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Multiple-element exposure and metabolic syndrome in Chinese adults: A case-control study based on the Beijing population health cohort

Weichunbai Zhang[a,b], Jing Du[b], Hong Li[b], Yi Yang[b], Chang Cai[c], Qun Gao[b], Yang Xing[b], Bing Shao[a,b,d,*], Gang Li[b,*]

[a] School of Public Health, Capital Medical University, Beijing, China
[b] Beijing Key Laboratory of Diagnostic and Traceability Technologies for Food Poisoning, Beijing Center for Disease Prevention and Control, Beijing, China
[c] Research and Innovation Office, Murdoch University, Perth, Australia
[d] Beijing Advanced Innovation Center for Food Nutrition and Human Health, China Agricultural University, Beijing, China

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ABSTRACT

Background: Metabolic syndrome (MetS) patients have a considerably increased risk for noncommunicable diseases, which poses a serious burden on public health. The effects of different elements on MetS have received increasing attention in the field of noncommunicable diseases over the past decade. These elements can exert adverse or favourable effects on human health by synergistic or antagonistic actions. Nevertheless, few studies have explored the relationship between multiple-element exposure and MetS.

Method: A total of 2095 MetS patients and 2039 controls free of major cardiovascular disease at baseline and follow-up visits were frequency matched for age (± 5 years) and sex. The internal exposure levels of 15 elements in serum were investigated. Logistic regression models were employed to estimate odds ratios (ORs) of MetS for element concentrations categorized according to quartiles in the controls.

Result: Magnesium (Mg), selenium (Se), barium (Ba) and mercury (Hg) were significantly associated with MetS in the multi-element exposure model. The ORs for the extreme quartiles of Mg, Se, Ba, and Hg were 0.29 (95% CI: 0.23–0.37, *P*-trend < 0.001), 0.52 (95% CI: 0.42–0.65, *P*-trend < 0.001), 1.86 (95% CI: 1.51–2.28, *P*-trend < 0.001), and 2.61 (95% CI: 2.11–3.22, *P*-trend < 0.001), respectively. Ba may be antagonistic to Mg and Se in the human body.

Conclusions: Our study suggested that MetS was negatively associated with Mg and Se and positively associated with Ba and Hg. There were significant dose-response relationships between Mg, Se, Ba and Hg and the prevalence of MetS, suggesting that multiple elements may be involved in MetS.

1. Introduction

Noncommunicable diseases (NCDs) have increasingly become one of the main causes of death worldwide. Approximately 41 million people die of NCDs annually, which is equivalent to 71% of all deaths globally (Ali et al., 2015). Metabolic syndrome (MetS), an important risk factor for NCDs, has seriously increased the burden of public health (Lakka et al., 2002; Wilson et al., 2005). Approximately one-quarter of the adult population is estimated to suffer from MetS worldwide (Saklayen, 2018), and approximately 454 million adults in China are affected by MetS (Lu et al., 2017).

To date, the causes of MetS are ambiguous. Genetics (Yang et al., 2018), lifestyle (Wang et al., 2018a, 2018b), diet (Joyce et al., 2019), and environmental factors (Lind et al., 2017) have been reported to be possibly associated with MetS. Recent studies have implied that exposure to environmental pollutants such as metals and metalloids (Bulka et al., 2019; Planchart et al., 2018) may be positively associated with MetS components. Heavy metals such as cadmium (Cd), lead (Pb), and mercury (Hg) have attracted extensive concern because of their toxicity to humans. The results of studies using model organisms suggest a possible association between Cd (Treviño et al., 2015), Pb (Tyrrell et al., 2017), and Hg (Kawakami et al., 2012) and MetS or associated conditions, whereas human data appear conflicting. For example, several cross-sectional studies among adults in South Korea and Norway found no significant association between Cd in blood (Moon, 2013; Simić et al., 2017) and the diagnosis of type II diabetes (T2D). Studies among Korean and Polish adults aged 50–75 years (Rotter et al., 2015) found no significant association between blood Pb levels and

* Corresponding authors at: School of Public Health, Capital Medical University, No. 10 Xitoutiao, You'anmen Fengtai District, Beijing, China (B. Shao).
E-mail addresses: shaobingch@sina.com (B. Shao), ligang@bjcdc.org (G. Li).

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MetS. However, more studies have indicated a positive association between blood Pb concentrations and MetS components, including increased triglyceride (TG) (Moon, 2014; Novo et al., 2013), waist circumference (WC) (Moon, 2014) and fasting plasma glucose (FPG) levels (Ettinger et al., 2014). Several cross-sectional studies in South Korea (Eom et al., 2014; Moon, 2014) found a positive association between blood Hg levels and MetS. In addition to these toxic metalloids and heavy metals, epidemiological studies have been performed to investigate the association between levels of other elements, such as magnesium (Mg) (La et al., 2016), manganese (Mn) (Lee and Kim, 2011; Shan et al., 2016), and selenium (Se) (Bleys et al., 2008; Laclaustra et al., 2010), in blood and MetS or MetS components. La found a decrease in Mg levels in adults with MetS by meta-analysis (La et al., 2016). Several American studies found that high serum Se was associated with elevated TG and HDL-C in the National Health and Nutrition Examination Survey (NHANES) (Bleys et al., 2008; Laclaustra et al., 2010). Furthermore, blood Mn levels were associated with an increased risk of hypertension in the Korean population (Lee and Kim, 2011). In addition, a case-control study in a Chinese population showed that the relationship between plasma Mn and T2D was U shaped (Shan et al., 2016).

The probabilities of human exposure to various elements are gradually increasing with accelerating urbanization and industrialization. Humans can be exposed to multiple elements in various ways, and these elements can synergistically exert an adverse or favourable effect. However, most epidemiological studies have focused on the effect of a single element on MetS, ignoring the role of multiple-element exposure, thus resulting in inconsistent conclusions. Therefore, this study explored multiple-element interactions with MetS based on a human epidemiological investigation of the Beijing Population Health Cohort.

