

# Associations of exposure to multiple metals with blood pressure and hypertension: a cross-sectional study in Chinese preschool children

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## Research Article

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## Abstract

**Background:** Exposure to metals might be a risk factor for hypertension, which contributes largely to the global burden of disease and mortality. However, relevant epidemiological studies of associations between metals exposure with hypertension among preschoolers are limited. This study aimed to explore the associations of urine metals with blood pressure and hypertension among Chinese preschoolers.

**Methods:** A total of 1220 eligible participants who had urine metals measurement, blood pressure measurements, and relevant covariates were included in this cross-sectional study. Urine concentrations of metals were measured by inductively coupled plasma mass spectrometer. The single and multiple metals regression models were used to investigate the associations of urine metal with blood pressure and the risk of hypertension after adjusting for potential confounders.

**Results:** We observed urine concentrations of chromium, iron, and barium were negatively associated with levels of systolic blood pressure, diastolic blood pressure and the risk of hypertension in the single metal model (all  $P$ -FDR adjustment  $< 0.05$ ). Significant associations of urine chromium concentrations with systolic blood pressure, diastolic blood pressure and the risk of hypertension were found in the multi-metal model ( $\beta$  or odds ratio (95% confidence interval) was -3.07 (-5.12, -1.02), -2.25 (-4.29, -0.22), and 0.51 (0.26, 0.97) for 3rd quartile, compared with 1st quartile, respectively). The same association was found for barium concentrations in the multi-metal model, while none of the associations among iron quartiles was significant. In addition, urine chromium, iron and barium may have joint effects on levels of systolic blood pressure and diastolic blood pressure and risk of hypertension. Children's age and body mass index could modify the associations of chromium, iron, and barium concentrations with blood pressure.

**Conclusions:** Our findings suggested that exposure to chromium, iron, and barium was inversely associated with blood pressure and hypertension among preschool children. These findings need further validation in prospective studies.

## Background

Hypertension is a leading cause of morbidity and mortality worldwide. The Global Burden of Disease Study estimated that increased blood pressure was the world's leading risk of death, contributing to  $> 10$  million deaths in 2016 [1]. The global prevalence of hypertension was 31.1%, representing about 1.39 billion adults aged  $\geq 20$  years worldwide [2]. A recent survey reported that almost 250 million people have hypertension in China, while the awareness and control rate of hypertension is still not optimistic [3]. Several factors, including living habits, hereditary susceptibility and dietary factors, are related to the occurrence of hypertension. Numerous epidemiological studies have indicated environmental exposure to metals was associated with the risk of hypertension [4–7].

Although there is now a growing interest in the association between metals exposure and hypertension risk, results from epidemiological studies are inconsistent.

Essential metals, such as chromium, vanadium, manganese, and selenium, are reported to be critical factors to maintain normal blood pressure levels and possess protective effects on hypertension [8–11]. However, accumulations of essential metals might also induce adverse effects in blood pressure levels [12–14]. In addition, some toxic metals, such as arsenic, lead and barium, was reported to be associated with an increased risk of hypertension and cardiovascular disease [5, 7, 15–17]. Nevertheless, several population-based studies observed the positive association of hypertension with cadmium exposure, but null and even negative associations were both suggested [18–21].

However, most epidemiological studies have focused on the subjects have been mainly from the ordinary adult population or the occupational worker, and the evidence is not sufficient in the preschool children [22–25]. Continuous

increase in blood pressure during childhood would lead to adult hypertension and increase the risk of cardiovascular disease in adulthood [26–29]. If childhood hypertension is reversed before adulthood, the risk of cardiovascular disease in the future will be significantly reduced [30]. Therefore, prevention and control of blood pressure in childhood are of great significance [27, 31]. In this study, we explored the potential association of 23 metal concentrations in urine with the levels of blood pressure as well as the risk of hypertension among preschool children in China. The multi-metal model was applied to investigate the simultaneous impacts of multiple metals on blood pressure and hypertension. Subgroup analysis was conducted to further explore the associations in various stratified groups.

## Methods

### Study population

We used cluster sampling to investigate 7 kindergartens in Shiyan City, Hubei Province, China in 2019. A total of 1595 preschoolers aged 2 ~ 6 years old were included in the study. Briefly, an interviewer-administered questionnaire on demographic characteristics including basic information for children (e. g. sex, age, birth weight, physical activity, salt intake, etc.), and parental information (e. g. parents height, weight, education level, family income, and history of hypertension) was performed by trained interviewers. Parents/guardians of children were asked to complete the questionnaire and physical examinations with help of the researcher and to provide morning urine specimens (5 mL). Physical examination including height, weight and blood pressure was performed by qualified physicians. Body mass index (BMI) was calculated as body mass / height<sup>2</sup> (kg/m<sup>2</sup>). Overweight and obesity was defined by BMI using child growth standards established by the World Health Organization. After excluding those with unrecovered questionnaire ( $n = 50$ , a recovery rate of 96.87%), missing basic information ( $n = 110$ ), missing physical examination ( $n = 206$ ), insufficient urine samples ( $n = 9$ ), a total of 1220 participants were eligible for further analysis. The study was approved by the Ethics Committee of Hubei University of Medicine (2019-TH-80), and consent from parents was obtained before completing the questionnaires.

### Measurement of blood pressure and hypertension

The blood pressure measurements were performed by a trained operator as described in 2018 Chinese guidelines for the management of hypertension. Blood pressure determinations were taken in a sitting position after 5 min rest using an electronic sphygmomanometer. Hypertension was defined as systolic blood pressure (SBP) and/or diastolic blood pressure (DBP)  $\geq P_{99} + 5$  mmHg of blood pressure in children of the same sex, age, and height according to the 2018 Chinese guidelines for the management of hypertension.

