Association of Whole Blood Copper, Magnesium and Zinc Levels with Metabolic Syndrome Components in 6–12-Year-Old Rural Chinese Children: 2010–2012 China National Nutrition and Health Survey

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Research

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Abstract

Background: Metabolic syndrome (MetS) is a major public health problem in the world and some studies indicated that it is significantly associated with the future risk of cardiovascular disease. There is also a certain prevalence of Mets in childhood and shows a trend of younger age. Previous studies on the relationship between elements and MetS were mostly seen in adults with single element analysis, and reports on children and the combined effects of multiple elements were very limited. With the data form 2010–2012 China National Nutrition and Health Survey, we aim to investigate the association between whole blood Cu, Mg and Zn in both single and combined effects and MetS components in 6–12-year-old rural Chinese children.

Methods: A total of 911 children (51.2% male, 48.7% female) aged 6–12 years were enrolled. Basic characteristics, metals and MetS component parameters were collected. Multivariate logistic regression analysis was performed to examine the independent relationship between metals and MetS components.

Results: Copper was positively associated with elevated waist (OR=2.00, 1.18–3.28) and negatively associated with elevated TG (OR=0.33, 0.16-0.65). When high Cu combined with Zn, the association with elevated waist and elevated TG both disappeared. In the combination of Cu and Mg, high Cu with high Mg had a positive association with elevated waist (OR=2.03, 1.26-3.27) and high Cu with low Mg had a negative asscoiation with elevated TG (OR=0.40, 0.16-0.95).

Conclusions: Our study suggested that both the single and combined effects of Cu, Mg and Zn were associated with MetS components, especially in elevated waist and TG. And the comprehensive analysis of multiple elements was different from the results of single element analysis, which provide new avenues for the early screening of MetS. Additional research is needed to confirm these findings in other populations.

1. Introduction

Metabolic syndrome (MetS) is associated with a cluster of related risk factors of metabolic origin that promote the development of cardiovascular disease and increase the risk for development of type 2 diabetes [1]. It may be the result of the interaction of environmental, genetic and lifestyle factors. Currently, MetS is increasing worldwide and approximately 34% of the population meet the criteria for MetS; 33.9% of the Chinese population meet this criteria[2]. The prevalence of this chronic disease is increasing rapidly and showing a trend of impacting younger age groups. In Chinese children, the prevalence of MetS increased from 2.3% in 2004–2010 to 3.2% in 2011–2014 [3]. In recent years, there are also some studies [4, 5] shown that metabolic syndrome is significantly associated with the future risk of cardiovascular disease. Therefore, it is particularly important to explore the risk factors of metabolic syndrome and preventive methods in early life.

Copper (Cu), magnesium (Mg) and zinc (Zn) are all important trace elements involved in various metabolic pathways [6, 7]. It was first recognized by Hart et al. [8] in 1928 that Cu is an essential metal for normal growth and development as an electron transfer intermediate in redox reactions [9], which has a high level of oxidation and may lead to excessive damaging reactive oxygen species (ROS) by redox reactions [10, 11]. Zn also play an important role in oxidative stress and inflammation [12, 13], as a co-factor of antioxidant enzymes according to the report [14]. Magnesium as the second most abundant intracellular ion, it deficiency is associated with several diseases, such as coronary heart disease and type 2 diabetes [15]. One hypothesis suggests that a key mechanism leading to MetS involves oxidative stress caused by redox imbalance [16]. Thus, metals may be related to the development of MetS. Several studies have found relationships between single metal levels, such as Zn [17], Cu [18] and Mg [19], and MetS. Although diet or environmental exposures are often related to multiple elements at the same time, reports on the joint analysis are very limited. The Dongfeng cohort in China first explored the relationship between 23 elements in the plasma of the elderly and type 2 diabetes[20], and found that the combined effect of multi-element is different from that of single element analysis, which reminds us that we need to pay attention to the simultaneous analysis of multiple elements to health outcomes.

In this cross-sectional study, we aim to investigated the association between single and combined effect of whole blood Cu, Mg, Zn and MetS components in Chinese children from the 2010–2012 China National Nutrition and Health Survey (CNNS). And we hope to provide new ideas for further understanding of the occurrence and development of chronic diseases.

2. Materials And Methods

2.1 Subjects

The study was based on data obtained from the 2010–2012 CNNS, which was a cross-sectional, nationally-representative survey. According to Green's rule of numbers of participants used to examine relationships, a reasonable sample size is greater than 50 + 8 m (where m is the number of independent variables) for testing a multiple correlation [21]. In this study, the number of independent variables was 15 and the minimum sample size was 170. We randomly selected 1008 participants (equally from females and males) from the 2010–2012 CNNS who were aged 6 to 12 years and from 72 rural areas, which all had complete physical detections and laboratory tests. Children were sampled by a multi-stage stratified random sampling method. All children were re-examined after physical and biological data collection with the following exclusion criteria: 1) missing data for variables (excluded 33 children); 2) data does not meet test standards (excluded 41 children); 3) outlier for statistical analysis (excluded 23 children). Due to the exclusion of certain children, 911 children were finally recruited in this study. All children and their guardians gave informed consent for inclusion before they participated in the study. The study protocol was approved by the Ethics Committee of the Institute for Nutrition and Food Safety, Chinese Center for Disease Control and Prevention (now known as the National Institute for Nutrition and Health, China CDC; file number 2013-018).