2. Materials and methods

2.1. Study population and sampling

Study subjects comprised individuals living in Beijing who were recruited in 2017 as part of the Beijing Population Health Cohort study with a total of 24,990 subjects. The Beijing Population Health Cohort study is a large prospective dynamic cohort study focusing on the relationships between health effects and exposure to pollutants among those living in Beijing. Participants in this study had been living in Beijing for at least 2 years, and the age of the participants diagnosed with MetS ranged from 50 to 75 years old (n = 7064). We excluded individuals who lacked serum samples and insufficient element measurements (n = 1432), experienced cardiac disease, malignancy or recent surgery (n = 3458), or took related drugs such as hormones (n = 15) and lacked MetS components (n = 64). Consequently, a total of 2095 MetS patients were included in the analysis. The controls (2039 participants) were recruited from an unselected population undergoing a routine health check-up in the same cohort and were frequency matched for age (± 5 years) and sex (Fig. S1). Ultimately, a total of 4134 participants were recruited in this study (2043 male and 2091 female). The study protocol was approved by the Ethical Review Committee of the Center for Disease Control and Prevention (CDC) [No. 2017D (6)]. Written informed consent was obtained from each participant.

After an overnight fast, blood samples were collected in the morning in coagulation tubes. Serum was obtained by centrifugation within two hours of sampling. Biochemical analysis was immediately performed, and the remaining samples were stored in a freezer at −20 °C until elemental analysis.

2.2. Analytical methods

A total of 4134 serum samples were analysed in this study. The concentrations of 15 elements, Mg, aluminium (Al), chromium (Cr), Mn, iron (Fe), cobalt (Co), nickel (Ni), copper (Cu), zinc (Zn), arsenic (As), Se, Cd, barium (Ba), Hg, and Pb, were determined. Serum samples were diluted 1:10 with a solution containing 4% ammonia, 0.01% EDTA and 0.01% Triton X-100. Serum samples were analysed by Agilent 8800 ICP-MS with an octopole-based collision/reaction cell (Agilent Technologies).

Serum concentrations of these 15 elements were measured using inductively coupled plasma mass spectrometry (ICP-MS, Agilent, 8800 Series, USA) with the following instrument conditions: radio frequency power was 1550 W, RF matching was 1.60 V, the sample depth was 8 mm, the peristaltic pump was 0.3 r/min, the carrier gas velocity was 0.99 L/min, and the integration time was 0.3 s. Bismuth, scandium, germanium, rhodium and indium were added online with a mixing-T prior to introduction into the nebulizer for use as an internal standard solution. A standard addition experiment was performed for each test with spiking recoveries ranging between 90% and 110% to assure the reliability of the method.

The serum concentrations of FPG, TG and high-density lipoprotein cholesterol (HDL-C) were measured using a Hitachi automatic analyzer 7600 (Tokyo, Japan).

All laboratory tests were performed in the laboratory of the Beijing CDC.

2.3. Quality assurance and quality control (QA/QC)

The standard curve was necessary for the detection of serum elements, and the correlation coefficient of the standard curve was above 0.999. Bismuth, scandium, germanium, rhodium and indium were selected as internal standards to improve the accuracy of detection. The quality control serum samples were simultaneously processed with the samples to be tested and assessed once every 20 sample intervals to observe the accuracy of the method. The detection limits of all elements are shown in Table S1. The concentrations for undetected elements below the limits of detection (LODs) were set to LOD/$\sqrt{2}$(CDC, 2011). For external quality assurance and control, this laboratory was certified and fulfilled all the requirements from the China National Accreditation Service for Conformity Assessment and China Inspection Body and Laboratory Mandatory Approval. This laboratory was also subjected to external examination from the National Center for Clinical Laboratories by proficiency testing.

2.4. Definition of MetS

In this study, the diagnosis of MetS was performed according to the criteria of the International Diabetes Federation (IDF) published in 2005 (Alberti et al., 2005). According to the IDF definition, for a person to be diagnosed with MetS, he or she must have central obesity (defined as a WC with Chinese-specific values: WC ≥ 90 cm in men or WC ≥ 80 cm in women) and two of the following abnormalities: HDL-C < 1.03 mmol/L in men (< 1.29 mmol/L in women) or treatment for dyslipidaemia; TG ≥ 150 mg/dL (1.7 mmol/L) or treatment for dyslipidaemia; FPG ≥ 100 mg/dL (5.6 mmol/L) or treatment for diabetes; or systolic blood pressure (SBP) ≥ 130 mmHg, diastolic blood pressure (DBP) ≥ 85 mmHg or antihypertensive treatment.

2.5. Assessment of other variables

The following variables were identified as potential confounders: age, sex, education level, smoking status, alcohol intake status, physical activity, body mass index (BMI), BP, WC, and family history of related diseases. Education level was categorized as less than junior middle school, junior middle school and high school or higher. Smoking status was classified as “nonsmoker” (those who reported smoking fewer than 100 cigarettes in their lifetime), “past smoker” (reported ever smoking at least 100 cigarettes in their lifetime but do not currently smoke), or “current smoker” (smoked at least 100 cigarettes and currently smoked

some days or every day). Alcohol intake status was defined as “frequent drinker” (at least five days a week), “occasional drinker” (1 to 4 days per week) or “nondrinker” (Ahn et al., 2014). Based on the International Physical Activity Questionnaire (IPAQ), physical activities related to work, transportation, home gardening and leisure in the past seven days were investigated. The metabolic equivalent was calculated according to the relevant standards, and physical activities were classified as vigorous, moderate or low (IPAQ group, 2002).

A detailed personal and family history of physical illness and current medications were noted from “yes” or “no” responses to relevant questions. Body weight and height were recorded to the nearest 0.1 kg and 0.1 cm, respectively, with the participants wearing light indoor clothing and no shoes. BMI was calculated as weight in kilograms divided by the square of height in metres. BP was measured while subjects were seated following a 5-min rest and was measured on three occasions using a Hg sphygmomanometer on the right arm. The reported results are averages of three measurements. WC was measured midway between the costal margin and iliac crest at the end of a normal expiration.