### Measurement of metal exposure

Urinary concentrations of 23 metals (Aluminum (Al), Titanium (Ti), Vanadium (V), Chromium (Cr), Manganese (Mn), Iron (Fe), Cobalt (Co), Nickel (Ni), Copper (Cu), Zinc (Zn), Arsenic (As), Selenium (Se), Rubidium (Rb), Strontium (Sr), Molybdenum (Mo), Cadmium (Cd), Tin (Sn), Antimony (Sb), Barium (Ba), Tungsten (W), Thallium (Tl), Lead (Pb), Uranium (U)) were measured using inductively coupled plasma-mass spectrometer (ICP-MS, Thermo Fisher, USA) based on a previously published protocol for the measurement of urinary metal concentrations with minor modifications [32]. All the collected samples were sent to the laboratory within 4 h, and then stored at  $-80^{\circ}\text{C}$  before further analysis. Before analysis, frozen urine samples were thawed at room temperature before centrifugation. Total 200  $\mu\text{L}$  of the supernatant was transferred to 5 mL polypropylene tubes and acidified with 40  $\mu\text{L}$  nitric acid (Thermo Fisher, USA) at  $4^{\circ}\text{C}$  overnight. The urine samples were allowed to stand at room temperature for 30 min the next day, brought to room temperature and diluted to 4 mL with butanol, and then centrifuged (3000 r/min,  $r = 20$  cm, 10 min). The accuracy of ICP-MS was checked by analyzing

multi-element reserve solution and internal standard liquid (United States), urinary sample quality controls (Sero, Billingstad, Norway)) and standard reference materials 1640a (Trace Elements in Natural Water, National Institute of Standards and Technology, Gaithersburg, MD) in every 50 samples. We further utilized a spiked pooled urine sample (100 samples randomly pooled together) as an inter-laboratory comparison to ensure the precise and accurate detection of titanium, iron, rubidium, strontium, molybdenum, barium, tungsten, uranium (no available certified reference agents). The standard recovery rate was in the range of 73.51–126.44% and the regression coefficients ( $r^2$ ) of the calibration standard solutions were greater than 0.999. The limits of detection (LOD) of each element were in the range 0.10–134.57 ng/L, and values below the LOD were given the value LOD/2.

## Statistical analysis

Baseline characteristics were compared using  $t$ -tests or Mann Whitney  $U$  tests for continuous variables and chi-square tests for categorical variables. We used Spearman's rank correlation analysis to explore correlations between urine metal concentrations, after natural log-transformation to account for their right-skewed distributions. Multivariate linear regression models were used to test linear regression coefficient ( $\beta$ ) and 95% confidence intervals (CIs) for SBP and DBP among the participants and individual urine metals categorized into quartiles according to distributions. The lowest quartiles were assigned to be the reference groups. We also used multivariate logistic regression models to estimate odds ratios and 95% CIs for hypertension and urine metals. Linear trend  $P$ -values were derived by modeling the median value of each metal quartile as a continuous variable in the regression model. Model 1 was adjusted for sex (boys, girls) and age (continuous), and model 2 was further adjusted for children's BMI (continuous), birthweight (continuous), salt intake (little, normal and salty), physical activity (yes, no), paternal BMI (continuous), maternal BMI (continuous), paternal education (middle school or below, high school, and university and above), maternal education (middle school or below, high school, and university and above), family income (RMB) (< 4999, 5000–7999 and > 8000), family history of hypertension (yes, no) and urine creatinine (continuous).

False discovery rate (FDR) corrections of 23 hypothesis tests were conducted based on an available spreadsheet software [33]. Restricted cubic spline (RCS) analysis was used to explore non-linear associations. For metals with significant trends both for SBP, DBP and hypertension after FDR corrections in the multivariate regression model, we further evaluated the simultaneous effects of the co-exposure to multiple metals on the levels of SBP and DBP and risk of hypertension by constructing multi-metal regression models considering potential confounders. In addition, a sensitivity analysis was performed among preschool children with no family history of hypertension. Stratified analyses according to sex (boys, girls), age (2–3 years old, 4 years old, 5 years old, 6 years old), and children's BMI (overweight and obesity or not) were conducted. We also evaluated the interaction between two metals that were significant in the multi-metal models. There was statistical significance for  $P$  value  $\leq 0.05$ . All data were analyzed using R (3.6.2).

## Results

### Characteristics of preschool children

Table 1 shows the characteristics of preschool children. Among the 1220 preschool children, 1125 (92.2%) individuals had normal blood pressure, while 95 (7.8%) individuals had hypertension. There were no statistical differences between the non-hypertension group and the hypertension group in sex, age, children's BMI, birthweight, salt intake, paternal BMI, maternal BMI, paternal education, maternal education, family income, family history of hypertension, and urine creatinine. Compared with the non-hypertension group, children with hypertension were more likely to have a higher percentage of physical activity, and higher levels of SBP and DBP (all  $P < 0.05$ ).

Table 1  
Basic characteristic among the study participants.