2.2 Data collection

Physical examinations were performed by trained medical staff following standardized procedures. Height was measured by a Seca 213 Portable Stadiometer Height-Rod with a precision of 0.1 cm. Body weight was measured by a Seca 877 electronic flat scale with a precision of 0.1 kg. During the measurements, child was required to take off shoes, hats, and coats, and females untied their braids to ensure the accuracy of measurements. Body mass index (BMI) was calculated as weight (kg)/square of height (m^2). Waist circumference was measured two centimeters above the navel by a tape with a precision of 0.1 cm. Systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg) were assessed in the right upper arm using a mercury sphygmomanometer. The blood pressure of each child was the average of three measurements. Venous blood was collected from all children in the morning after 10–14 h of fasting, and each sample was divided between an anticoagulation tube and serum separator tube. Blood samples in serum separator tubes were promptly centrifuged at 3000 g for 15 min, and divided into serum aliquots and frozen at − 80 °C for subsequent assays. Serum fasting glucose (FG), high density lipoprotein-cholesterol (HDL-C), and triglyceride (TG) levels were measured by an enzymatic method using a Hitachi 7600 automatic biochemical analyzer (Japan). Whole blood Cu, Mg and Zn concentrations were measured by inductively coupled plasma mass spectrometry (NexION 350D, PerkinElmer) from the anticoagulation tube in Kinetic Energy Discrimination (KED) model.

2.3 Definition of MetS and its components

As the children in this study were aged 6 to 12 years, no consistent definition of MetS could be used in this analysis. We adopted a modified criteria for MetS from the American Academy of Pediatrics and International Diabetes Federation [22], which indicate MetS has the presence of ≥ 3 of the risk factors. The MetS components were defined as follows: 1) obesity: waist circumference ≥ 95th percentile of children of the same age and sex, or BMI ≥ 95th percentile of children of the same age and sex; 2) hypertension: blood pressure ≥ 95th percentile of children of the same age and sex (fast identification: systolic BP ≥ 120 mmHg or diastolic BP ≥ 80 mmHg); 3) dyslipidemia: a. Reduced HDL-C (< 1.03 mmol/L); or b. Elevated TG (≥ 1.47 mmol/L); 4) hyperglycemia: FG ≥ 5.6 mmol/L.

2.4 Statistic analysis

Statistical analyses were performed using SPSS version 19.0. The results of descriptive characteristics were expressed as average ± standard deviation. The relationships among clinical indexes and the number of MetS components were analyzed using the Kruskal-Wallis test. Spearman correlation coefficients were applied to assess the relationship between metals and MetS components. The odds ratios (ORs) and 95% confidence intervals (95%CIs) were determined by multivariate logistic regression to investigate the associations between MetS components and tertiles of whole blood metals. We categorized the level of whole blood Cu, Zn, the ratio of Cu to Zn, and Mg into tertiles and used the lowest tertile as the reference. P-trend analysis involved treating the tertiles as a continuous variable in regression analyses. The combination of metals defined as low was a concentration < 50% of the range, and those defined as high was the concentration ≥ 50% percentage whole value. All statistical tests were two-sided and statistical significance was considered at $P < 0.05$.

3. Results

3.1 Characteristics of the study population

This study examined 911 individuals (444 females, 467 males) with complete data on MetS components and whole blood Cu, Mg and Zn concentrations. Basic characteristics of the children are shown in Table 1. There were sex-based differences in the comparison of clinical and biological indexes: the waist circumference, HDL-C and Cu concentrations, and Cu/Zn ratio were higher in males, but the TG concentration was higher in females. We also analyzed these variables using different numbers of MetS components. We observed that age, BMI, height, weight, waist, rate of obesity, levels of FG and Cu, the Cu/Zn ratio and SBP exhibited an ascending trend, while HDL-C levels had a descending trend, with an increasing number of MetS components. We also examined the differences between groups defined as exhibiting different numbers of MetS components. Participants in the group with one or two MetS components were more likely to have a greater age, BMI, DBP, height, waist, weight, rate of obesity, FG and TG level, and a lower HDL-C level, compared with the non-MetS components group. The waist circumference, concentrations of FG and Cu, the Cu/Zn ratio and obesity rate were significantly higher in the group with three MetS components compared with groups exhibiting one, two or no MetS components.

Table 1
Basic characteristics of children according to sex and the number of MetS components.

