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Relationship between prenatal metals exposure and neurodevelopment in one-year-old infants in the CLIMB study

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ABSTRACT

Background: Prenatal metals exposure and its effects on infant neurodevelopment have garnered significant attention. However, most studies focus on individual metals, neglecting combined effects.
Objectives: We aimed to assess the effects of both single and combined prenatal metals exposure on one-year-old infants' neurodevelopment.
Methods: This study included 189 mother-infant pairs from the Complex Lipids in Mothers and Babies (CLIMB) cohort. The concentrations of 21 metallic elements and 2 metalloids in umbilical cord blood (UCB) serum were measured using inductively coupled plasma mass spectrometry (ICP-MS). Neurodevelopment was measured using Chinese version of Bayley Scales of Infant Development (BSID) for the Psychomotor Development Index (PDI) and the Mental Development Index (MDI). Multiple statistical methods, including linear models, restricted cubic splines (RCS), weighted quantile sum (WQS) regression, and Bayesian kernel machine regression (BKMR).
Results: After adjusting for potential confounders, prenatal arsenic (As) and strontium (Sr) levels were associated with lower PDI scores (As: $\beta = -2.324$; 95 % CI: −4.61, −0.04; Sr: $\beta = -2.426$; 95 % CI: −4.67, −0.18) by linear regression, while Sr was associated with lower MDI scores ($\beta = -2.841$; 95 % CI: −5.44, −0.25). RCS models revealed nonlinear dose-response relationships between manganese (Mn) and calcium (Ca) with PDI, and for Mn, As, and zirconium (Zr) with MDI. Interactions between certain metals were also identified. Metals mixture had an overall negative effect on both PDI and MDI scores, with Mn being the primary contributor.
Conclusion: Prenatal exposure to selected metals or metal mixtures is associated with poorer neurodevelopment in one-year-old infants.

1. Introduction

Human neurodevelopment begins as early as the second week of gestation and continues throughout pregnancy, a critical period in which the fetal brain is particularly vulnerable to environmental toxins (H. Chen et al., 2023; Erikson and Aschner, 2019). Growing evidence indicates that exposure to environmental chemicals during this time can significantly impact brain function and development, with potential effects on health later in life (Balasundaram and Avulakunta, 2024; Jiang et al., 2019).

Metals, as a class of environmental exposures, have garnered significant attention due to their persistence in the environment and potentially harmful effects on human health (Zhao et al., 2023). Because metals can easily cross the placental barrier, the development of the

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nervous system in utero is susceptible to the detrimental effects of both excess and deficiency of trace metals (C. Li et al., 2020). Specifically, epidemiological studies indicate that manganese (Mn) exposure in the intrauterine environment may affect early psychomotor development in children (Takser et al., 2003). Prenatal arsenic (As) exposure may lead to impaired fetal and neonatal development, including neurodevelopmental disorders as well as cardiovascular and respiratory issues (Téllez-Rojo et al., 2023; Wang et al., 2018). The placental barrier does not prevent heavy metals such as lead (Pb), cadmium (Cd), and mercury (Hg) from crossing into the fetal circulation by passive diffusion (Caserta et al., 2013; Gundacker and Hengstschläger, 2012). Prenatal Pb exposure has been associated with an increased risk of cognitive developmental delays in children (Z. Jia et al., 2023), and Hg exposure can disrupt fetal brain development, leading to neurodevelopmental deficits in early life (Nyanza et al., 2021). Meanwhile, studies have shown that essential trace elements such as selenium (Se), zinc (Zn), and magnesium (Mg) have protective effects on infant neurodevelopment (Adamo and Oteiza, 2010; Ajmone-Cat et al., 2022; Oddie et al., 2015; Shayganfard, 2022).

Many studies have explored the impact of prenatal exposure to single metals on fetal growth. However, metals exposure invariably occurs as part of mixtures. Evaluating the health effects of exposure to a single trace metal may underestimate the true impact due to potential interactions with other metals. Additionally, it is recognized that the highly correlated nonlinear and non-additive effects between metals may mask the actual effects of individual metals (Dou et al., 2022; C. Li et al., 2020).

During pregnancy, the mother and fetus exchange nutrients, oxygen, and waste through the umbilical cord, with the composition of umbilical cord blood (UCB) reflecting that of the fetal circulation (J. Liu et al., 2023). Therefore, UCB is commonly used as a biological specimen to study element exposure, helping to determine whether elements have crossed the placental barrier and reached the fetus during pregnancy (Bocca et al., 2019). In order to further assess the potential impact of prenatal metals exposure on neurodevelopment, we explored the impact of UCB serum metals exposure and metal mixtures at delivery on the neurodevelopment of one-year-old infants. Both linear and nonlinear relationships were considered, including interactions, to assess the overall effects of metal mixtures.