2.6. Statistical analysis

To describe the basic characteristics of patients with MetS and the controls, the mean ± standard deviation is used to represent the continuous variables under the normal distribution, the median (interquartile range) is used to represent the nonnormally distributed variables, and classification variables are expressed in percentage terms. A *t*-test was used to compare normal data, the Mann-Whitney *U* test was used to compare nonnormal data, and the chi-square test was used to compare counting data. Spearman's rank correlation coefficients were used to evaluate intermetal correlations. Logistic regression was used to calculate the ratio of serum elemental concentrations by quartile and 95% CI for MetS. For the single-element model, the following models were used: Model 1: Adjusted for potential confounding factors, including education level, smoking status, alcohol intake status, BMI, physical activity, and family history of disease. Model 2: Elements with statistical significance in the single-element model (Model 1) were included in the logistic regression, which adjusted for other covariates. The relationships between the components of MetS and the concentration of multiple elements in serum were further analysed.

The logistic regression analysis of the multiple-element model was based on the subgroups of age, sex, education level, smoking status, alcohol intake status and family history of disease. The significant element-to-element interactions in the polymetallic model were also assessed. To overcome the inherent limitation of elemental levels as a grade variable analysis, restricted cubic spline (RCS) was used to analyse the dose response of elements in the multiple-element model, which still showed a significant trend. Each ln-transformed element model used RCS with knots at the 20th, 40th, 60th, and 80th percentiles of its distribution; the reference value (OR = 1) was set at the 10th percentile (Moon et al., 2013).

All statistical analyses were performed using SPSS 17.0 and STATA 14.0. A two-sided test was used in all statistical tests, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic and serum characteristics

Among the 4134 participants, 50.7% met the IDF criteria of MetS to form a case group, with 49.2% male and 50.8% female. The demographic characteristics of the case and control groups are listed in Table 1. Compared with the control group, patients with MetS had a lower education level ($P < 0.001$), more frequent smoking and drinking ($P < 0.001$), higher BMI ($P < 0.001$) and were more likely to have a family history of disease ($P < 0.001$). There was no significant difference in physical activity level. In addition, patients with MetS had higher WC, TG, FPG, SBP, and DBP and lower HDL-C levels (Table 1). The concentrations of Mg, Al, Mn, Fe, Co, Ni, Cu and Se in MetS patients were lower than those of the controls, while the concentrations of Cr, Zn, As, Ba, Hg and Pb were higher (Table 2). Cd mainly exists in cells, which leads to low concentrations in serum (Nordberg et al., 1971). The detection frequencies of Cd were lower

Table 1
Basic characteristics of study participants at baseline.

	Cases(n = 2095)	Controls(n = 2039)	P-Value[a]
Age (years)	60.1 ± 5.8	59.9 ± 6.1	0.219
Sex, *n* (%)			0.740
Male	1030(49.2%)	1013(49.7%)	
female	1065(50.8%)	1026(50.3%)	
Education level, *n* (%)			< 0.001
Primary school or below	443(21.1%)	276(13.5%)	
Middle school	793(37.9%)	702(34.4%)	
High school or beyond	859(41.0%)	1061(52.0%)	
Smoking status, *n* (%)			< 0.001
Current smoker	556(26.6%)	582(28.5%)	
Former smoker	208(9.9%)	107(5.2%)	
Never smoker	1331(63.5%)	1350(66.2%)	
Alcohol intake status, *n* (%)			< 0.001
Frequent drinkers	377(18.0%)	311(15.3%)	
Occasional drinker	263(12.6%)	175(8.6%)	
Non-drinker	1455(69.4%)	1553(76.2%)	
Physical Activity, *n* (%)			0.344
Low	484(23.1%)	433(21.2%)	
Moderate	726(34.7%)	730(35.8%)	
Vigorous	885(42.2%)	876(43.0%)	
BMI	27.52 ± 7.83	24.68 ± 7.67	< 0.001
Family history of disease, *n* (%)			
Hypertension	1074(51.3%)	780(38.3%)	< 0.001
Diabetes	535(25.5%)	411(20.2%)	< 0.001
Coronary Heart Disease	266(12.7%)	215(10.5%)	0.012
WC (cm)	94.1 ± 9.1	84.1 ± 9.7	0.002
SBP (mmHg)	139.47 ± 22.35	118.50 ± 27.87	< 0.001
DBP (mmHg)	84.93 ± 15.52	74.51 ± 17.78	< 0.001
FPG (mmol/L)	6.70 ± 2.02	5.38 ± 0.65	< 0.001
TG (mmol/L)	2.30 ± 1.95	1.38 ± 0.81	< 0.001
HDL-C (mmol/L)	1.33 ± 0.33	1.53 ± 0.35	< 0.001

Note: Age, BMI, WC, SBP, DBP, FPG, TG and HDL-C were normally distributed variables presented as the mean ± SD. Sex, education level, smoking status, alcohol intake status, physical activity and family history of disease were categorical variables presented as numbers (percentage).

[a] *P*-Values were derived from Student’s t-tests for continuous variables according to the data distribution, and chi-square test for the category variables.

Table 2
Concentrations of serum elements among study participants.

Element (μg/L)	Cases(n = 2095)	Controls(n = 2039)	*P-Value*[a]
Mg[b]	19.44(18.13–20.93)	20.72(19.37–22.19)	< 0.001
Al	68.03(50.47–88.90)	68.72(53.00–89.68)	0.202
Cr	2.44(1.18–3.70)	2.31(1.43–3.46)	0.825
Mn	1.26(0.95–1.64)	1.31(0.95–1.73)	0.022
Fe	1275.92(1035.31–1570.41)	1376.52(1095.33–1715.80)	< 0.001
Co	0.12(0.07–1.18)	0.14(0.09–0.19)	< 0.001
Ni	0.62(0.25–1.07)	0.64(0.26–1.07)	0.506
Cu	1087.15(959.31–1241.80)	1090.24(962.88–1240.72)	0.549
Zn	865.76(756.76–973.89)	864.32(770.90–973.58)	0.063
As	0.49(0.33–0.81)	0.48(0.31–0.84)	0.426
Se	78.22(67.02–90.41)	84.64(73.74–95.91)	< 0.001
Cd	0.03(0–0.06)	0.037(0–0.822)	< 0.001
Ba	3.47(2.3–5.12)	3.03(2.02–4.67)	< 0.001
Hg	0.61(0.34–1.00)	0.49(0.30–0.81)	< 0.001
Pb	0.45(0.30–0.68)	0.36(0.27–0.57)	< 0.001

Note: Non-normally distributed variables were presented as median (IQR).