Indexes	Total	Male	Female	CVD risk factors		
	(N = 911)	(N = 467)	(N = 444)	0(N = 497)	1(N = 336)	≥ 2(N = 78)
Age(years)	9.12 ± 1.7	9.01 ± 1.7	9.23 ± 1.7	8.93 ± 1.69	9.31 ± 1.68	9.51 ± 1.68#
Height(m)	131.52 ± 11.84	131.06 ± 11.41	132.01 ± 12.27	130.08 ± 10.71	132.71 ± 12.58	135.59 ± 13.87#
Weight(kg)	28.95 ± 8.74	29.17 ± 8.96	28.71 ± 8.49	26.95 ± 6.81	30.33 ± 9.27	35.74 ± 12.21#
Waist(cm)	55.96 ± 7.91	56.76 ± 7.93	55.11 ± 7.82*	53.40 ± 5.01	57.58 ± 8.69	65.25 ± 10.41#
BMI(kg/m2)	16.41 ± 2.78	16.66 ± 2.98	16.15 ± 2.53	15.72 ± 2.27	16.86 ± 2.82	18.92 ± 3.65#
Obesity(%)	16.02%	14.56%	17.56%	0%	27.08%	70.51%#
TG(mmol/L)	0.79 ± 0.48	0.74 ± 0.46	0.85 ± 0.5*	0.67 ± 0.29	0.93 ± 0.62	1.00 ± 0.56#
HDL-C (mmol/L)	1.27 ± 0.3	1.31 ± 0.3	1.23 ± 0.29*	1.40 ± 0.26	1.15 ± 0.28	1.01 ± 0.21#
FG (mmol/L)	4.85 ± 0.71	4.9 ± 0.73	4.8 ± 0.68	4.71 ± 0.53	4.94 ± 0.77	5.36 ± 1.08#
SBP(mmHg)	92.44 ± 11.42	92.68 ± 10.88	92.19 ± 11.96	91.44 ± 10.16	92.92 ± 12.31	96.77 ± 13.73#
DBP(mmHg)	60.23 ± 8.65	60.23 ± 8.07	60.23 ± 9.24	59.41 ± 7.72	60.77 ± 9.47	63.18 ± 9.77#
Cu(mg/L)	1.01 ± 0.13	1.03 ± 0.14	0.99 ± 0.13*	1.00 ± 0.13	1.01 ± 0.13	1.07 ± 0.14#
Zn(mg/L)	5.21 ± 1.07	5.19 ± 1.06	5.24 ± 1.08	5.21 ± 1.05	5.22 ± 1.09	5.19 ± 1.11
Cu/Zn	0.2 ± 0.05	0.20 ± 0.05	0.20 ± 0.04*	0.20 ± 0.04	0.20 ± 0.05	0.21 ± 0.04#
Mg(mg/L)	41.44 ± 5.28	41.29 ± 5.24	41.6 ± 5.32	41.16 ± 5.26	41.74 ± 5.34	41.92 ± 5.04

BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; FG, fasting glucose; HDL-C, high density lipoprotein-cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure; TG, triglycerides;*, $p < 0.05$ for sex; #, $p < 0.05$ for trend; a, compared with the non-MetS component group; b, compared with the one MetS component group; c, compared with the two MetS component group.

3.2 The association between tertiles of Cu, Zn, Cu/Zn and Mg and MetS component indicators

The relationships between Cu, Zn, Cu/Zn and Mg and MetS component indicators are shown in Table 2. The values of BMI, DBP and waist circumference tended to be higher in the upper tertiles of Cu, whereas the TG value was lowest in the third tertile of Cu. For blood Zn, both DBP and SBP had an ascending trend with increasing tertiles of Zn levels. But in the Cu/Zn group, the trend was opposite, with the values of DBP, SBP and TG decreased as Cu/Zn tertiles increased. In the Mg group, there was a significantly ascending trend for DBP, FG and TG values as the Mg tertiles increased. We also assessed the correlation between metals and MetS component indicators. Whole blood Cu was positively associated with DBP and waist circumference, and negatively associated with TG. There were positive correlations between Zn and FG, TG, DBP and SBP. In contrast to the Cu correlations, the ratio of Cu to Zn was negatively correlated to DBP, SBP and TG. However, waist circumference was also positively associated with the Cu/Zn ratio. Blood Mg levels showed a correlation only with DBP.

Table 2
Distribution of metabolic syndrome component indicators by tertiles (T1-T3) of blood copper (Cu), zinc (Zn), the Cu/Zn ratio and magnesium (Mg) lev

Indexes	**Cu (mg/L)**				**Zn (mg/L)**				**Cu/Zn**				**Mg (mg/L)**		
	T1	**T2**	**T3**	***P* value**	**T1**	**T2**	**T3**	***P* value**	**T1**	**T2**	**T3**	***P* value**	**T1**	**T2**	**T3**
	< 0.94	**0.94-1.06**	**> 1.06**		**< 4.64**	**4.64-5.70**	**> 5.70**		**< 0.17**	**0.17-0.21**	**> 0.21**		**< 38.89**	**38.89–43.66**	**> 43.66**
N = 911	294	315	302		300	310	301		295	311	305		300	310	301
BMI(kg/m2)	16.16	16.23	16.85	**0.004**	16.21	16.45	16.58	0.250	16.45	16.48	16.31	0.733	16.25	16.56	16.42
Waist(cm)	55.91	55.21	56.78^{*}	**0.046**	55.52	55.98	56.36	0.430	55.96	56.36	55.54^{*}	0.444	55.13	56.10	56.64
TG(mmol/L)	0.86	0.78	$0.74^{\#}$	**0.011**	0.74	0.82	0.82^{*}	0.063	0.91	0.75	$0.72^{\#}$	**0.001**	0.73	0.85	0.79
HDL-C (mmol/L)	1.28	1.27	1.26	0.085	1.25	1.28	1.28	0.325	1.28	1.28	1.26	0.695	1.26	1.28	1.27
FG(mmol/L)	4.79	4.89	4.88	0.201	4.82	4.81	4.93^{*}	0.062	4.87	4.87	4.82	0.601	4.81	4.80	4.95
SBP(mmHg)	92.27	91.94	93.13	0.412	90.54	92.94	93.83^{*}	**0.001**	93.86	92.84	$90.67^{\#}$	**0.002**	91.22	92.84	93.25
DBP(mmHg)	59.28	60.21	61.19^{*}	**0.026**	58.58	60.95	61.15^{*}	**0.001**	61.17	60.35	$59.21^{\#}$	**0.02**	58.98	60.56	61.15^{*}