2. Method

2.1. Study population

This study utilizes data from the Complex Lipids in Mothers and Babies (CLIMB) study, conducted at the First Affiliated Hospital of Chongqing Medical University and Chongqing Health Centre for Women and Children in China from September 2015 to June 2017. The study design and protocol have been previously detailed (Huang et al., 2017). A total of 1500 pregnant women were recruited for the CLIMB study. Participants were recruited for the CLIMB study if they were between 20 and 40 years of age and were at 11–14 weeks gestation with a singleton pregnancy. A total of 242 UCB serum samples were collected at birth. Among them, 17 participants were excluded from this study due to insufficient blood volume and 36 were excluded from the study as their infants did not perform the Chinese version of Bayley Scales of Infant Development (BSID) at one year of age. This resulted in 189 CLIMB participants who were eligible for this analysis (Fig. 1). The statistical power reached 0.87 with an effect size of 0.15 and an alpha level of 0.05 (Fig. S1). The study was approved by the Ethics Committee of Chongqing Medical University (2014034). Written informed consent was obtained from all participants included in the study at enrollment. The informed consent form explicitly stated that the collected data and biospecimens could be used for future unspecified research, in accordance with the conditions defined at the time of consent.

2.2. Metals exposure measurement

Analytical and internal standards were purchased from Agilent Technologies. Inductively coupled plasma-mass spectrometry (ICP-MS) grade nitric acid (65 %) was obtained from ANPEL Laboratory Technologies (Shanghai, China). Ultrapure deionized water (18 mΩ) was provided by a water purification system (Aoside, China). A working standard solution was prepared by diluting 10 μg mL^{-1} of mixed-element standard solutions or single-element standard solutions (Multi-element Calibration Standard 2A-HG: Hg). An internal standard solution was also prepared by diluting 100 μg·mLˆ-1 of ICP-MS Internal Standard Mix in 5 % HNO_3.

UCB was collected after delivery into vacutainer tubes containing separator gel and separated by centrifugation twice (3000 rpm at 4 °C for 10 min, then 4000 rpm at 4 °C for another 10 min) to obtain the UCB serum and stored at −80 °C until analysis. A 100 μL aliquot of each thawed sample was transferred into 15 mL PTFE (polytetrafluoroethylene, G70D20CN1P-D2(S0), Galanz) digestion tubes. Then, 200 μL of 65 % nitric acid was added, and the tubes were capped for the digestion reaction. The PTFE tubes were placed in a microwave oven at 100 % power for 20 min. After cooling, the samples were transferred to 15 mL centrifuge tubes and made up to a volume of 3 mL with deionized water.

Serum metal concentrations were measured using ICP-MS (Agilent

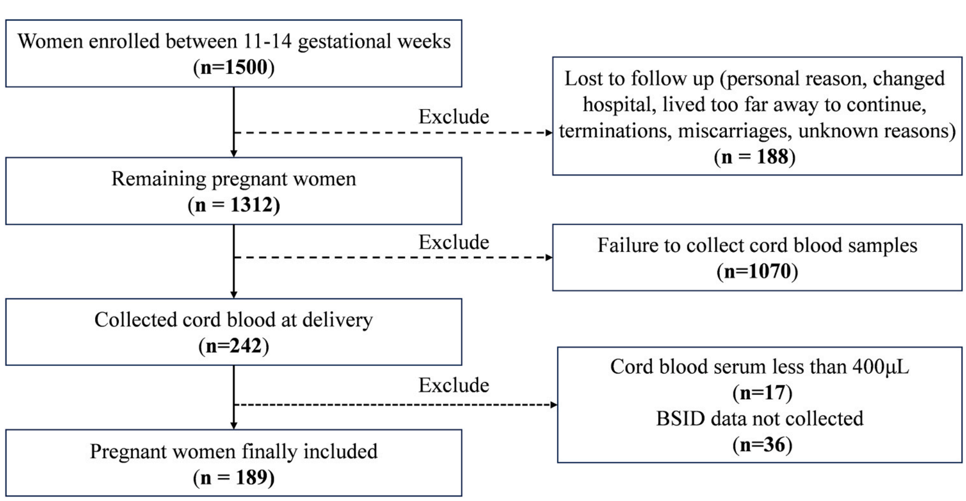

Fig. 1. The flowchart of the inclusion of subjects.

8900, USA), with a 1 μg L^{-1} mixed solution of Cerium (Ce), Cobalt (Co), Lithium (Li), Mg, and Thallium (Tl) (Agilent Technologies) serving as the tuning solution and argon as the combustion gas (Y. Liu et al., 2022). In total, 23 elements were measured, including 21 metallic elements and 2 metalloids: aluminum (Al), calcium (Ca), Mn, iron (Fe), Co, nickel (Ni), copper (Cu), Zn, gallium (Ga), As (metalloid), Se (metalloid), rubidium (Rb), strontium (Sr), yttrium (Y), zirconium (Zr), molybdenum (Mo), Cd, cesium (Cs), lanthanum (La), Ce, gadolinium (Gd), ytterbium (Yb), and uranium (U). Values below the limit of detection (LOD) were imputed by dividing the LOD by the square root of 2. We restricted all analysis to 18 elements with detection rates above 80 %: Al, Ca, Mn, Fe, Co, Ni, Cu, Zn, As, Se, Rb, Sr, Y, Zr, Cs, La, Ce, and U (Johnson et al., 2013).