Variables <sup>a</sup>	Total (N = 1220)	Non-hypertension (N = 1125)	Hypertension (N = 95)	P Value <sup>b</sup>
Sex, boys (%)	662 (54.3)	601 (53.4)	61 (64.2)	0.055
Age (years)	4.45 (1.06)	4.46 (1.07)	4.34 (1.05)	0.277
Children's BMI (kg/m <sup>2</sup> )	16.32 (1.69)	16.30 (1.62)	16.63 (2.37)	0.061
Birthweight (kg)	3.38 (0.63)	3.38 (0.63)	3.40 (0.66)	0.743
Salt intake (%)				
Little	369 (30.2)	344 (30.6)	25 (26.3)	0.476
Normal	808 (66.2)	743 (66.0)	65 (68.4)	
Salty	43 (3.5)	38 (3.4)	5 (5.3)	
Physical activity (% yes)	1079 (88.4)	988 (87.8)	91 (95.8)	0.03
Paternal BMI (kg/m <sup>2</sup> )	23.82 (2.82)	23.82 (2.81)	23.75 (2.96)	0.809
Maternal BMI (kg/m <sup>2</sup> )	21.44 (2.45)	21.45 (2.44)	21.34 (2.54)	0.67
Paternal education (%)				
Middle school or below	135 (11.1)	128 (11.4)	7 (7.4)	0.48
High school	446 (36.6)	409 (36.4)	37 (38.9)	
University and above	639 (52.4)	588 (52.3)	51 (53.7)	
Maternal education (%)				
Middle school or below	161 (13.2)	147 (13.1)	14 (14.7)	0.886
High school	585 (48.0)	541 (48.1)	44 (46.3)	
University and above	474 (38.9)	437 (38.8)	37 (38.9)	
Family Income (RMB) (%)				
< 4999	785 (64.3)	726 (64.5)	59 (62.1)	0.703
5000–7999	370 (30.3)	338 (30.0)	32 (33.7)	
> 8000	65 (5.3)	61 (5.4)	4 (4.2)	
Family history of hypertension (% yes)	131 (10.7)	117 (10.4)	14 (14.7)	0.255
Urine creatinine (mmol/L)	1897.75 (1340.38, 2711.00)	1897.35 (1346.09, 2698.02)	1941.00 (1300.34, 2749.93)	0.722
SBP (mmHg)	97.92 (12.40)	95.92 (10.09)	121.60 (12.78)	< 0.001
DBP (mmHg)	58.58 (12.07)	56.95 (10.03)	77.87 (16.67)	< 0.001

Variables <sup>a</sup>	Total (N = 1220)	Non-hypertension (N = 1125)	Hypertension (N = 95)	<i>P</i> Value <sup>b</sup>
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.				
<sup>a</sup> Data are presented as means ± SD, median (25th, 75th), or n (%).				
<sup>b</sup> <i>P</i> Value were derived from Student's t-test or Mann-Whitney U test for continuous variables according to the data distribution, and Chi-square test for the category variables.				

## Distributions of the urinary metals

Concentrations (µg/L) of urine 23 urine metals are presented in Table S1. Undetection rates (N% < LOD) of all the metals were < 1.3%. Compared with non-hypertension, children with hypertension had lower concentrations of Cr, Fe, and Ba (all *P* < 0.05, see Table S2). In the Spearman's rank correlation analysis, we found positive and significant associations among most metals, with  $r_s$  ranging from 0.05 to 0.92 (*P* < 0.05) (Fig. S1).

## Associations between metal exposure and blood pressure

The associations of metals in urine with the levels of SBP and DBP were investigated in the multivariable linear regression model (Fig. 1 and Table S3). After adjusting for sex, age, children's BMI, birthweight, salt intake, physical activity, paternal BMI, maternal BMI, paternal education, maternal education, family income, family history of hypertension and urine creatinine, urine Cr, Fe, Mo, and Ba concentrations were negatively related to SBP and DBP pressure (all *P* < 0.05). These associations remained unchanged in the linear model and FDR-adjustments (all FDR adjusted *P* < 0.05). Compared with those in the lowest quartiles, individuals in the highest quartiles of Cr, Fe, Mo, and Ba concentrations had significantly inverse associations for SBP levels, with the  $\beta$  of -3.18 (95%CI: -5.12 to -1.23), -2.44 (95% CI: -4.38 to -0.49), -3.42 (95%CI: -5.57 to -1.26) and - 3.28 (95%CI: -5.26 to -1.31), respectively; and for DBP levels, with the  $\beta$  of -2.80 (95%CI: -4.73 to -0.87), -2.56 (95%CI: -4.49 to -0.63), -3.01 (95%CI: -5.15 to -0.88) and - 2.25 (95%CI: -4.21 to -0.29), respectively. RCS analyses showed significant linear associations of Cr, Fe, and Ba concentrations with levels of SBP and DBP (all *P* for overall association < 0.05) (Fig. 2). Meanwhile, we observed a decreasing non-linear trend of SBP levels with Cr concentrations (*P* for non-linearity = 0.016). In addition, there were significant and negative associations of urine Cd with SBP levels, and urine Al and As with DBP levels, while positive associations of U quartiles with increasing SBP levels. After FDR-adjustment, the associations remained significant (all FDR-adjusted *P* < 0.05) (Fig. 1).

For metals (Cr, Fe, and Ba) that were statistically significantly associated with levels of SBP and DBP and risk of hypertension among preschool children, we included them together in the multi-metals model. After adjusting for potential confounders, we found significant inverse associations of metals quartiles with SBP and DBP levels in the multi-metal models, except for Fe (all *P* trend < 0.05) (Table 2). Compared with the lowest quartiles, urine Cr and Ba concentrations in the highest quartile decreased SBP by -2.53 (95%CI: -4.89, -0.17) mmHg, and - 2.83 (95%CI: -4.84, -0.81) mmHg (*P* for trend = 0.044, 0.002, respectively). Urine Cr and Ba was associated with a decreased levels of DBP in the third quartile compared to the reference group ( $\beta$  = -2.25, 95% CI: -4.29 to -0.22;  $\beta$  = -2.34, 95% CI: -4.28 to -0.39, respectively). It should be noted that the linear trend association of DBP levels with Cr concentrations was insignificant. The above observed associations were robust and did not drastically change in the sensitivity analyses (Table S4).

Table 2

Associations of urinary metals with blood pressure and hypertension based on the multi-metal model.