BMI, body mass index; DBP, diastolic blood pressure; FG, fasting glucose; HDL-C, high density lipoprotein-cholesterol; SBP, systolic blood pressure; TG, triglyce positive correlation; $^{\#}$, negative correlation.

3.3 Odds ratios for MetS components in tertiles of Cu, Zn, Cu/Zn and Mg.

Table 3 summarizes the ORs and 95%CIs for MetS components associated with concentrations of whole blood Cu, Mg and Zn, and the Cu/Zn ratio, each categorized into tertiles. For elevated waist circumference measurements, significant associations were found for Cu and Cu/Zn using a crude model. After adjusting for age, BMI and sex, the multivariable adjusted ORs (95%CIs) were 2.00 (1.56–3.89) for Cu and 2.08 (1.22–3.55) for Cu/Zn. No significant correlations were found between Mg or Zn and elevated waist. All of the metals were associated with elevated TG, either in the crude or adjusted model. The risk of elevated TG was significantly decreased in the tertile 3 group compared with the tertile 1 (T1) group for Cu and Cu/Zn values. The ORs and 95% CIs for Cu and Cu/Zn were 0.34 (0.17–0.66) and 0.31 (0.15–0.62), respectively, in the crude model. These trends persisted after adjustment, with Cu and Cu/Zn showing ORs (95%CI) of 0.33 (0.16–0.65) and 0.35 (0.17–0.71), respectively. However, TG levels were inversely associated with Mg and Zn. The ORs (95%CI) for elevated TG in individuals categorized in the Mg and Zn tertile 2 (T2) groups were 2.36 (1.20–4.62) and 2.27 (1.18–4.35), respectively, without adjustment. The ORs (95%CIs) were attenuated but remained statistically significant after adjustment [T2 vs. T1: 2.12 (1.10–4.10) for Zn, 2.34 (1.19–4.61) for Mg]. There was no significant association between metals and hypertension, reduced HDL-C and hyperglycemia.

Table 3

Odds ratios (95% confidence intervals) for metabolic syndrome components according to whole blood metals.

Index		**Cu**				**Zn**				**Cu/Zn**				**Mg**	
		T1	**T2**	**T3**	***P***	**T1**	**T2**	**T3**	***P***	**T1**	**T2**	**T3**	***P***	**T1**	**T2**
N = 911		294	315	302		300	310	301		295	311	305		300	310
Elevated Waist	n	32	44	70		51	50	45		37	50	59		40	49
	Crude	1	1.32 (0.82–2.16)	**2.47 (1.56–3.89)**	**0.001**	1	0.93 (0.61–1.43)	0.85 (0.55–1.32)	0.789	1	1.33 (0.84–2.11)	**1.67 (1.07–2.61)**	**0.053**	1	1.22 (0.77–1.91)
	Adjusted	1	1.23 (0.71–2.12)	**2.00 (1.18–3.28)**	**0.001**	1	0.78 (0.48–1.28)	0.62 (0.37–1.04)	0.194	1	1.32 (0.77–2.28)	**2.08 (1.22–3.55)**	**0.019**	1	1.21 (0.71–2.04)
Hypertension	n	9	7	13		7	8	14		14	10	5		9	9
	Crude	1	0.72 (0.26–1.95)	1.42 (0.59–3.38)	0.334	1	1.10 (0.39–3.09)	2.04 (0.81–5.13)	0.205	1	0.66 (0.29–1.52)	0.33 (0.12–0.94)	0.096	1	0.96 (0.37–2.47)
	Adjusted	1	0.94 (0.33–2.64)	1.95 (0.79–4.82)	0.175	1	0.91 (0.32–2.60)	1.48 (0.70–2.85)	0.513	1	0.83 (0.35–1.93)	0.58 (0.20–1.69)	0.610	1	0.85 (0.32–2.24)
Elevated TG	n	34	20	13		14	31	22		34	21	12		13	30
	Crude	1	**0.51 (0.29–0.92)**	**0.34 (0.17–0.66)**	**0.002**	1	**2.27 (1.18–4.35)**	1.61 (0.80–3.21)	**0.041**	1	**0.55 (0.31–0.93)**	**0.31 (0.15–0.62)**	**0.002**	1	**2.36 (1.20–4.62)**
	Adjusted	1	**0.52 (0.28–0.93)**	**0.33 (0.16–0.65)**	**0.002**	1	**2.12 (1.10–4.10)**	1.41 (0.70–2.85)	0.066	1	0.57 (0.32–1.02)	**0.35 (0.17–0.71)**	**0.010**	1	**2.34 (1.19–4.61)**
Reduced HDL-C	n	62	62	75		74	66	59		53	73	73		68	64
	Crude	1	0.91 (0.61–1.36)	1.23 (0.84–1.81)	0.281	1	0.82 (0.56–1.20)	0.74 (0.51–1.09)	0.310	1	1.40 (0.94–2.08)	1.43 (0.96–2.13)	0.145	1	0.88 (0.60–1.30)
	Adjusted	1	0.90 (0.61–1.35)	1.23 (0.83–1.82)	0.282	1	0.81 (0.55–1.18)	0.72 (0.49–1.07)	0.266	1	1.40 (0.93–2.09)	1.48 (0.98–2.23)	0.132	1	0.88 (0.60–1.31)
Hyperglycemia	n	25	37	32		37	26	31		25	33	36		31	25
	Crude	1	1.43 (0.83–2.44)	1.27 (0.73–2.21)	0.414	1	0.65 (0.38–1.10)	0.81 (0.49–1.35)	0.277	1	1.28 (0.74–2.13)	1.44 (0.84–2.47)	0.399	1	0.76 (0.43–1.32)
	Adjusted	1	1.57 (0.91–2.70)	1.36 (0.77–2.39)	0.429	1	0.62 (0.36–1.06)	0.75 (0.45–1.26)	0.212	1	1.40 (0.80–2.44)	1.69 (0.97–2.95)	0.177	1	0.73 (0.41–1.27)