2.3. Assessment of infant neurodevelopment

Infant neurodevelopment at one year of age (range from 11 months and 15 days to 12 months and 15 days) was measured using the Chinese version of BSID (Y.T. Chen et al., 2021). The Chinese version of the BSID is a formal adaptation to the Chinese language and locally standardized to reflect culturally appropriate scoring, administered by a trained research associate according to standardized instructions (de Seymour et al., 2022). Infants received a score on two main indices: the Psychomotor Development Index (PDI) and the Mental Development Index (MDI). The PDI component comprised 81 items that assessed fine and gross motor skills. The MDI component included 163 items that assessed cognitive functioning, language development, and personal and social development (Yi et al., 1993). To ensure comparability across infants of different ages, the raw PDI and MDI scores were standardized based on the infant's age (in days) at the time of the test. Based on norms for the Chinese population, these index scores have a mean of 100 and a standard deviation of 15, with lower scores reflecting poorer performance (Y.T. Chen et al., 2021).

2.4. Covariates

Maternal clinical information, including maternal age, body mass index (BMI), gestational weight gain (GWG), smoking status, alcohol consumption, parity, delivery mode, marital status, ethnicity, family income, occupation, and education level, was collected at enrollment using a structured questionnaire. Between weeks 22 and 28 of gestation, plasma glucose levels were assessed through a 75-gram oral glucose tolerance test (OGTT). Diagnosis of Gestational Diabetes Mellitus (GDM) was made according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, participants were identified as having GDM if they had at least one of the following glucose levels: fasting plasma glucose (FG) of 5.1 mmol/L or higher, 1-h post-OGTT glucose level of 10.0 mmol/L or higher, or 2-h post-OGTT glucose level of 8.5 mmol/L or higher (Weinert, 2010). Additionally, infant characteristics such as sex, gestational age at delivery, birth weight, and birth length were extracted from medical records by trained nurses.

2.5. Statistical analysis

Descriptive analyses were performed for all variables. For basic characteristics, continuous variables that conformed to normal distribution were expressed as mean ± standard deviation (SD), continuous variables that did not conform to normal distribution were expressed as median [interquartile range (IQR)], and categorical variables were expressed as counts and percentages. Given the skewed distribution of metals in UCB serum, we performed a natural logarithm transformation. We then evaluated the pairwise correlations between the concentrations of these metals using Spearman correlation coefficients.

Firstly, we used general linear regression models (single-metal models) and multivariable linear regression models (multi-metal models) to calculate the beta coefficients (β) and their corresponding 95 % confidence intervals (CI), in order to evaluate the linear relationship between each metal element and PDI and MDI scores. Additionally, we explored the interaction effects between metals exposure and outcomes by including product terms in the models. Moreover, metal concentrations were categorized into quartiles with the lowest quartile serving as the reference group. In the linear regression models, the median value of each quartile was used to test for trends across increasing levels of metals exposure.

Restricted cubic splines (RCS) were used to investigate the potential nonlinear dose-response trends between different metals and PDI or MDI scores. The RCS models were built using the "gaussian" link function from the R package "rms", with the number of knots (3, 4, or 5) selected based on Akaike information criterion (AIC) values.

In reality, neurodevelopment is affected by a combination of metals that may be present in the human body at the same time; therefore, we used weighted quantile sum (WQS) regression to investigate the joint relationship between mixtures of metals and neurodevelopment. The model constructs a weighted index to estimate the mixed effects of all environmental chemical exposures on outcomes, allowing to assess the effect of the mixture as well as the relative importance of individual exposures simultaneously (Guo et al., 2022). In this study, we constructed a WQS index based on the quartiles of UCB serum metals. Forty percent of the data was used as the training set, while the remaining sixty percent was used as the validation set, with 1000 bootstrap samples drawn. The model assumes that all exposures included in the index are associated with the outcome in the same direction, meaning the model only estimated either positive or negative mixed effects, with the total weight of the index summing to 1 (Shi et al., 2022). We here hypothesized that mixed metals exposure is negatively correlated with children's neurodevelopment. Using the "gaussian" link functions from the R package "*g*WQS", we established the WQS model in the negative direction. To address the limitations of linearity and interaction issues in traditional regression analysis, we constructed the Bayesian Kernel Machine Regression (BKMR) model using the R package "bkmr", which was completed using a Markov Chain Monte Carlo (MCMC) algorithm with 10,000 iterations for parameter estimation and exploration of the posterior distribution (Benoit et al., 2022). Specific BKMR analysis results include: (1) the overall effect of metal mixtures on neurodevelopment; (2) the effect of individual metals; (3) the nonlinear and non-additive dose-response relationship between each metal and neurodevelopment outcomes; (4) the pairwise interactions between components of the mixtures. In addition, we calculated the posterior inclusion probability (PIP) for each metal in the mixture, with values ranging from 0 to 1, to indicate the relative significance of each metal in the overall mixture effect, with components considered relatively important if their PIP is ≥ 0.5 (Y. Zhang et al., 2019).