Outcomes	Urine metals	Linear Model	Quartiles of urinary metals ( $\mu\text{g/L}$ )				$P_{\text{trend}}$
			Q1	Q2	Q3	Q4	
SBP	Chromium						
	Model 1	-1.07 (-2.00, -0.15)	0 (Reference)	-1.70 (-3.69, 0.29)	-2.97 (-5.05, -0.90)	-2.87 (-5.26, -0.48)	0.028
	Model 2	-0.96 (-1.87, -0.04)	0 (Reference)	-1.71 (-3.67, 0.26)	-3.07 (-5.12, -1.02)	-2.53 (-4.89, -0.17)	0.044
	Iron						
	Model 1	-0.32 (-1.22, 0.59)	0 (Reference)	0.35 (-1.65, 2.35)	0.95 (-1.24, 3.15)	-0.42 (-2.79, 1.94)	0.697
	Model 2	-0.36 (-1.25, 0.53)	0 (Reference)	0.39 (-1.58, 2.37)	0.54 (-1.63, 2.71)	-0.52 (-2.85, 1.82)	0.636
Barium	Model 1	-0.81 (-1.84, 0.22)	0 (Reference)	0.43 (-1.52, 2.38)	-0.54 (-2.51, 1.44)	-1.76 (-3.76, 0.24)	0.051
	Model 2	-1.41 (-2.46, -0.37)	0 (Reference)	0.15 (-1.77, 2.07)	-1.19 (-3.15, 0.77)	-2.83 (-4.84, -0.81)	0.002
	DBP	Chromium					
	Model 1	-1.06 (-1.97, -0.15)	0 (Reference)	-1.34 (-3.30, 0.61)	-2.30 (-4.34, -0.26)	-2.35 (-4.70, 0.00)	0.067
Model 2	-0.92 (-1.83, -0.02)	0 (Reference)	-1.22 (-3.17, 0.73)	-2.25 (-4.29, -0.22)	-2.04 (-4.38, 0.30)	0.103	
Iron	Model 1	-0.28 (-1.16, 0.61)	0 (Reference)	0.13 (-1.84, 2.10)	0.54 (-1.61, 2.70)	-0.96 (-3.29, 1.36)	0.387
	Model 2	-0.33 (-1.22, 0.55)	0 (Reference)	0.11 (-1.85, 2.06)	0.30 (-1.86, 2.46)	-1.04 (-3.36, 1.29)	0.358
Barium	Model 1	-0.90 (-1.91, 0.11)	0 (Reference)	-0.81 (-2.73, 1.10)	-2.06 (-4.00, -0.12)	-1.55 (-3.52, 0.41)	0.075
	Model 2	-1.10 (-2.14, -0.07)	0 (Reference)	-0.90 (-2.81, 1.00)	-2.34 (-4.28, -0.39)	-1.79 (-3.79, 0.21)	0.043
Hypertension	Chromium						
	Model 1	0.76 (0.56, 1.02)	1 (Reference)	0.83 (0.47, 1.44)	0.54 (0.28, 1.01)	0.53 (0.25, 1.09)	0.182
	Model 2	0.75 (0.55, 1.02)	1 (Reference)	0.82 (0.46, 1.44)	0.51 (0.26, 0.97)	0.53 (0.25, 1.11)	0.104
	Iron						

Outcomes	Urine metals	Linear Model	Quartiles of urinary metals ( $\mu\text{g/L}$ )				$P_{\text{trend}}$
			Q1	Q2	Q3	Q4	
	Model 1	0.89 (0.65, 1.18)	1 (Reference)	0.90 (0.49, 1.62)	1.41 (0.75, 2.64)	0.82 (0.37, 1.73)	0.669
	Model 2	0.87 (0.64, 1.17)	1 (Reference)	0.86 (0.47, 1.56)	1.29 (0.67, 2.46)	0.78 (0.35, 1.67)	0.745
	Barium						
	Model 1	0.70 (0.51, 0.95)	1 (Reference)	1.01 (0.59, 1.72)	0.72 (0.40, 1.29)	0.35 (0.16, 0.69)	0.005
	Model 2	0.65 (0.47, 0.90)	1 (Reference)	0.97 (0.57, 1.68)	0.68 (0.37, 1.23)	0.31 (0.14, 0.63)	0.001
<p><math>P_{\text{trend}}</math> across quartiles of metals were obtained by including the median of each quartile (natural log-transformed) as a continuous variable in the regression models.</p> <p>Model 1: Adjusted for sex and age.</p> <p>Model 2: Based on Model 1 additionally adjusted for children's BMI, birthweight, salt intake, physical activity, paternal BMI, maternal BMI, paternal education, maternal education, family income, family history of hypertension, and urine creatinine.</p>							

## Associations between metal exposure and risk of hypertension

The association of urinary metals with the risk of hypertension was analyzed as both continuous and categorical variables with adjustments for potential covariates (Fig. 1 and Table S3). In fully adjusted single-metal regression models, there were significant associations of hypertension risk with urine V, Cr, Fe, Co, Cr, Sn and Ba concentrations (all  $P < 0.05$ ). Similar associations of urine metals and hypertension were observed in the linear model. After FDR adjustments at 5% alpha level, we found consistent results of Cr, Fe, and Ba quartiles with those from the models of single metal (all FDR adjusted  $P < 0.05$ ). Compared with the lowest quartile, children in the highest quartile of Cr, Fe and Ba had a 0.48-fold (95% CI: 0.25 to 0.88), 0.48-fold (95% CI: 0.24 to 0.90) and 0.28-fold (95% CI: 0.13 to 0.57) decreased odds of hypertension, respectively. We further evaluated these significant associations in single-metal models using RCS analysis. A negative dose-response relation was observed for urine Cr, Fe and Ba with hypertension risk ( $P$  for overall association = 0.0004, 0.029, and 0.007, respectively) (Fig. 2).