Adjusted = adjusted for age, BMI, sex; Crude = non-adjusted; HDL-C, high density lipoprotein-cholesterol; *P*, *P* for trend; TG, triglycerides; T, tertile.

3.4 Odds ratios for MetS components associated with tertiles of the combination of metals.

As the metals were all associated with MetS components, we combined each of them in pairs(Cu with Zn, Cu with Mg, Zn with Mg) to investigate joint correlations. In the joint analysis of Cu and Zn, the combination of low Cu and high Zn increased the risk of elevated TG [OR (95%CI), 2.21 (1.18–4.13)], when compared with the joint analysis of low Cu and low Zn. There was no significant association between MetS components and other Cu and Zn combinations. Correlations were also observed when we considered the interaction of Cu and Mg with MetS components. High Cu and high Mg were associated with an increased risk of elevated waist circumference [OR (95%CI), 2.03 (1.26–3.27)]. But when high Cu was combined with low Mg, the risk of elevated TG was attenuated to 0.40 (0.16–0.95). In the joint analysis of Zn and Mg, a significant correlation was only found for reduced HDL-C. We observed a negative association between reduced HDL-C and high Zn with low Mg. There was no association between the combination of Mg and Zn and other MetS components. The statistically significant results were shown in Fig. 1–3. And we also summarized the meaningful results of single and combined analysis in Table 4.

HDL-C, high density lipoprotein-cholesterol; TG, triglycerides; Low means < 50% concentration; High means ≥ 50% concentration; Low Cu + Low Zn,Low Cu + Low Mg and Low Zn + Low Mg were taken as the reference; Shown are the odds ratios (ORs) and 95% confidence intervals in parentheses.

HDL-C, high density lipoprotein-cholesterol; TG, triglycerides; Low means < 50% concentration; High means ≥ 50% concentration; Low Cu + Low Zn,Low Cu + Low Mg and Low Zn + Low Mg were taken as the reference; Shown are the odds ratios (ORs) and 95% confidence intervals in parentheses.

HDL-C, high density lipoprotein-cholesterol; TG, triglycerides; Low means < 50% concentration; High means ≥ 50% concentration; Low Cu + Low Zn,Low Cu + Low Mg and Low Zn + Low Mg were taken as the reference; Shown are the odds ratios (ORs) and 95% confidence intervals in parentheses.

Table 4
Odds ratios for MetS components associated with single and combined elements (partially meaningful results)

Single	**Cu**	**Zn**	**Mg**	**Cu/Zn**
	T3	**T2**	**T2**	**T3**
Elevated Waist	**2.00(1.18–3.28)**			**2.08(1.22–3.55)**
Elevated TG	**0.33(0.16–0.65)**	**2.12(1.10–4.10)**	**2.34(1.19–4.61)**	**0.35(0.17–0.71)**
Reduced HDL-C				
Combined	Cu + Zn	Cu + Mg		Mg + Zn
	Low Cu + High Zn	High Cu + Low Mg	High Cu + High Mg	High Zn + Low Mg
Elevated Waist			**2.03(1.26–3.27)**	
Elevated TG	**2.21(1.18–4.13)**	**0.40(0.16–0.95)**		
Reduced HDL-C				**0.47(0.28–0.77)**

HDL-C, high density lipoprotein-cholesterol; TG, triglycerides;Low means < 50% concentration; High means ≥ 50% concentration; Low Cu + Low Zn,Low Cu + Low Mg and Low Zn + Low Mg were taken as the reference; Shown are the odds ratios (ORs) and 95% confidence intervals.