According to previous literature and a directed acyclic graph (DAG) (Fig. S2), all models were adjusted for the following potential confounders: maternal age, BMI, GWG, occupations (full time work, part time work, student), parity (1, ≥2), tertiary education (yes, no), birth weight, infant sex (boy, girl). All analyses were carried out using R (version 4.4.0). P-values < 0.05 were considered as statistically significant.

We conducted two sensitivity analyses to assess the robustness of our findings. First, some findings suggest that GDM may have unfavorable effects on neurodevelopmental skills, especially associated with weaker expressive language skills (Kadam et al., 2024; Saros et al., 2023), so we included GDM as an additional covariate in our adjusted linear regression models. The initial models adjusted for maternal age, BMI, GWG, occupations, parity, tertiary education, birth weight and infant sex. By adding GDM to this set of covariates, we aimed to determine whether the associations between UCB serum metal levels and infant neurodevelopmental scores (PDI and MDI) remained consistent. Second, given previous reports of sexual dimorphism on metals exposure and infant neurodevelopment (Chiu et al., 2017; Polanska et al., 2018), we conducted sex-stratified analyses to explore whether metals exert sex-modifying effects on the neurodevelopmental outcomes of one-year-old infants.

3. Results

3.1. Basic characteristics

Table 1 summarizes the basic characteristics of 189 mother-child pairs. The average maternal age was 28.95 ± 3.68 years; median BMI was 22.00 kg/m^2; and average GWG was 13.28 ± 3.97 kg. Of the women, 97.35 % were married; 64.02 % had a monthly household income between 4000 and 7000 RMB; 99.47 % were of Han ethnicity; 70.89 % were employed; 73.54 % were primiparous; 0.53 % smoked or drank alcohol during pregnancy; 67.20 % had tertiary education; and 32.28 % had GDM. Furthermore, 50.26 % of the women had vaginal deliveries; the median gestational age was 39 weeks; the median birth weight was 3.35 kg; the median birth length was 50 cm; the sex distribution of the newborns was 49.21 % boys and 50.79 % girls. The PDI score for infants at one year of age was 86.03 ± 15.59, and the MDI score was 93.07 ± 17.95. UCB serum metal concentrations are shown in Table 2. Fig. S3 presents the pairwise Spearman correlation coefficients for the metals. Most metals exhibit positive correlations ranging from 0.15 to 0.91, with Al and Mn showing the strongest correlation ($r = 0.91$, $p < 0.001$). This supported the use of a mixture model to analyze the effects of metal mixtures on neurodevelopmental outcomes.

Table 1
Characteristics of the study population.

Characteristics	Value (mean ± SD or median [IQR] or n (%))
Mothers	
Maternal age (years)	28.95 ± 3.68
BMI (kg/m^2)	22.00 [20.00, 24.00]
GWG (kg)	13.28 ± 3.97
Marriage, n (%)	
Single	1 (0.53)
Married	184 (97.35)
Common-law marriage	4 (2.12)
Family income, n (%)	
< 2000 ¥ /month	38 (20.11)
< 4000 ¥ /month	68 (35.98)
< 7000 ¥ /month	53 (28.04)
< 10,000 ¥ /month	30 (15.87)
Han race, n (%)	
YES	188 (99.47)
NO	1 (0.53)
Occupations, n (%)	
Full time work	39 (20.63)
Part time work	95 (50.26)
Student	55 (29.11)
Parity, n (%)	
1	139 (73.54)
≥ 2	50 (26.46)
Smoking, n (%)	
YES	1 (0.53)
NO	188 (99.47)
Drinking, n (%)	
YES	1 (0.53)
NO	188 (99.47)
Tertiary education, n (%)	
YES	127 (67.20)
NO	62 (32.80)
GDM, n (%)	
YES	61 (32.28)
NO	128 (67.72)
Offspring	
Delivery mode, n (%)	
Vaginal birth	95 (50.26)
Cesarean section	94 (49.74)
Gestational age (week)	39.00 [38.00, 40.00]
Birth weight (kg)	3.35 [3.08, 3.58]
Birth length (cm)	50.00 [49.00, 51.00]
Infant sex, n (%)	
Boy	93 (49.21)
Girl	96 (50.79)
PDI	86.03 ± 15.59
MDI	93.07 ± 17.95

Note: SD, standard deviation; IQR, interquartile range; BMI, body mass index; GWG, gestational weight gain; GDM, gestational diabetes mellitus; PDI, psychomotor development index; MDI, mental development Index.