We explored the associations between urinary metals and the risk of hypertension in the multi-metal model, and found the metals were not significantly related to hypertension, except for Ba (Table 2). Quartiles of Ba in urine were suggested to be inversely related to the risk of hypertension, with the OR to be 0.31 (95% CI: 0.14 to 0.63) for the highest quartile. The association between urinary Ba and hypertension was similar in the sensitivity analysis excluding those who had a family history of hypertension (Table S4).

## Subgroup analyses and interaction analyses

As shown in Table 3, in the joint association analysis of multi-metals, combined high Cr and high Fe were associated with lower SBP and DBP, and with decreased risk of hypertension among preschool children ( $\beta$  (95% CI) = -2.63 (-4.24, -1.03), -2.35 (-3.94, -0.76), OR (95% CI) = 0.54 (0.32, 0.91), respectively) compared with combined low Cr and low Fe values. Similarly, the relationship has also been observed in combined high Cr and high Ba. In addition, children with high levels of Fe and Ba had significantly lower levels of SBP and DBP, and lower risk of hypertension than those with low levels of Fe and Ba ( $\beta$  (95% CI) = -3.38 (-5.19, -1.58), -2.90 (-4.69, -1.10), OR (95% CI) = 0.37 (0.19, 0.69),

respectively). However, no significant interaction was found between urine Cr, Fe, and Ba after being adjusted for confounders (all  $P$  interaction  $> 0.05$ ).

Table 3

Associations for blood pressure and hypertension according to the combined categories of metal concentrations.

Metals <sup>a</sup>	n	SBP		DBP		Hypertension	
		Crude $\beta$ (95%CI)	Adjusted $\beta$ (95%CI) <sup>b</sup>	Crude $\beta$ (95%CI)	Adjusted $\beta$ (95%CI) <sup>b</sup>	Crude OR (95%CI)	Adjusted OR (95%CI) <sup>b</sup>
Chromium + Iron							
Low Cr + Low Fe	447	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)	1 (Reference)	1 (Reference)
Low Cr + High Fe	163	-0.23 (-2.44, 1.99)	-0.49 (-2.67, 1.69)	-0.35 (-2.51, 1.81)	-0.51 (-2.67, 1.64)	1.12 (0.61, 2.00)	1.14 (0.61, 2.06)
High Cr + Low Fe	163	-1.96 (-4.17, 0.26)	-1.92 (-4.09, 0.25)	-1.61 (-3.77, 0.55)	-1.60 (-3.75, 0.55)	0.70 (0.33, 1.34)	0.68 (0.32, 1.32)
High Cr + High Fe	447	-2.63 (-4.25, -1.00)	-2.63 (-4.24, -1.03)	-2.49 (-4.07, -0.91)	-2.35 (-3.94, -0.76)	0.57 (0.34, 0.95)	0.54 (0.32, 0.91)
<i>P</i> <sub>interaction</sub>		0.781	0.887	0.731	0.878	0.512	0.476
Chromium + Barium							
Low Cr + Low Ba	348	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)	1 (Reference)	1 (Reference)
Low Cr + High Ba	262	-1.95 (-3.93, 0.03)	-2.85 (-4.81, -0.89)	-1.33 (-3.26, 0.60)	-1.62 (-3.57, 0.32)	0.51 (0.27, 0.89)	0.42 (0.22, 0.75)
High Cr + Low Ba	262	-2.62 (-4.60, -0.64)	-2.76 (-4.70, -0.81)	-1.72 (-3.65, 0.21)	-1.68 (-3.61, 0.25)	0.60 (0.34, 1.04)	0.52 (0.29, 0.92)
High Cr + High Ba	348	-3.68 (-5.51, -1.84)	-4.17 (-6.00, -2.34)	-3.50 (-5.29, -1.71)	-3.51 (-5.33, -1.70)	0.35 (0.19, 0.63)	0.30 (0.16, 0.56)
<i>P</i> <sub>interaction</sub>		0.531	0.303	0.745	0.88	0.755	0.479
Iron + Barium							
Low Fe + Low Ba	364	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)	1 (Reference)	1 (Reference)
Low Fe + High Ba	246	0.03 (-1.96, 2.03)	-0.86 (-2.83, 1.12)	-1.49 (-3.43, 0.46)	-1.73 (-3.69, 0.23)	0.68 (0.36, 1.22)	0.58 (0.31, 1.06)
High Fe + Low Ba	246	0.47 (-1.53, 2.46)	0.17 (-1.79, 2.13)	-1.06 (-3.01, 0.89)	-1.09 (-3.03, 0.85)	1.08 (0.63, 1.83)	1.00 (0.57, 1.72)

Metals <sup>a</sup>	n	SBP		DBP		Hypertension	
		Crude $\beta$ (95%CI)	Adjusted $\beta$ (95%CI) <sup>b</sup>	Crude $\beta$ (95%CI)	Adjusted $\beta$ (95%CI) <sup>b</sup>	Crude OR (95%CI)	Adjusted OR (95%CI) <sup>b</sup>
High Fe + High Ba	364	-2.74 (-4.54, -0.95)	-3.38 (-5.19, -1.58)	-2.78 (-4.53, -1.03)	-2.90 (-4.69, -1.10)	0.42 (0.22, 0.76)	0.37 (0.19, 0.69)
<i>P</i> <sub>interaction</sub>		0.025	0.057	0.869	0.957	0.219	0.33

<sup>a</sup> Low is defined as 'Q1 + Q2', High is defined as 'Q3 + Q4'.

<sup>b</sup> Adjusted for sex, age, children's BMI, birthweight, salt intake, physical activity, paternal BMI, maternal BMI, paternal education, maternal education, family income, family history of hypertension, and urine creatinine.