[a] *P*-Values were derived from Mann-Whitney U tests.

[b] The unit of serum magnesium is mg/L.

Table 3
Adjusted prevalence odds ratios and 95% CIs for the association between serum elements levels and MetS in the multielement exposure model.

Element[a](μg/L)	Q1	Q2	Q3	Q4	*P*-trend
Mg	< 18645.36	18645.36–20078.48	20078.48–21696.84	> 21696.84	
n(case/control)	718/316	586/447	423/611	368/665	
Model 1[b]	1	0.63(0.51–0.76)	0.33(0.27–0.40)	0.28(0.23–0.35)	< 0.001
Model 2[c]	1	0.63(0.52–0.78)	0.33(0.27–0.41)	0.29(0.23–0.37)	< 0.001
Al	< 51.42	51.42–68.51	68.51–89.16	> 89.16	
n(case/control)	541/478	489/530	506/513	501/518	
Model 1[b]	1	0.81(0.67–0.98)	0.86(0.71–1.04)	0.83(0.68–1.00)	0.014
Model 2[c]	1	0.92(0.75–1.12)	1.06(0.86–1.30)	1.10(0.90–1.36)	0.887
Mn	< 0.95	0.95–1.28	1.28–1.69	> 1.69	
n(case/control)	526/508	565/468	515/519	489/544	
Model 1[b]	1	1.09(0.90–1.32)	0.83(0.68–1.00)	0.77(0.63–0.93)	< 0.001
Model 2[c]	1	1.10(0.90–1.34)	0.86(0.70–1.05)	0.78(0.63–0.97)	0.001
Fe	< 1064.69	1064.69–1322.90	1322.90–1654.62	> 1654.62	
n(case/control)	589/445	545/488	530/504	431/602	
Model 1[b]	1	0.81(0.67–0.98)	0.72(0.59–0.87)	0.48(0.39–0.59)	< 0.001
Model 2[c]	1	0.89(0.73–1.08)	0.80(0.66–0.99)	0.62(0.49–0.77)	0.011
Co	< 0.08	0.08–0.13	0.13–0.18	> 0.18	
n(case/control)	621/413	510/523	473/561	491/542	
Model 1[b]	1	0.70(0.58–0.85)	0.62(0.51–0.75)	0.68(0.56–0.82)	0.002
Model 2[c]	1	0.73(0.60–0.89)	0.69(0.57–0.85)	0.80(0.65–0.98)	0.076
Ni	< 0.27	0.27–0.63	0.63–1.07	> 1.07	
n(case/control)	528/506	540/493	501/533	526/507	
Model 1[b]	1	1.05(0.87–1.27)	0.97(0.80–1.17)	1.04(0.86–1.26)	0.036
Model 2[c]	1	1.10(0.91–1.35)	1.09(0.89–1.33)	1.30(1.06–1.60)	0.387
Zn	< 763.87	763.87–864.93	864.93–973.89	> 973.89	
n(case/control)	550/484	492/541	529/505	5224/509	
Model 1[b]	1	0.78(0.64–0.94)	0.89(0.73–1.08)	0.92(0.76–1.12)	< 0.001
Model 2[c]	1	1.07(0.87–1.31)	1.50(1.22–1.86)	2.50(1.98–3.16)	< 0.001
Se	< 70.17	70.17–81.52	81.52–93.49	> 93.49	
n(case/control)	666/368	546/487	455/579	428/605	
Model 1[b]	1	0.64(0.52–0.77)	0.46(0.38–0.56)	0.42(0.35–0.52)	< 0.001
Model 2[c]	1	0.68(0.55–0.83)	0.52(0.42–0.63)	0.52(0.42–0.65)	< 0.001
Ba	< 2.17	2.17–3.30	3.30–4.89	> 4.89	
n(case/control)	444/590	514/519	550/484	587/446	
Model 1[b]	1	1.20(0.99–1.45)	1.40(1.15–1.69)	1.63(1.35–1.98)	< 0.001
Model 2[c]	1	1.33(1.09–1.62)	1.61(1.31–1.97)	1.86(1.51–2.28)	< 0.001
Hg	< 0.32	0.32–0.54	0.54–0.90	> 0.90	
n(case/control)	476/558	469/564	525/509	625/408	
Model 1[b]	1	1.00(0.83–1.21)	1.26(1.04–1.52)	1.94(1.59–2.36)	< 0.001
Model 2[c]	1	1.14(0.93–1.39)	1.57(1.29–1.93)	2.61(2.11–3.22)	< 0.001

[a] Quartile cut-offs are based on raw data.
[b] Model 1: Adjustment of education level, smoking status, alcohol intake status, BMI, physical activity, family history of disease.
[c] Model 2: Elements that were significant in Model 1 (*P*-trend < 0:05) were included in the logistic regression model simultaneously (multiple-element model) and adjusted for the same variables as Model 1.

than 65%. Therefore, Cd was excluded from further analysis (Table S1). There seemed to be a certain correlation among the elements (Spearman's rank correlation coefficients −0.091 to 0.360; Table S2).

3.2. Serum element levels and MetS

Ten elements exhibited statistical significance in the single-element model, so Mg, Al, Mn, Fe, Co, Ni, Zn, Se, Ba and Hg needed to be included in the multi-element model (Table S3). Other elements had no significant *P*-value in the single-element model.