3.2. Linear regression analysis

The results of the linear regression analysis on UCB serum metal levels and infant neurodevelopment are presented in Table S1. In the unadjusted single-metal models, a 1-unit increase in the natural-log transformed concentrations of As and Sr was significantly associated with lower PDI scores, with β values of −2.338 (95 % CI: −4.56, −0.11) and −2.378 (95 % CI: −4.60, −0.15), respectively. The results remained similar in the adjusted model for As (β = −2.324; 95 % CI: −4.61, −0.04) and Sr (β = −2.426; 95 % CI: −4.67, −0.18). Additionally, in the adjusted model, each unit increase in log-Sr levels was significantly associated with lower MDI scores (β = −2.841; 95 % CI: −5.44, −0.25). In the unadjusted multi-metal model, Cs levels were significantly associated with higher PDI scores, with a β value of 2.823 (95 % CI: 0.17, 5.48).

The linear interactions between various metals are shown in Table S2 and Fig. 2. For the PDI score, evidence of an interaction between Mn and Zn was apparent, with an estimated value of 1.803, indicating that the interaction of these two metals positively influences the psychomotor development of one-year-old infants. For the MDI score, the interactions between Fe and Zr, Zn and As, and Rb and La are significant, with estimated values of 2.970, 1.992, and −4.152, respectively. This suggests that the interactions between Fe and Zr, and Zn and As positively affect the mental development of one-year-old infants, while the interaction between Rb and La has a negative impact.

The association of metals quartiles with PDI and MDI are shown in Table S3. Specifically, compared to participants in the lowest quartile of Mn and Zr concentrations, those in the highest quartile showed a significant decrease in PDI scores (Mn: β = −9.822; 95 % CI: −16.15, −3.49; *p* for trend = 0.004; Zr: β = −6.419; 95 % CI: −12.90, 0.06; *p* for trend = 0.027). A similar pattern was observed for MDI scores, with a significant decrease as Mn, Sr and Zr concentrations increased from Q1 to Q4 (Mn: β = −8.818; 95 % CI: −16.21, −1.43; *p* for trend = 0.043; Sr: β = −7.589; 95 % CI: −14.99, −0.18; *p* for trend = 0.048; Zr: β = −11.364; 95 % CI: −18.71, −4.01; *p* for trend = 0.003).

3.3. Nonlinear dose-response relationships

RCS analysis demonstrated a nonlinear association between some metals and infant neurodevelopmental outcomes (Fig. 3 and Fig. S4-S5). Specifically, a nonlinear dose-response relationship (U-shaped) was observed between Ca and Mn with PDI, in addition to between Mn, As, and Zr with MDI, with nonlinear P-values of 0.039, 0.005, 0.011, 0.024, and 0.001, respectively.

3.4. Mixed effects of metals exposure on neurodevelopment

The WQS regression model was utilized to examine the relationship between metal mixtures and infant cognitive development. As shown in Fig. 4, the β values for the negative WQS models for both outcomes are less than 0, and the P-values are less than 0.05, indicating that metal mixtures increase the risk of delayed psychomotor and mental development in infants. Specifically, for PDI scores, Mn contributed the most to the WQS index (0.170), followed by Zr (0.139), Cu (0.114), and Ca (0.098); for MDI scores, Se contributed the most to the WQS index (0.157), followed by Mn (0.140), Cu (0.124), and Zr (0.116).

The results of the BKMR analysis are presented through overall effects, individual metal effects, and univariate and bivariate exposure-response plots. In relation to PDI scores, the overall effect of the metal

Table 2
The limits of detection, detection rates and distributions of metals in umbilical cord blood serum.

Metals	LOD (μg/L)	Detection rate (%)	P5	P25	P50	P75	P95
Al	3.300237	92.59 %	2.520	5.827	10.578	18.542	32.921
Ca	1.817446	100.00 %	346.690	434.888	478.707	514.063	577.329
Mn	0.014075	99.47 %	0.119	0.208	0.317	0.552	1.065
Fe	0.080968	100.00 %	49.354	73.893	94.395	133.817	373.237
Co	0.002757	98.41 %	0.005	0.008	0.013	0.021	0.051
Ni	0.082092	91.01 %	0.036	0.161	0.355	0.876	3.311
Cu	0.195323	99.47 %	6.120	8.590	10.852	15.315	23.911
Zn	0.421839	100.00 %	23.655	28.832	33.450	40.014	120.827
Ga	0.017280	28.04 %	0.003	0.008	0.013	0.019	0.032
As	0.011743	80.25 %	0.005	0.014	0.028	0.046	0.095
Se	0.062079	99.47 %	0.413	0.560	0.657	0.814	1.021
Rb	0.028826	100.00 %	6.237	9.554	12.457	16.062	23.344
Sr	0.082610	99.47 %	1.542	1.964	2.481	3.060	4.871
Y	0.005412	82.54 %	0.004	0.007	0.011	0.016	0.030
Zr	0.021733	98.41 %	0.031	0.055	0.083	0.126	0.241
Mo	0.008461	72.49 %	0.004	0.007	0.018	0.034	0.521
Cd	0.006086	48.15 %	0.001	0.004	0.006	0.018	0.045
Cs	0.003178	99.47 %	0.011	0.031	0.053	0.086	0.128
La	0.000902	99.47 %	0.003	0.009	0.013	0.018	0.032
Ce	0.003134	100.00 %	0.061	0.106	0.143	0.216	0.445
Gd	0.002284	64.55 %	0.001	0.002	0.003	0.004	0.006
Yb	0.002956	31.22 %	0.001	0.001	0.002	0.003	0.004
U	0.000683	87.83 %	0.001	0.002	0.003	0.021	0.097