The association of Cr and Fe with blood pressure was modified by children's age. Stratified analyses suggested that DBP was negatively associated with Cr concentrations in the 4th quartile aged 2–3 years old ( $\beta$  (95% CI) = -8.04 (-15.35, -0.74),  $P_{\text{interaction}} < 0.001$ ), and positively associated with Fe concentrations in the 3rd quartile aged 6 years old ( $\beta$  (95% CI) = 4.84 (0.11, 9.57),  $P_{\text{interaction}} = 0.006$ ) (Table S6). For children with overweight and obesity, urine Ba quartiles was related to lower SBP levels (3rd vs. 1st quartile = -4.31 (-8.21, -0.41), 4th vs. 1st quartile = -6.48 (-10.35, -2.62),  $P_{\text{interaction}} = 0.031$ ) (Table S5), as well as lower DBP levels (3rd vs. 1st quartile = -4.80 (-8.90, -0.71), 4th vs. 1st quartile = -5.75 (-9.81, -1.69),  $P_{\text{interaction}} = 0.003$ ). There was no interaction between metals of Cr, Fe and Ba with Children's sex, age and BMI on the risk of hypertension (Table S7).

## Discussion

In this study, we explored the relationships of urinary 23 metals with blood pressure as well as hypertension in Chinese preschool children. Overall, we observed the negative associations of Cr, Fe and Ba quartiles with levels of SBP and DBP and risk of hypertension. These linear dose-response associations were confirmed in the RCS models. Joint effect to Cr, Fe and Ba could greatly decrease the levels of SBP and DBP, and the risk of hypertension. Besides, modification effects of children's age and BMI on the associations of Cr, Fe, and Ba concentrations with blood pressure have also been suggested in the subgroup analysis.

Essential metals are suggested to be critical factors to normalize blood pressure levels and possess protective effects on hypertension [10, 11, 34]. The deficiencies of these trace metals have been suggested to decrease oxidative defense and exacerbate the adverse effects of toxicants [35]. A meta-analysis included 15 trials studies indicated Cr significantly reduced DBP (weighted mean difference: -2.36 mmHg, 95% CI: -4.13, -0.60) compared to placebo [36]. Another random-effects meta-analysis of 11 eligible RCTs with 637 participants demonstrated the significant decline in both SBP (weighted mean difference: -2.51 mmHg; 95% CI: -4.97, -0.05) and DBP (weighted mean difference: -1.04 mmHg; 95% CI: -1.96, -0.12) following supplementation with Cr [8]. A case-control study with 331 participants suggested that low Cr was significantly associated with high blood pressure [37]. Our data provided a supporting result on the negative association of urine Cr with blood pressure as well as hypertension, which are in accordance with the previous epidemiological studies. In addition, significant interactions were found between the urine Cr concentration and age in our study. Urine high Cr quartiles were more strongly associated with lower DBP levels in children aged 2–4 years old.

The present study observed inverse associations of urine Fe concentrations with blood pressures and hypertension. A cross-sectional study, including 17 population samples from Japan, China, the United Kingdom and the United States about 4680 adults, observed higher iron intake was associated with  $-1.44$  mm Hg (95%CI:  $-2.46$ :  $-0.43$ ) lower SBP, and  $-0.71$  mm Hg (95%CI:  $-1.41$ :  $-0.02$ ) lower DBP [38]. A randomized controlled trial of 285 low birth weight infants in Swedish concluded that Fe supplementation is significantly and inversely associated with the risk of elevated SBP (OR:  $0.32$ ; 95% CI:  $0.11$ ,  $0.96$ ) [39]. Although there are numerous studies to explore the association between Fe levels and hypertension risk, the association was still controversial. For example, a prospective cohort study included 1303 participants reported no association between urine Fe concentrations with blood pressure in adults [40]. Furthermore, a case-control study of 502 hypertension patients and 502 healthy participants indicated urine Fe was associated with increased odds of hypertension [23]. Similar associations were found for another cross-sectional study [24]. Therefore, whether Fe concentrations were associated with hypertension risk needs to be investigated in further studies. Additionally, there are substantial differences in study design, study populations (e.g., location and age groups), metals sample (i.e., blood or urine), and blood pressure assessment protocols, which may account for the variability observed in the existing literature.

Findings on the associations of urine Ba levels with blood pressure and hypertension were limited and inconsistent. Accumulating epidemiological studies have demonstrated an increased risk for hypertension of Ba exposure. A prospective cohort study included 1832 individuals in the US observed pregnant women with higher Ba had a  $0.12$  mmHg (95% CI:  $0.04$ ,  $0.20$ ) greater increase in SBP [41]. A cross sectional findings from the 1999–2006 National Health and Nutrition Examination Survey showed higher concentrations of Ba were associated with higher SBP [6]. Meanwhile, a review of the health impacts of barium spanning from 1875 to 2014 demonstrated that low and moderate doses of Ba caused elevated blood pressure in animal studies [16]. However, there was a null association of Ba concentrations with SBP or DBP levels [42]. In this study, an inverse association between urinary Ba concentrations and blood pressure levels and hypertension risk was found. Previous literature in drinking water suggested high-Ba communities had lower cardiovascular disease and total mortality [43, 44], which was similar to our results. Additionally, this study showed a significant interaction effect on blood pressure between urine Ba and overweight and obesity among children, which was consistent with Swayze et al. study [45]. The study included 12256 participants from the continuous National Health and Nutrition Examination Survey 1999–2016 and suggested a greater effect of barium on hypertension in those with obesity. Padilla et al [46] using data from National Health and Nutrition Examination Survey 1999–2002 highlighted toxic metal of Ba was positively related to BMI. These associations suggested the possibility that environmental exposure to metals may contribute to variations in human weight gain. The potential mechanistic pathways for these associations may be related to oxidative stress. Reactive oxygen species generated by metals can inhibit the normal mitochondrial metabolic function, and prevent the mitochondria from producing energy, which would cause the liver to divert metabolites to lipogenesis [47].