In the multi-element exposure model (Table 3), after adjusting for the relevant confounding factors and the significant elements in the single-element model, the ORs of Mg (OR = 0.29, 95% CI: 0.23–0.37 for Q4 vs. Q1, *P*-trend < 0.001), Mn (OR = 0.78, 95% CI: 0.63–0.97 for Q4 vs. Q1, *P*-trend = 0.001), Fe (OR = 0.62, 95% CI: 0.49–0.77 for Q4 vs. Q1, *P*-trend = 0.011), Zn (OR = 2.50, 95% CI: 1.98–3.16 for Q4 vs. Q1, *P*-trend < 0.001), Se (OR = 0.52, 95% CI: 0.42–0.65 for Q4 vs. Q1, *P*-trend < 0.001), Ba (OR = 1.86, 95% CI: 1.51–2.28 for Q4 vs. Q1, *P*-trend < 0.001) and Hg (OR = 2.61, 95% CI: 2.11–3.22 for Q4 vs. Q1, *P*-trend < 0.001) were similar to those in the single-element model. However, Al, Co and Ni showed no statistical significance.

Spline regression analysis indicated significant nonlinear associations for Mg, Se and Hg (*P* for nonlinearity ≤ 0.0001) (Fig. 1). However, the association between Ba and MetS was linear (*P* for nonlinearity = 0.6386)

3.3. Serum elements and MetS components

The relationship between serum element concentrations and MetS components was further analysed in this study (Table 4). For the general population, Mg was negatively correlated with increased WC, elevated FPG, elevated BP, elevated TG and reduced HDL-C, and Se was negatively correlated with elevated TG and reduced HDL-C. Moreover, Ba was positively correlated with elevated WC, elevated TG and reduced HDL-C, and Hg was positively correlated with elevated WC, elevated BP and elevated TG.

3.4. Subgroup analysis

The relevant covariate was adjusted using logistic regression of multiple-element models (Table S4) after stratification according to age, sex, education level, smoking status, alcohol intake status and family history of disease. It was found that most of the results for Mg, Se, Ba and Hg were consistent with those from the total population. Individual subgroups had limited results due to the small sample size. However, the results for Mn, Fe, and Zn stratification were quite

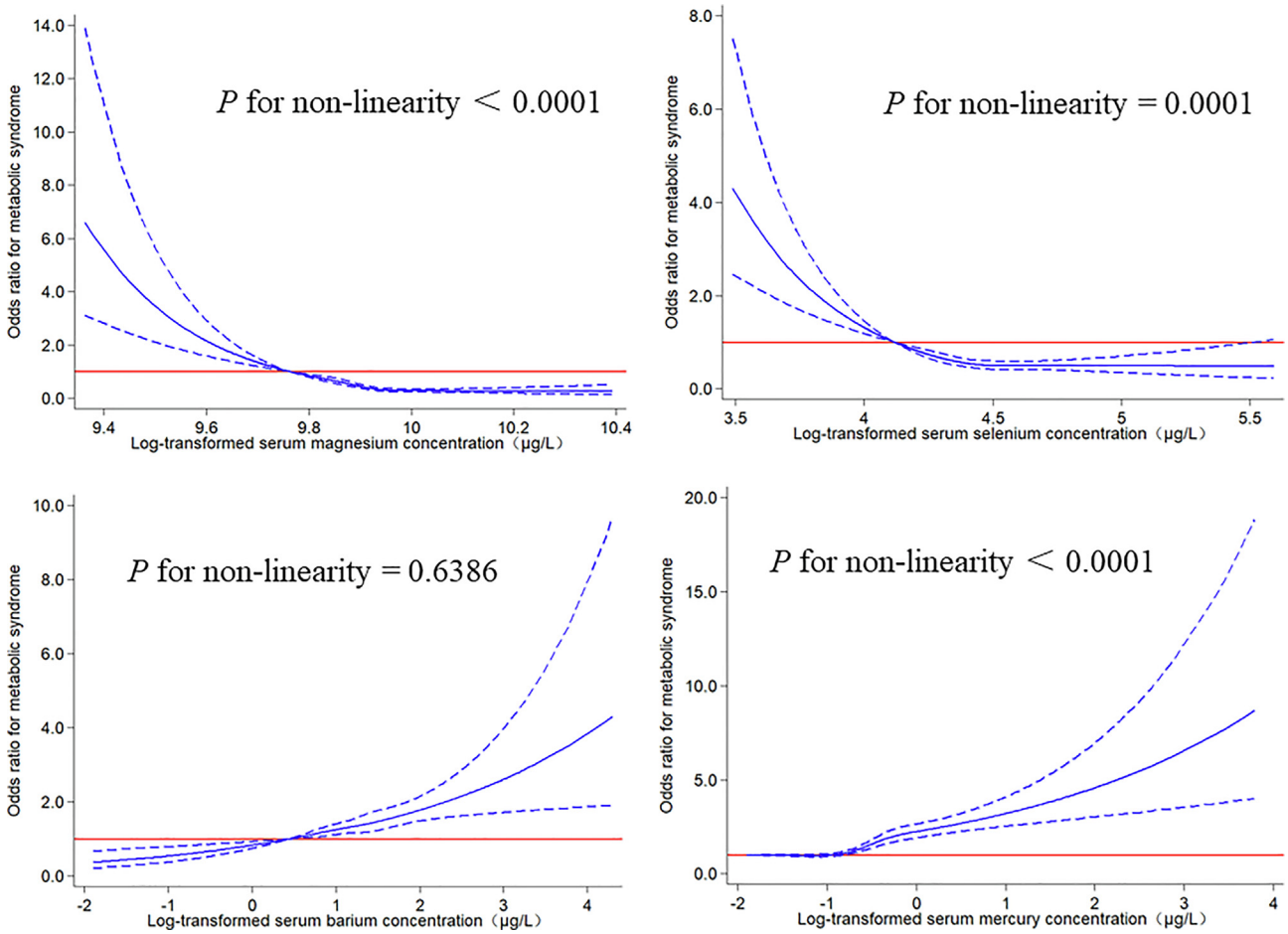

Fig. 1. The restricted cubic spline for the association between serum elements and MetS. The lines represent adjusted odds ratios based on restricted cubic splines for the log-transformed levels of serum magnesium, selenium, barium and mercury in regression model. Knots were placed at the 20th, 40th, 60th, and 80th percentiles of the serum element distribution, and the reference value was set at the 10th percentile. Adjustment factors were education level, smoking status, alcohol intake status, BMI, physical activity, family history of disease.

different, and the specific reasons need to be further explored.