Note: LOD, limits of detection; P5, 5th percentile; P25, 25th percentile; P50, 50th percentile; P75, 75th percentile; P95, 95th percentile.

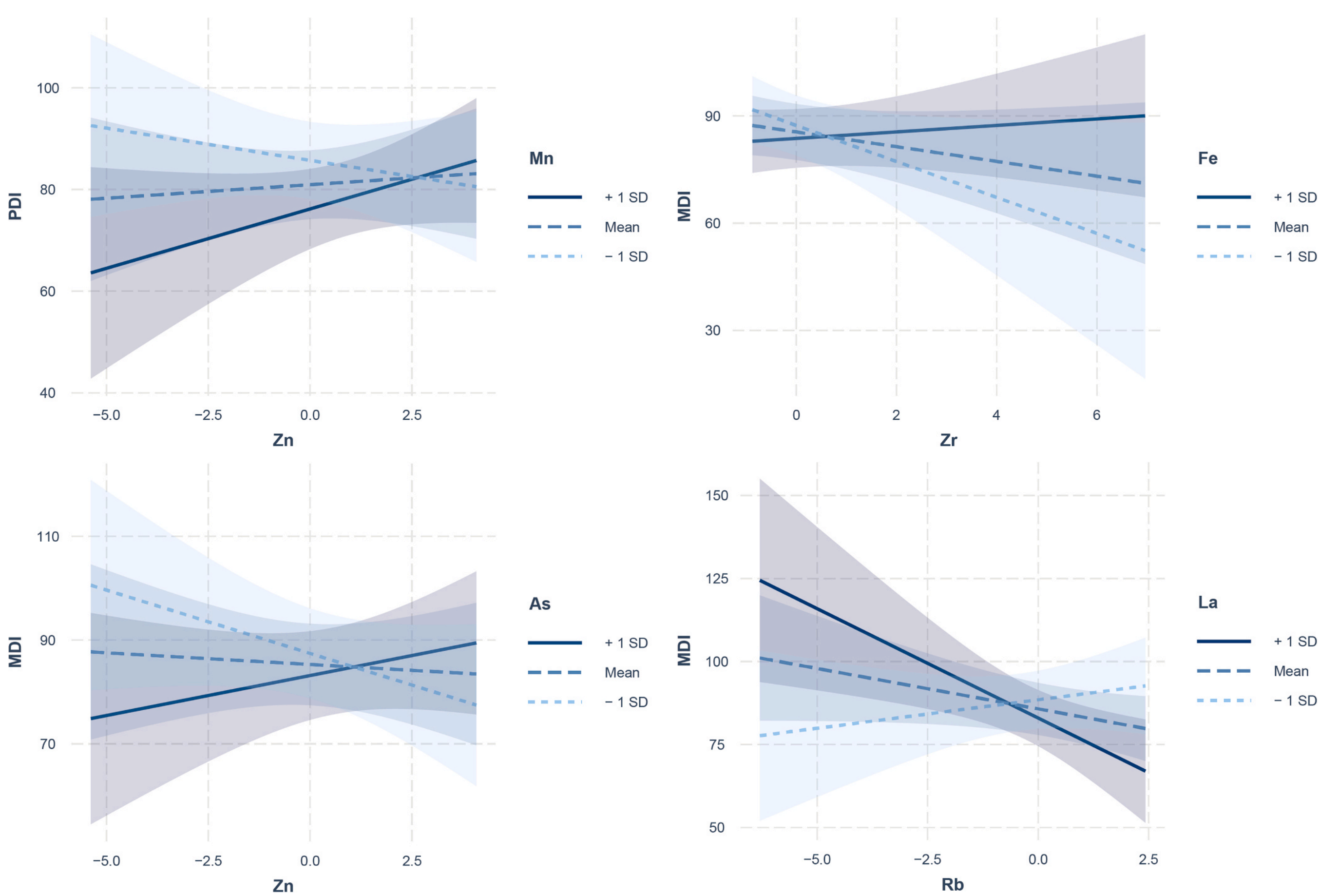

Fig. 2. Interaction effects between metals exposure. The horizontal axis represents the independent variable; the left side of the vertical axis represents the outcome; the right side of the vertical axis represents the moderator variable, which is divided into three lines: the mean and ± 1 SD. The model was adjusted for covariates including maternal age, BMI, GWG, occupations, parity, tertiary education, birth weight, infant sex. The concentration of metals in umbilical cord blood serum were natural-log transformed.