This study evaluated the potential associations of urine 23 metal concentrations with blood pressure levels and hypertension risk among Chinese children aged 2–7 years old. However, several limitations should be noticed. First, the participants of our study were selected from an urban area, which might lead to selection bias. Second, spot urine samples were used to measure the internal exposure levels of metals, which might lead to exposure misclassification. Third, measurements of 23 metals in the same urine sample might lead to measurement errors and increase the false positive rates, although FDR-method had been applied. Finally, the current findings were based on a cross-sectional study, thus we could not ensure the causal relationship of metal exposure with blood pressure and hypertension. Further studies with prospective design are required to confirm our findings.

## Conclusion

Our study demonstrated an inverse association between urine metals concentrations (Cr, Fe and Ba) and blood pressure and hypertension in Chinese preschool children. The association of Cr, Fe, and Ba concentrations with blood pressure could be modified by children's age and BMI. Further studies are warranted to confirm our findings in prospective cohorts and to elucidate the potential mechanisms underlying the relationship between metals and hypertension.

## Abbreviations

BMI  
Body mass index  
SBP  
Systolic blood pressure  
DBP  
Diastolic blood pressure  
Al  
Aluminum  
Ti  
Titanium  
V  
Vanadium  
Cr  
Chromium  
Mn  
Manganese  
Fe  
Iron  
Co  
Cobalt  
Ni  
Nickel  
Cu  
Copper  
Zn  
Zinc  
As  
Arsenic  
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Sr  
Strontium  
Mo  
Molybdenum  
Cd  
Cadmium

Sn  
Tin  
Sb  
Antimony  
Ba  
Barium  
W  
Tungsten  
Tl  
Thallium  
Pb  
Lead, U:Uranium  
Cl  
Confidence interval.

## Declarations

### Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of the Hubei University of Medicine [No. 2019-TH-80].

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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Conceptualization: Yanli Liu, Jing Wang. Investigation: Lili Yu, Meiqin Zhu, Wei Lin, Yang Liu, Mingzhu Li, Yao Zhang, Hongxian Ji, Data curation: Lili Yu, Meiqin Zhu, Methodology: Yanli Liu, Lili Yu, Meiqin Zhu. Software and Writing - original draft preparation: Yanli Liu. Project administration: Yao Zhang, Hongxian Ji, Jing Wang. Supervision: Hongxian Ji, Jing Wang. Writing - Review & editing, Funding acquisition: Jing Wang. All authors read and approved the final manuscript