3.5. Interaction analyses

Table S5 describes the interactions of different elements. It was found that Ba had significant associations with Mg and Se in the analysis of the association between the two elements. In terms of prevalence, Mg and Se could weaken the effect of a high Ba level. When the level of Ba was high, there was a significant difference between the two groups of Mg and Se levels. Although the prevalence of Mg, Se and Hg changed, there was no significant *P*-interaction among Mg, Se and Hg.

4. Discussion

To our knowledge, this is the first time that the potential association between exposure to multiple elements and MetS has been assessed in Chinese adults. In this study, serum concentrations of Mg and Se were negatively associated with MetS, while Ba and Hg presented positive associations. We used the RCS model to study the shape of the dose-response curve and further confirmed the existence of the dose-response relationship. In addition, it was fully verified that the level of elements in the human body can significantly affect the level of blood lipids, FPG and BP and then affect the occurrence and development of MetS.

This study found that serum Mg had a significant effect on MetS (OR = 0.29, 95% CI: 0.23–0.37 for Q4 vs. Q1, *P*-trend < 0.001), which was consistent with previous studies. A meta-analysis of 18 studies with a total of 5496 participants found that Mg levels in the MetS group were significantly lower than those in the healthy group (SMD = −0.98, 95% CI: −1.44 to −0.52) (La et al., 2016). Wang et al. investigated the prevalence of MetS in 962 patients with knee osteoarthritis in Wuhan and found that the OR of the highest quartile (0.99 mmol/L) compared to the lowest quartile (0.82 mmol/L) of serum Mg was 0.56 (95% CI: 0.34–0.93, $P = 0.024$) (Wang et al., 2018a, 2018b). The main source of Mg in the body is diet. A meta-analysis based on eight cross-sectional studies and two prospective cohort studies found that the pooled relative risk of MetS per a 150 mg/day increase in Mg intake was 0.88 (95% CI, 0.84–0.93; $I^2 = 36.3\%$) (Ju et al., 2014).

In addition, because of the influence of serum Mg on FPG, BP and blood lipids, the mechanism of the Mg effect on MetS was diverse. The activities of enzymes can be affected by Mg, which influences the metabolism of carbohydrates and lipids (Mahfouz and Kummerow, 1989; Touyz, 2003). Mg plays important roles in the modulation of blood glucose by insulin. Furthermore, Mg deficiency reduces the activity of insulin receptor tyrosine kinase, which leads to insulin resistance and reduces the utilization of glucose in cells (Barbagallo and Dominguez, 2007; Paolisso and Barbagallo, 1997). On the other hand, the physiological function of insulin was affected by Mg as a second messenger (Paolisso et al., 1990). As a cofactor of lipoprotein lipase (Kishimoto et al., 2010), low Mg increased the activity of lecithin cholesterol acyltransferase and HMG coenzyme A reductase, which may lead to hyperlipidaemia and abnormal lipid distribution in the body (Simental-Mendía et al., 2017). Mg was also involved in the regulation of BP. As a calcium blocker, it can lower BP by inhibiting calcium channels (Fujita,

Table 4
Adjusted prevalence odds ratios and 95% Cis for the association between serum element levels and individual components of MetS.