4. Discussion

In this study, we explored whether the level of metals would affect the risk of metabolic syndrome components. The present findings provide evidence that whole blood Cu levels and the ratio of Cu to Zn were both positively associated with a higher OR of elevated waist and negatively associated with a higher OR of elevated TG either in crude or adjusted models. We also observed that whole blood Mg and Zn levels were positively associated with the risk of elevated TG. In addition, we performed multi-element joint analysis. In the combination of Cu and Zn, there was no association between MetS components and Zn with high Cu. Considering the interaction of Cu and Mg, high Cu with high Mg was positively associated with the risk of elevated waist, but high Cu with low Mg was negatively associated with elevated TG.

In our study, whole blood concentrations of Cu and Zn were all in the normal range (0.61–1.9 mg/L Cu, 3.1–9.8 mg/L Zn), referring to a study of Swedish adolescents [23]. We observed that a higher level of whole blood Cu leads to an increased risk of elevated waist, which was representative of obesity. In agreement with our results, Catherine et al. [24] observed a positive relationship between serum Cu and abdominal obesity. We also observed that the risk of elevated TG was decreased with ascending tertiles of Cu. It is established that Cu has affects lipid metabolism, but the reported effects of Cu on each index of lipid metabolism remains inconsistent. Some studies suggested that serum Cu levels were positively associated with total cholesterol, TG or low density lipoprotein, such as those examining 15–80-year-old Kuwaiti people[25] and young American adults [26]. But in the NHANES 2011–2014, there were no associations between serum Cu and TG levels in children and adolescents [27]. In contrast, Leslie et al. [28] reported that increased total cholesterol and reduced HDL-C levels were observed in children with low Cu levels, consistent with our results.

In the current study, we also observed that tertiles of Zn were positively associated with the risk of elevated TG, in agreement with studies of Tehran's urban population (OR = 1.60) [29] and Korean adults (OR = 1.47) [30]. Some research indicated that Zn overload would lead to Cu deficiency and reduced HDL-C levels [31]. As a consequence, the interaction of Cu and Zn should not be mutually exclusive, as they act as residual confounding factors for each other. This suggests that we need to reconsider previous analysis of single elements and consider interactions among these metals. Sukalski et al. found that a reduced serum Cu concentration leads to reduced Cu/Zn superoxide dismutase activity [32]. The Cu/Zn ratio can be used to determine the level of oxidative stress. In this study, all the values of Cu/Zn were less than 1.0, indicating the antioxidant mechanism in this population was normal [33]. In addition, the correlations of Cu/Zn with elevated waist and elevated TG were consistent with the correlations found with Cu, and with the findings reported by Fedor et al. [34]. Surprisingly, in our investigation of the combination of Cu and Zn, we found that there was no association of Zn and high Cu with MetS components, which was differenct from single element analysis.

As for the result of Mg, unlike some reports indicating that Mg supplements reduced TG levels and blood pressure [35], we observed an increased risk of elevated TG with the second tertile of Mg. Other studies suggested that Mg supplements were negatively associated with the risk of MetS [36, 37], so it is possible that low levels of Mg may be associated with some MetS components. In the current study, the risk of reduced HDL-C was increased by the combination of a high Zn level and a low Mg level. There was a significant association between a high Cu level combined with a low Mg level and the risk of elevated TG, which was consistent with the function of single metals. When Cu and Mg were both at high levels, the risk of an elevated waist circumference was raised. This was in agreement with a cross-sectional study conducted by Beydoun et al. [38].

The current study has several strengths. Firstly, this study focused on exploring the effects of elements on metabolic syndrome components in children. It could provide new avenues for the early screening of chronic diseases and protect the health of children and even for the elderly. Secondly, this is the first article that uses data from the China National Nutrition and Health Survey, which is a well-designed nationally representative cross-sectional study, to assess the relationship between elements and MetS components in rural children. It can provide a more comprehensive and detailed supplement to reflect the affect of elements on chronic diseases on Chinese children. Thirdly, it toke the preliminary exploration of the combined effect of multiple elements in MetS components, which could provide new ideas for further understanding of the occurrence and development of disease.

Several limitations of our study need to be considered. First, the physiological functions of Cu and Zn may influence the process of inflammation. However, we could not adjust for inflammatory indicators, such as C-reaction protein, as confounding factors in the analysis because such factors were not measured in this study. Secondly, as there is currently no satisfied statistical method for multi-element analysis, this article is just a preliminary exploration through a simple combination of elements. Thirdly, because of the relatively small age of the sample population, the prevalence of MetS was also very low, so we investigated the relationship between the metals and components of MetS.

Conclusion

In this article, we discussed the relationship between elements in both the single and combined effects and MetS components with the nationally representative data on rural children in China. We found that there is indeed a certain association between the elements and the components of MetS children. When different elements were analyzed individually and jointly, the conclusions was different. Therefore, it is necessary to pay attention to the combined analysis of multi nutrients, which could provide new avenues for the early screening and prevention of chronic diseases. We will verify the relevant results in different populations and do more exploration in statistics to better analyze the combined effect of multiple elements in the future.

Abbreviations

MetS: metabolic syndrome; AAP:American Academy of Pediatrics; IDF:International Diabetes Federation; BMI, body mass index; TG, triglycerides; HDL-C,high density lipoprotein cholesterol;FG, fasting glucose; SBP,systolic blood pressure; DBP, diastolic blood pressure;

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Institute for Nutrition and Food Safety, China CDC (now change to National Institute for Nutrition and Health, China CDC) (file number 2013-018).