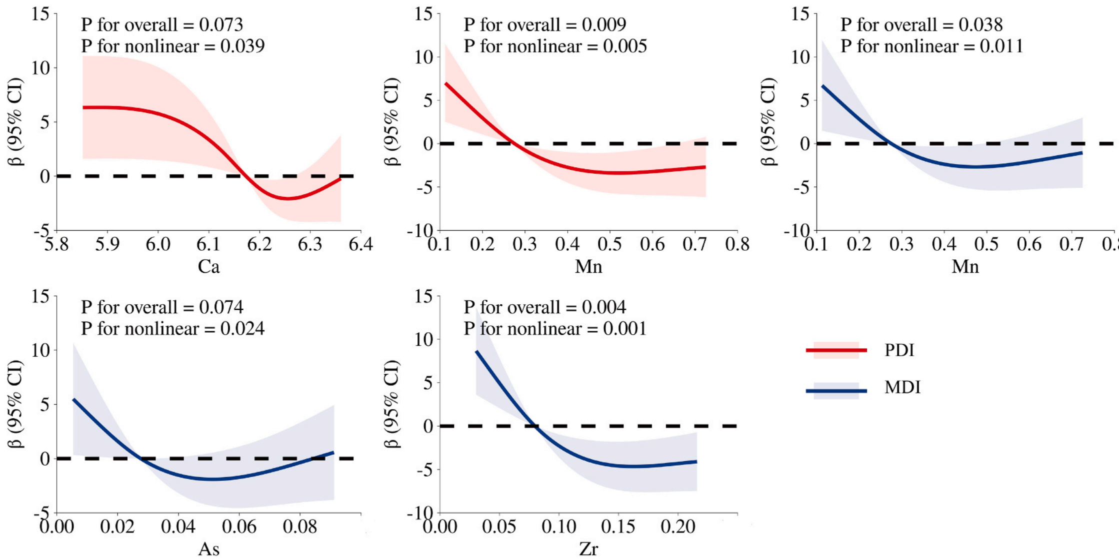

Fig. 3. Dose-response relationship of metal concentrations with PDI and MDI estimated using RCS models. The model was adjusted for covariates including maternal age, BMI, GWG, occupations, parity, tertiary education, birth weight, infant sex. The concentration of metals in umbilical cord blood serum were natural-log transformed.

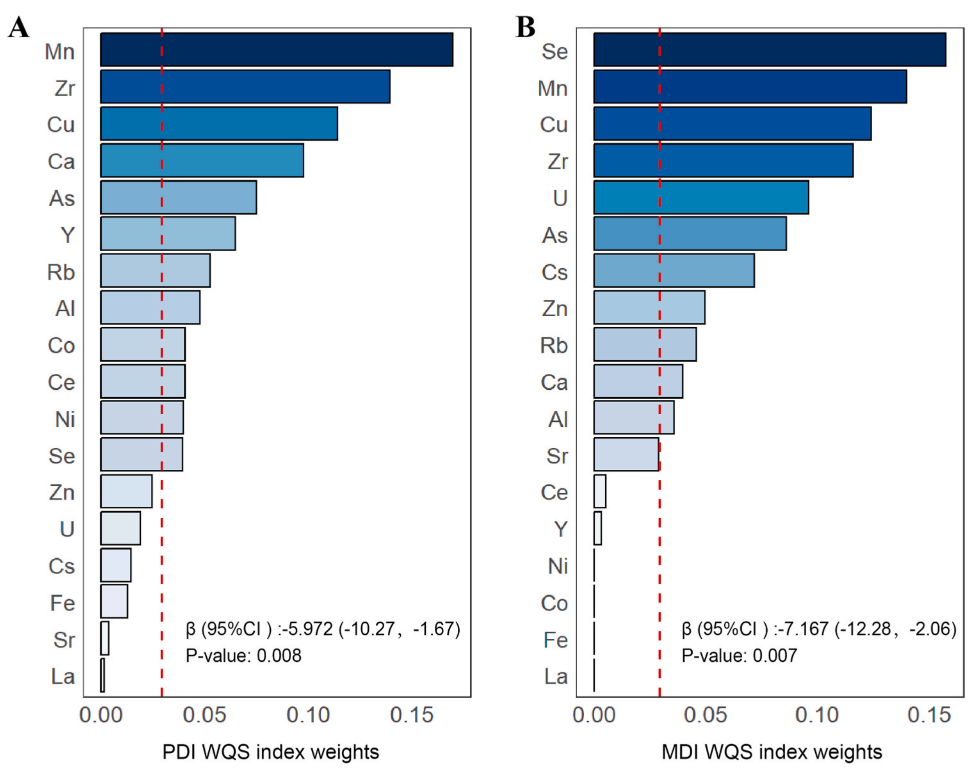

Fig. 4. Estimated weights assigned to each metal based on WQS regression modeled in the negative direction with respect to PDI (A) and MDI (B). The model was adjusted for covariates including maternal age, BMI, GWG, occupations, parity, tertiary education, birth weight, infant sex. The concentration of metals in umbilical cord blood serum were natural-log transformed.

