41 (0.98,2.02)	1.51 (0.85,2.69)
Q3[a]	96 (40.2)	143 (59.8)	1.29 (0.89,1.87)	1.68 (0.91,3.10)
Q4[a]	132 (48.5)	140 (56.9)	0.93 (0.65,1.32)	0.72 (0.41,1.27)
Transferrin				
Q1[a]	66 (24.5)	203 (75.5)	1	1
Q2[a]	108 (38.8)	175 (61.8)	**0.56 (0.38,0.82)**[d]	**0.39 (0.21,0.73)**[d]
Q3[a]	153 (56.3)	119 (43.8)	**0.27 (0.19,0.40)**[d]	**0.22 (0.12,0.41)**[d]
Q4[a]	162 (57.9)	118 (42.1)	**0.29 (0.19,0.42)**[d]	**0.22 (0.12,0.42)**[d]
sTfR				
Q1[a]	43 (15.5)	234 (84.5)	1	1
Q2[a]	154 (49.8)	155 (50.2)	**0.20 (0.13,0.31)**[d]	**0.24 (0.13,0.45)**[d]
Q3[a]	143 (57.3)	107 (44.4)	**0.17 (0.11,0.25)**[d]	**0.15 (0.08,0.28)**[d]
Q4[a]	149 (55.6)	118 (42.1)	**0.18 (0.12,0.27)**[d]	**0.19 (0.10,0.36)**[d]

Bold text: Significant OR was revealed at both 0.05 and 0.01 level.
[a] Hepcidin quartiles were <26.20, 26.20–32.33, 32.33–39.41, and >39.41 μg/L; serum iron quartiles were <11.90, 11.90–15.45, 15.45–18.90, and >18.90 μmol/L; serum ferritin quartiles were <40.00, 40.00–56.00, 56.00–73.00, and >75.00 μg/L; transferrin quartiles were <2.08, 2.08–2.37, 2.37–2.68, and >2.68 g/L; sTfR quartiles were <2.70, 2.70–3.30, 3.30–3.80, and >3.80 mg/L.
[b] Adjusted for age, gender, physical activities, and dietary behaviors.
[c] The *OR* is significant at the 0.05 level.
[d] The *OR* is significant at the 0.01 level.

demonstrated that low HDL level is independently associated with markers of inflammation and early state of atherosclerosis [25]. Therefore, it can be speculated that higher hepcidin levels might be related to the early progression of atherosclerosis. However, the mechanism of the association between hepcidin and low HDL levels necessitated further study.

The status of serum iron, transferrin, and sTfR levels and their association with cardiometabolic risk

A series of studies have shown that iron metabolism is closely associated with CVDs [26–28]. These findings most commonly suggested iron overload, but iron deficiency has also been described regarding higher cardiometabolic risk in adults [28,29]. Our present study has revealed lower serum iron levels and a higher prevalence of iron deficiency in children with MetS components. In addition, a higher level of serum iron contributed to reduced cardiometabolic risk. The results in the present study imply that iron deficiency may also be associated with cardiometabolic risk in children.

Previous studies have reported higher sTfR levels in children with diagnosed MetS [30], whereas the sTfR levels did not differ between adults with and without MetS components [31]. The present study, however, showed lower transferrin and sTfR levels in children with MetS components, indicating that the status of transferrin and sTfR levels is different between children with individual MetS components and diagnosed MetS. Our study also reported that children with more than three MetS components had higher transferrin and sTfR levels; this finding is similar to the study conducted in the Chinese population that serum transferrin concentrations elevated gradually with an increasing number of MetS components [11]. As increased transferrin and sTfR levels in subjects with iron deficiency were related to elevated erythropoietic activity [32,33], we speculate that erythropoiesis was less active in subjects with one or two MetS components than in the healthy children, which needs to be investigated further.

Meanwhile, several studies in adults suggested that both higher sTfR and transferrin levels were associated with higher cardiovascular risk, including MetS and impaired glucose tolerance [11,12], whereas studies on the association between cardiometabolic risk and circulating sTfR and transferrin levels in children are limited. A recent study in children indicated that sTfR levels are associated with a higher risk of MetS in children [30], which is different from the results in our study. In the present study, both higher sTfR and transferrin levels were related to lower cardiometabolic risk and the potential reason might be that most of the children in the case group in this study had only one or two MetS components, which were insufficient for diagnosed MetS. Hence, further investigation on the relationship between the transferrin and sTfR levels and cardiometabolic risk factors is needed.

The present study has several limitations. First, as the study was conducted in a case–control design, the causal sequence underlying the relationships between iron metabolic parameters and dyslipidemia can hardly be detected. Meanwhile, the study was based on multiple testing, and therefore we are unable to discard the associations by chance. Second, compared with the conventional diet and physical activity questionnaire, we developed a questionnaire focusing on collecting information of food pattern and activities duration, which was more practical and eligible to apply in a large population study among children. As the reliability and validity of the questionnaire have been examined, it is very unlikely that this limitation would challenge the validity of our study. In addition, this study did not measure the inflammatory and hepatic factors, such as C-reactive protein, fibrinogen, and transaminases, which are relevant confounders of iron markers. Therefore, it is necessary to further investigate the relationship between these biomarkers in future.

In conclusion, children with cardiometabolic risk factors had higher hepcidin level and lower levels of serum iron, transferrin, and sTfR in comparison with their healthy counterparts. Moreover, higher hepcidin levels were associated with a higher risk of low HDL levels, while higher levels of transferrin and sTfR were associated with a lower risk of low HDL levels. Higher levels of serum iron and sTfR were associated with a lower risk of abdominal obesity. Furthermore, higher levels of serum iron, transferrin, and sTfR were related to the lower general cardiometabolic risk in children. These findings suggested that a higher level of hepcidin was associated with a higher risk of dyslipidemia in children, which might contribute to the increased risk of atherosclerosis and related CVD in adulthood, whereas higher levels of serum iron, transferrin, and sTfR might be negatively associated with a lower risk of cardiometabolic disease in adulthood. Thus, regulation of the iron metabolic disorders in children could be a new preventive strategy for CVD occurrence in the adult stage.

Disclosure

The authors declared that they have no potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2016.03.005.

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