Consent for publication

The authors consent to the publication of the data.

Availability of data and materials

The datasets used or analysed during the current study are available from the corresponding author Lichen Yang on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

H.Z. and Q.M. wrote the paper and analyzed data; P.S.,S.L, and Y.Q. provided essential materials; X.L.conducted research; L.W. performed statistical analysis; L.Y. designed research and had primary responsibility for final content. All authors read and approved the final manuscript.

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Figures

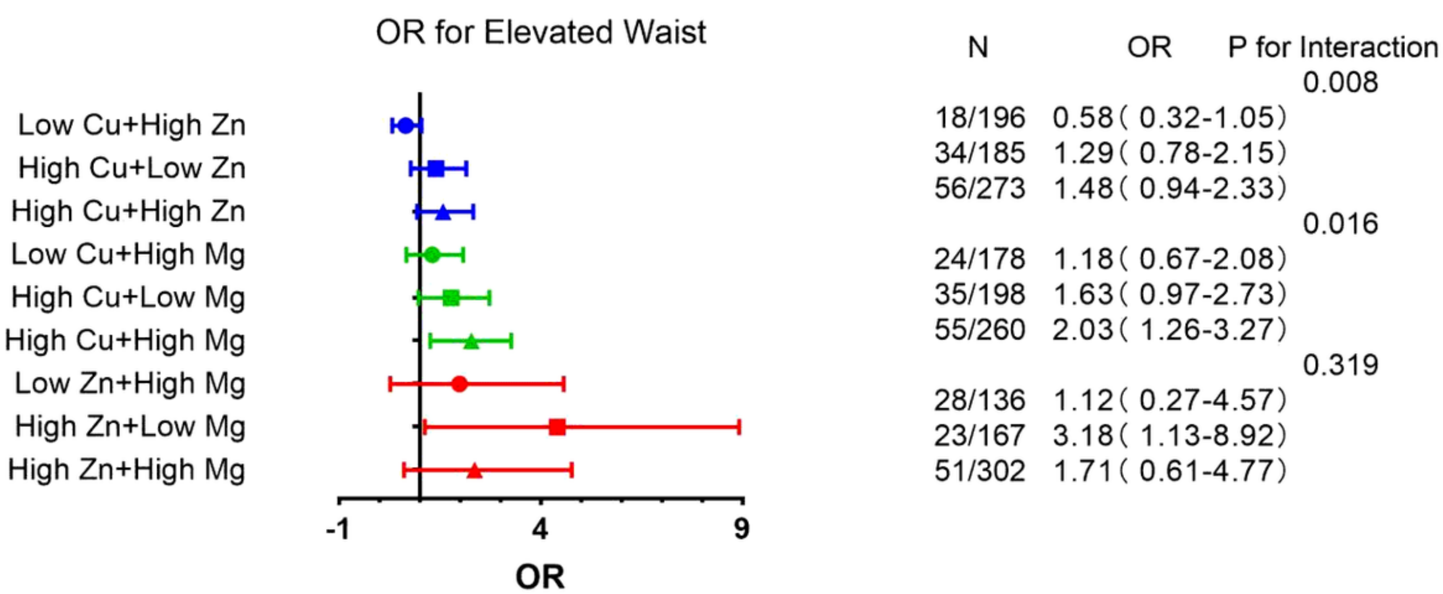

Figure 1

Associations of blood element levels with elevated waist. HDL-C, high density lipoprotein-cholesterol; TG, triglycerides; Low means <50% concentration; High means ≥50% concentration; Low Cu+ Low Zn,Low Cu+ Low Mg and Low Zn+ Low Mg were taken as the reference; Shown are the odds ratios (ORs) and 95% confidence intervals in parentheses.