Element[a]	Q1	Q2	Q3	Q4	*P*-trend
Mg[b]					
Increased WC	1	0.67(0.52–0.87)	0.54(0.41–0.70)	0.50(0.38–0.66)	< 0.001
Elevated FPG	1	0.67(0.55–0.80)	0.43(0.36–0.53)	0.38(0.31–0.47)	< 0.001
Elevated BP	1	0.71(0.58–0.87)	0.54(0.44–0.67)	0.45(0.36–0.56)	< 0.001
Elevated TG	1	0.81(0.68–0.98)	0.69(0.57–0.83)	0.53(0.43–0.66)	< 0.001
Reduced HDL-C	1	0.84(0.68–1.03)	0.68(0.55–0.85)	0.72(0.56–0.92)	0.002
Mn[b]					
Increased WC	1	1.03(0.80–1.32)	0.80(0.63–1.02)	0.89(0.69–1.16)	0.411
Elevated FPG	1	1.22(1.01–1.47)	1.06(0.88–1.28)	1.16(0.95–1.41)	0.609
Elevated BP	1	1.06(0.87–1.29)	1.11(0.91–1.35)	1.03(0.84–1.27)	0.318
Elevated TG	1	1.18(0.98–1.42)	1.04(0.86–1.26)	1.06(0.87–1.29)	0.311
Reduced HDL-C	1	1.11(0.89–1.37)	0.99(0.79–1.23)	0.86(0.68–1.10)	0.052
Fe[b]					
Increased WC	1	1.10(0.86–1.42)	0.89(0.69–1.14)	0.80(0.62–1.04)	0.567
Elevated FPG	1	0.88(0.73–1.06)	0.89(0.74–1.08)	0.83(0.68–1.02)	0.423
Elevated BP	1	0.95(0.78–1.15)	0.89(0.73–1.08)	0.85(0.69–1.05)	0.516
Elevated TG	1	1.15(0.95–1.38)	1.04(0.86–1.25)	0.99(0.81–1.22)	0.928
Reduced HDL-C	1	0.76(0.62–0.94)	0.63(0.50–0.78)	0.48(0.37–0.61)	< 0.001
Zn[b]					
Increased WC	1	1.14(0.89–1.47)	1.39(1.07–1.81)	1.58(1.19–2.09)	0.262
Elevated FPG	1	1.12(0.93–1.35)	1.23(1.02–1.50)	1.65(1.33–2.04)	0.005
Elevated BP	1	1.01(0.83–1.23)	1.14(0.93–1.39)	1.45(1.16–1.82)	0.228
Elevated TG	1	1.21(1.00–1.46)	1.24(1.02–1.51)	1.98(1.60–2.45)	< 0.001
Reduced HDL-C	1	0.93(0.74–1.16)	1.01(0.80–1.27)	1.49(1.16–1.92)	0.305
Se[b]					
Increased WC	1	0.85(0.66–1.10)	0.76(0.59–0.98)	0.81(0.62–1.05)	0.054
Elevated FPG	1	0.93(0.77–1.13)	0.94(0.78–1.14)	0.98(0.81–1.20)	0.621
Elevated BP	1	0.84(0.69–1.03)	0.71(0.58–0.87)	0.76(0.61–0.93)	0.070
Elevated TG	1	0.74(0.62–0.90)	0.73(0.61–0.89)	0.79(0.65–0.96)	0.010
Reduced HDL-C	1	0.66(0.54–0.82)	0.53(0.43–0.66)	0.38(0.29–0.48)	< 0.001
Ba[b]					
Increased WC	1	1.42(1.13–1.80)	1.58(1.24–2.01)	1.78(1.39–2.28)	< 0.001
Elevated FPG	1	1.16(0.97–1.40)	1.35(1.12–1.63)	1.24(1.02–1.49)	0.390
Elevated BP	1	1.06(0.88–1.29)	0.99(0.82–1.21)	1.01(0.83–1.23)	0.540
Elevated TG	1	1.10(0.91–1.32)	1.13(0.94–1.37)	1.19(0.98–1.44)	0.613
Reduced HDL-C	1	0.98(0.78–1.23)	1.33(1.06–1.67)	1.71(1.37–2.14)	< 0.001
Hg[b]					
Increased WC	1	1.27(1.00–1.61)	1.32(1.04–1.68)	2.00(1.55–2.60)	0.029
Elevated FPG	1	0.98(0.81–1.18)	1.12(0.93–1.36)	1.30(1.07–1.58)	0.742
Elevated BP	1	1.08(0.89–1.31)	1.35(1.11–1.64)	1.91(1.55–2.34)	0.034
Elevated TG	1	1.16(0.96–1.40)	1.23(1.02–1.49)	1.56(1.29–1.89)	0.032
Reduced HDL-C	1	1.04(0.83–1.31)	1.15(0.92–1.45)	1.42(1.14–1.78)	0.211

[a] Quartile cut-offs are based on raw data, quantile division is consistent with Table 3.
[b] Adjustment of education level, smoking status, alcohol intake status, BMI, physical activity, family history of disease.

2006), and its ion increased the release of synthesizing vasodilatory prostacyclin from human endothelial cells, thus promoting vasodilation (Houston, 2011). However, increases in aldosterone and vascular inflammation were stimulated by a deficiency of Mg, which may lead to hypertension (Kostov and Halacheva, 2018).

The results of the present study showed a negative association between the serum Se level and risk of MetS. However, the results of the present study were inconsistent with previous research. Some studies have found that high Se levels are a risk factor for MetS (Tajaddini et al., 2015). A nested case-control study investigated MetS in adults over 40 years old and showed that the ORs from the highest and lowest serum Se fractions were 2.72 (95% CI: 1.43–5.20) in the male population and 5.30 (95% CI: 3.31–8.74) in the female population, respectively (Fang et al., 2019). Moreover, a U-shaped dose-response relationship between Se and cardiovascular mortality was found in the NHANES III study of American adults. The curve showed that there was a negative correlation between Se and cardiovascular mortality at low concentrations and a positive correlation between Se and cardiovascular mortality at high concentrations (Bleys, 2008). Because MetS is a clinical syndrome that occurs precardiovascular disease, there seems to be a U-shaped dose-response relationship between Se and MetS. Wilhelm et al. (Wilhelm et al., 2004) reported a reference range for plasma or serum Se of 50–120 μg/L. In the two studies reporting a positive correlation between Se and MetS, the Se concentrations in the case groups were 146.3 (106.8–202.2) μg/L (Yuan et al., 2015) and 141.5 ± 26.1 μg/L (Obeid et al., 2008), which were beyond the range. However, the Se concentration of the control group in our study was 84.64 μg/l, which was close to that of the control group in the study (Yuan et al., 2015) and provided a certain basis for previous speculation. Our spline analysis showed that at a higher exposure level, the correlation is negative but gradually flattens. It also indirectly proved this conjecture. However, the lack of higher concentrations in population data further supports this hypothesis.

The mechanism of the Se effect on MetS and its components may be related to oxidative stress. An increasing number of studies have shown the effects of oxidative stress on MetS and related biochemical indicators (Beydoun et al., 2012; Sharma et al., 2005). Se, a component of glutathione peroxidase (GSH-PX), plays an important role in the process of antioxidant defence and can alleviate the metabolic disorder caused by oxidative stress (Zwolak and Zaporowska, 2012). In addition, chronic inflammation is also one of the mechanisms of the Se effect on MetS. Furthermore, serum complement 3 is considered an early marker of MetS (van Oostrom et al., 2007). Puchau et al. found a negative correlation between Se and serum complement 3 levels in Spain (Puchau et al., 2009).