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## Figures

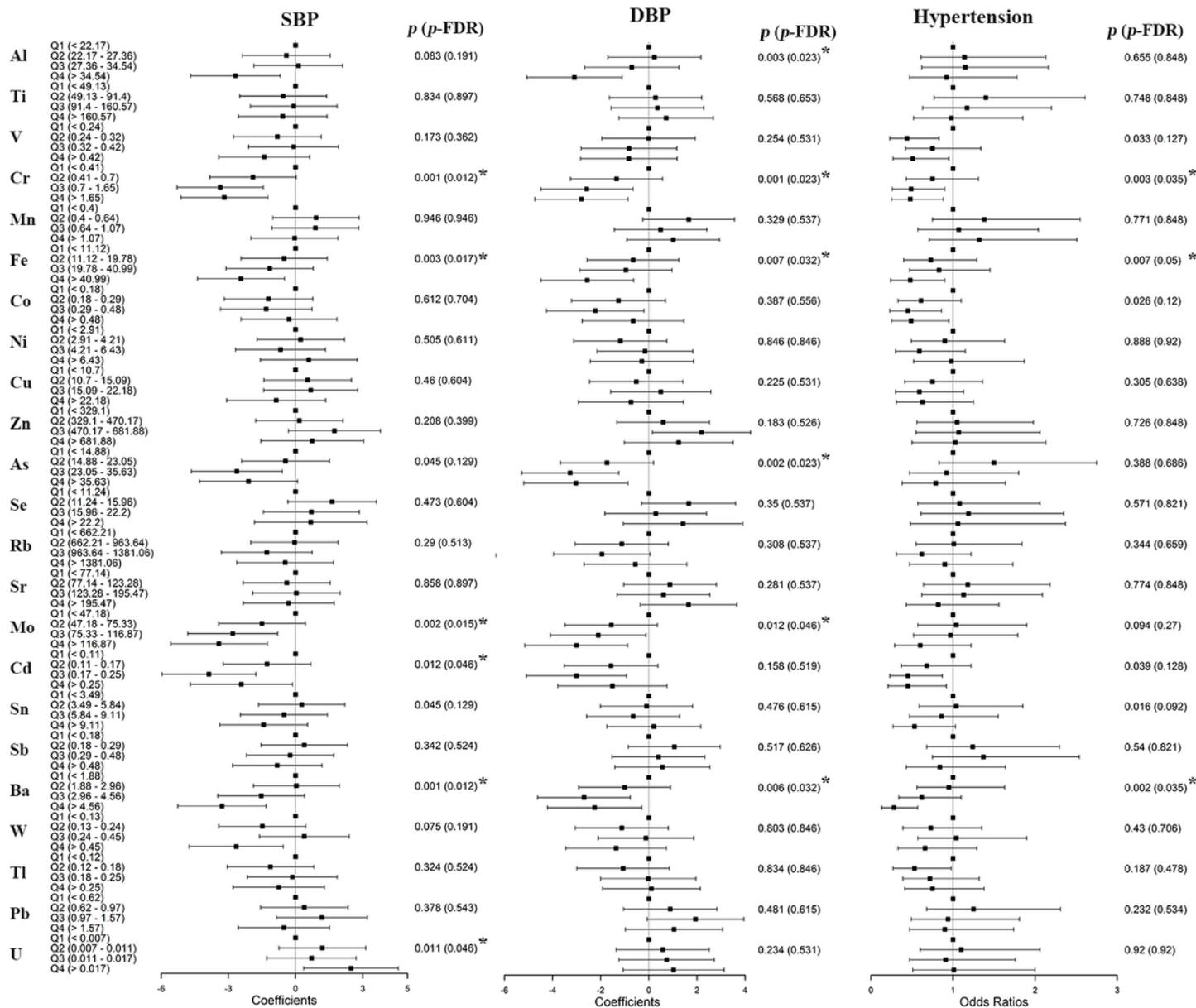
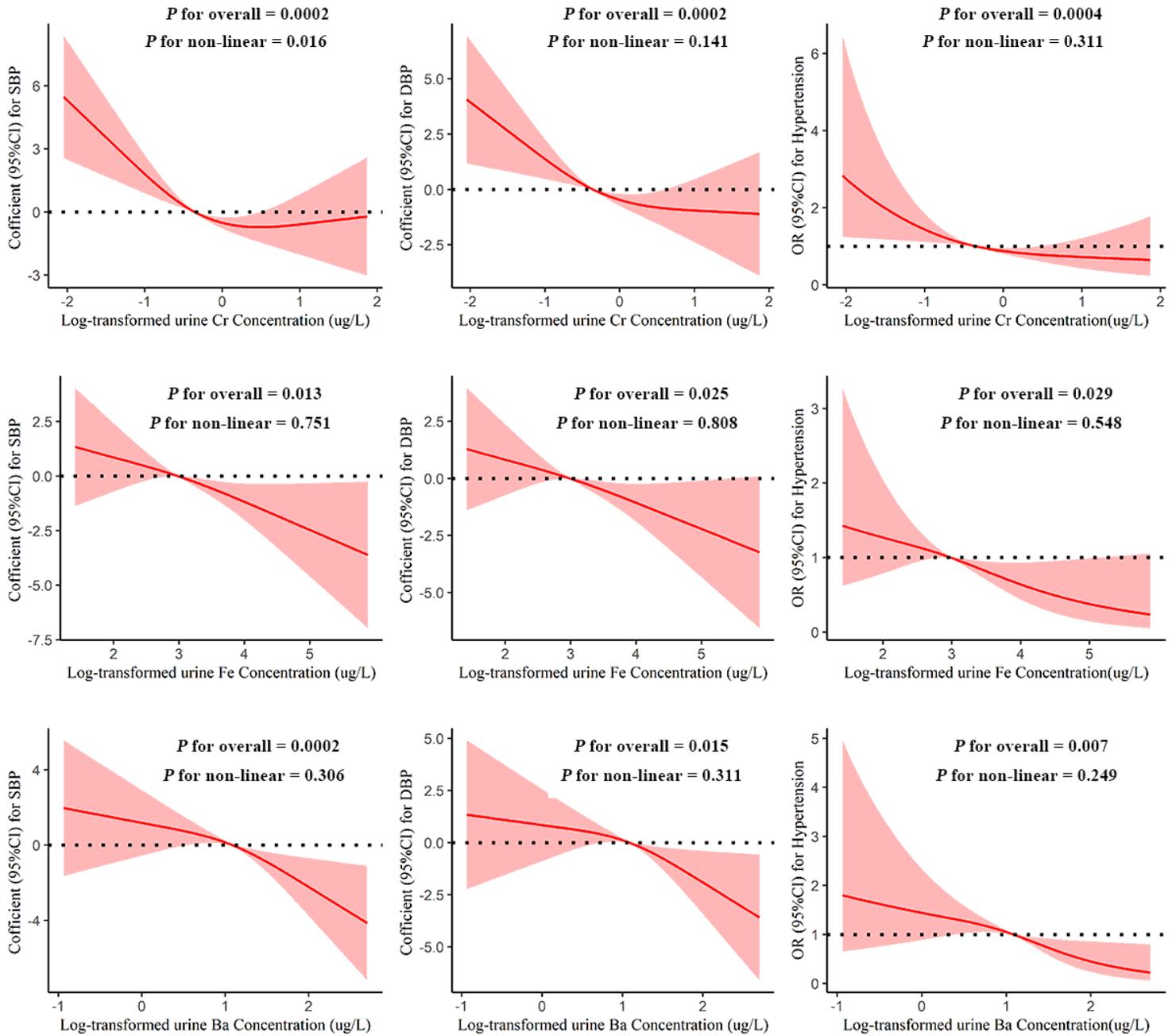


Figure 1

Associations of metal concentration with blood pressure and risk of hypertension.

The quartiles of metals were classified according to the natural log-transformed metal concentrations in urine ( $\mu\text{g/L}$ ), with the first quartiles to be the reference groups. The single metal model were adjusted with sex, age, children's BMI, birthweight, salt intake, physical activity, paternal BMI, maternal BMI, paternal education, maternal education, family income, family history of hypertension, and urine creatinine. Squares = coefficients or ORs; horizon lines = 95% CIs; vertical gray solid lines = 0 or 1;  $p$  =  $p$ -values for metals;  $p$ -FDR = FDR-adjusted  $p$ -values for metals; \*  $p$ -FDR < 0.05.



**Figure 2**

**Adjusted restricted cubic spline for associations of metal concentrations (log-transformed) with blood pressure and hypertension.**

The lines represent coefficients (95%CI) based on restricted cubic splines for the log-transformed urine Cr, Fe, and Ba in the single metals regression model, after adjusting for sex, age, children's BMI, birthweight, salt intake, physical activity, paternal BMI, maternal BMI, paternal education, maternal education, family income (RMB), family history of hypertension and urine creatinine.

## Supplementary Files

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