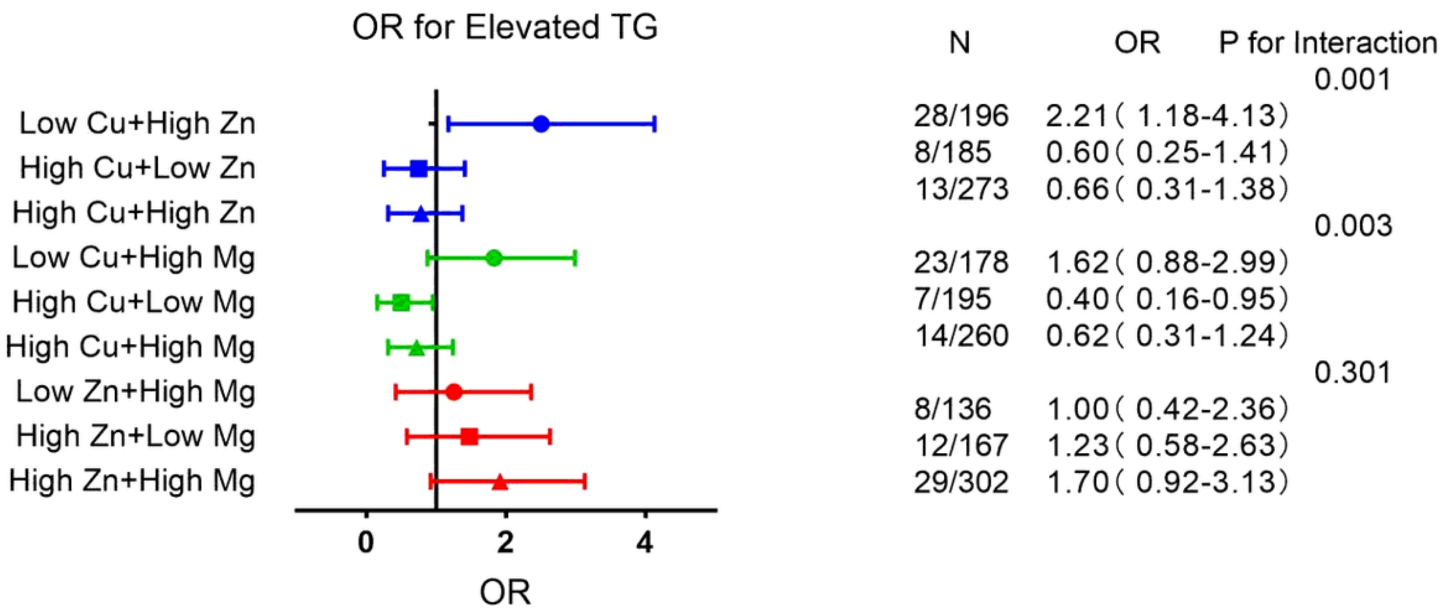

Figure 2

Associations of blood element levels with elevated triglycerides. HDL-C, high density lipoprotein-cholesterol; TG, triglycerides; Low means <50% concentration; High means ≥50% concentration; Low Cu+ Low Zn,Low Cu+ Low Mg and Low Zn+ Low Mg were taken as the reference; Shown are the odds ratios (ORs) and 95% confidence intervals in parentheses.

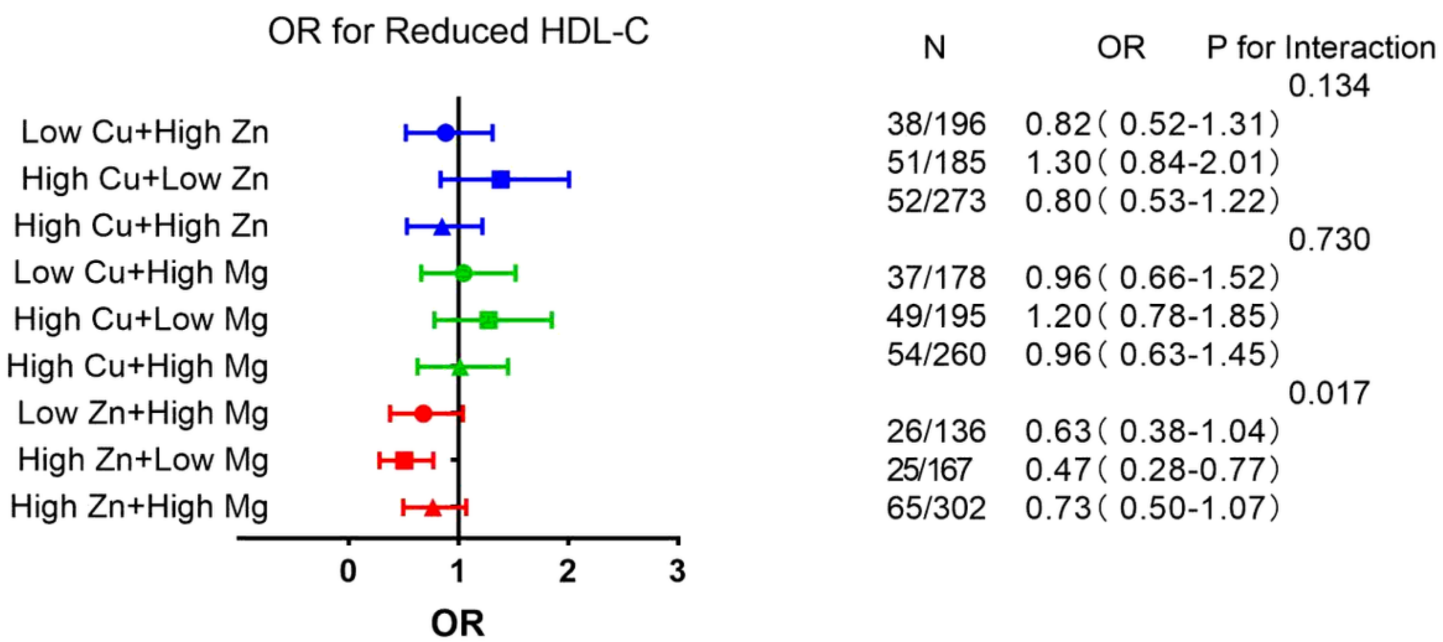

Figure 3

Associations of blood element levels with reduced HDL-C HDL-C, high density lipoprotein-cholesterol; TG, triglycerides; Low means <50% concentration; High means ≥50% concentration; Low Cu+ Low Zn,Low Cu+ Low Mg and Low Zn+ Low Mg were taken as the reference; Shown are the odds ratios (ORs) and 95% confidence intervals in parentheses.