This was the first study to report a significant positive correlation

between serum Ba and MetS. Ba, a common metal in daily life, is widely used in the electronics industry, pigments, medical treatments, fireworks and other products. However, medical studies on Ba have mainly focused on the use of Ba agents, and few people have paid attention to the role of Ba in the body. (Wang et al., 2015; Kooi et al., 2019). A nested case-control study that included 3242 people found that plasma Ba was positively correlated with coronary heart disease. The OR was 1.44 (95% CI: 1.15–1.79, $P = 0.002$) compared with the lowest quartile, but no significant difference was found between the two in the polymetal-exposure model (Yuan et al., 2017). Its mechanism may be related to oxidative stress. Omole et al. found that malondialdehyde (MDA), advanced oxidation protein products (AOPPs) and NO levels increased in a dose-dependent manner after exposing rats to different concentrations of barium chloride ($BaCl_2$) for 7 consecutive days, suggesting that excessive free radicals were produced after oxidative stress injury and that the antioxidant defence system was out of balance (Omole et al., 2019). In the blood lipid index, the levels of total cholesterol, TG and low-density lipoprotein cholesterol increased significantly with high Ba chloride concentrations, but the levels of HDL-C decreased significantly (Omole et al., 2019). Moreover, Elwej et al. confirmed that exposure to Ba increased circulating lipid levels (Elwej et al., 2017). The results of these animal experiments also supported our finding that Ba was positively correlated with abdominal obesity and HDL-C decline. In addition, the proinflammatory effect of Ba was also considered. Compared with that in the control rats, the total number of leukocytes in Ba-treated rats decreased significantly, and the platelet/lymphocyte ratio and neutrophil/lymphocyte ratio increased. Levels of interleukin-6 (IL-6), which is a proinflammatory cytokine level in cardiopulmonary tissue, increased significantly, indicating the induction of inflammation. However, the underlying mechanism of the association remains to be explored.

There have been many studies of the relationship between Hg and MetS, and the results of those studies were consistent with our results (Chung et al., 2015; Eom et al., 2014; Park and Seo, 2016). A case-control study of a nonoccupationally exposed population of 2114 people found that the risk of MetS in the high Hg group (> 4.88 μg/L) was 1.68-fold higher than that in the low Hg group (< 2.99 μg/L) (95% CI: 1.25–2.55, $P < 0.01$) (Eom et al., 2014). Another study found that each 2-fold increase in blood Hg concentration resulted in an increase in the risk of MetS in men by 20% (95% CI: 1.05–1.36). Notably, however, the same increase in blood Hg concentration showed little effect on the risk of MetS in women (Chung et al., 2015).

The results from previous toxicological studies supported our findings that serum Hg mainly affected triglycerides and BP. Bashandy et al. demonstrated that Hg affected lipid metabolism by subcutaneous injection of 5 mg/kg mercuric chloride, which resulted in a nearly threefold increase in TG levels in rats (Bashandy et al., 2011). On the one hand, Hg exposure is related to an increase in oxidative stress, which increases the production of free radicals by binding to sulfhydryl groups, destroys the expression of genes related to lipid metabolism and induces hyperlipidaemia (Shi et al., 2018). On the other hand, Hg could cause low-grade inflammation in the body (Pollard et al., 2019), which increases the synthesis of triglycerides (Vairappan and Chandrasekar, 2019). In addition, a meta-analysis of 29 studies found that Hg exposure increased the risk of hypertension (Hu et al., 2018). It was speculated that Hg inhibited the activity of nitric oxide synthase (Rizzetti et al., 2013) and reduced the bioavailability of vasodilators (Azevedo et al., 2012). It promotes endothelial dysfunction, which in turn leads to hypertension.

Regarding the interaction between elements, we found that Ba interacts with Mg and Se. Chronic inflammation is considered one of the most important mechanisms of MetS (Welty et al., 2016). Mg (Bernstein et al., 2019) and Se (Puchau et al., 2009) have certain anti-inflammatory effects. Indeed, oral administration of Mg can alleviate inflammation and reduce the IL-6 response (Steward et al., 2019). However, Ba significantly increased the level of interleukin-6 and induced chronic inflammation (Omole et al., 2019). This suggested an antagonistic mechanism between Mg and Ba in the inflammatory response. Therefore, Ba, Mg and Se may antagonize one another, thus affecting MetS. Oxidative stress was significantly associated with lipid abnormalities. An increase in the Ba level led to the depletion of glutathione involved in the redox process (Omole et al., 2019). In contrast, an increase in the level of Se, the main active component of GSH-PX (Zwolak and Zaporowska, 2012), strengthened the antioxidant level of the organism and then reduced the degree of Ba oxidative damage (Elwej et al., 2017). Metallothionein, the main detoxifying substance in the body, may also regulate the metabolism of many elements in the organism (Freisinger and Vasak, 2013). However, we need to further verify whether Mg and Se can alleviate the adverse effects caused by Ba and provide a possibility for public health intervention.

There were several limitations in this study. First, it was difficult to determine the causal relationship among these relationships due to the case-control study. Therefore, further prospective studies are needed to assess the potential causal basis for these relationships between serum elements and MetS. Second, it was impossible to further explore the effects of elements on body metabolism. One reason for this was the challenge of distinguishing the valence and form of the elements from the blood. The concentration of serum elements may not represent the metabolism of all elements in the body. Since the data collected were not enough to calculate the energy intake of the respondents, this study did not adjust for energy intake, which may lead to small errors. In addition, since the subjects were from the baseline data of the cohort, they were all prevalent cases, including new cases and previous cases, so there was a certain prevalence-incidence bias (Neyman bias) (Neyman, 1955). However, there were several advantages in this study. First, 15 elements in serum samples were systematically detected, and the association between elements and MetS from the perspective of multiple-element exposure was assessed. Second, this is the first large-scale case-control study on elements and MetS based on baseline cohort data in Beijing, China. Third, subgroup analysis was applied to ensure the reliability of the results. Moreover, the interactions between elements and the dose-response relationship were explored in detail.

5. Conclusions

This is the first report of the association of multiple-element exposure with MetS based on a large cohort comprising a Chinese adult population. Mg and Se were negatively associated with MetS, while Ba and Hg were positively associated with MetS. Further prospective studies are needed to confirm the causal relationship between the internal coexposure of multiple elements and MetS.

CRediT authorship contribution statement

Weichunbai Zhang: Investigation, Formal analysis, Writing - original draft. **Jing Du:** Data curation, Investigation. **Hong Li:** Resources. **Yi Yang:** Resources. **Chang Cai:** Resources. **Qun Gao:** Validation. **Yang Xing:** Validation. **Bing Shao:** Conceptualization, Resources, Writing - review & editing. **Gang Li:** Methodology, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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