mixture is not statistically significant at any percentile relative to the median (Fig. 5 (A)). However, a monotonic downward trend in the overall effect was observed, suggesting that PDI scores may decrease with increasing concentrations of the metal mixtures. Fig. S6 illustrates the estimated change in PDI scores when a single metal changes from the 25th to the 75th percentile, while the other 17 metals are held constant at the 25th, 50th, or 75th percentile. In this study, Mn exhibited a significant negative effect on PDI scores. The univariate exposure-response relationships between each metal and PDI are shown in Fig. S7, where Ca, Mn, and Ni may exhibit non-linear relationships with PDI when all other metal concentrations are held at the median. The bivariate exposure-response plots (Fig. S8) suggest potential interactions between Mn and Cs, Mn and Co, and Mn and Y in their association with PDI. For MDI scores, as shown in Fig. 5 (B), the metal mixture is significantly negatively associated with MDI when the mixture is below the 45th percentile compared to the median, with an overall monotonic downward trend. In the univariate effect models, no statistically significant effects were observed on MDI when any metal increased from the 25th to

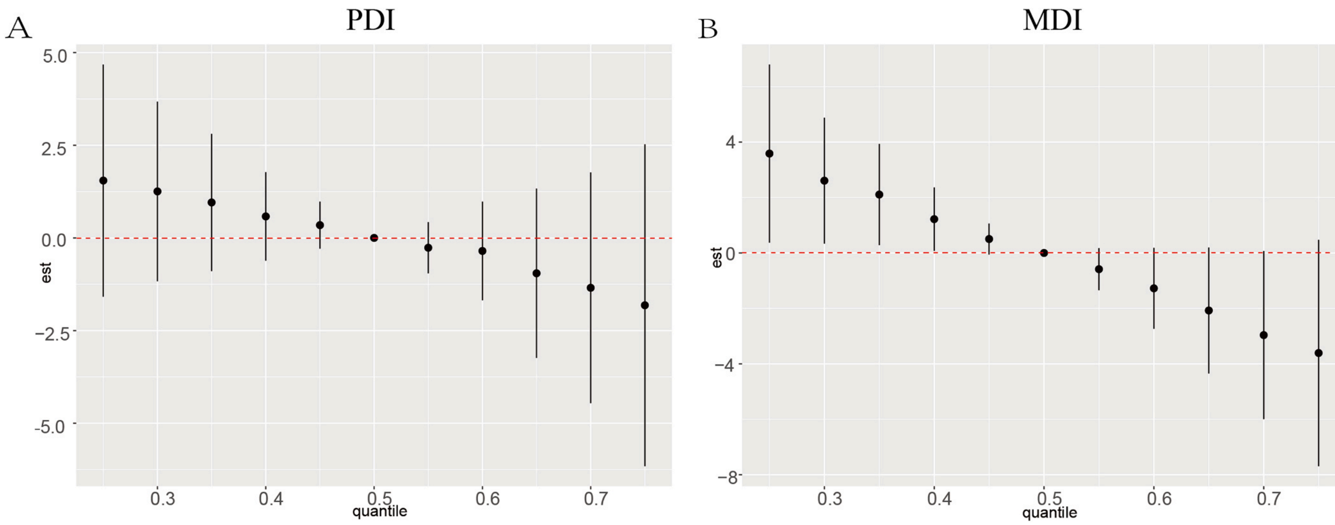

Fig. 5. Overall effects of the metal as a mixture on PDI (A) and MDI (B). Dots represent posterior mean difference values; black vertical lines represent 95 % CI. The model was adjusted for covariates including maternal age, BMI, GWG, occupations, parity, tertiary education, birth weight, infant sex. The concentration of metals in umbilical cord blood serum were natural-log transformed.

the 75th percentile, while other metals were set at the 25th, 50th, or 75th percentile (Fig. S9). A non-linear relationship between Zr and MDI may exist when all other metal concentrations are held at the median (Fig. S10). The bivariate exposure-response plots suggest a potential interaction between Fe and Zr in their association with MDI (Fig. S11). Based on the PIP values generated by the BKMR model (Table S4), the component with the highest conditional PIP value for PDI is Mn (0.605). For MDI, the PIP values range from 0.019 to 0.207, which are relatively low.

3.5. Sensitivity analysis

We refitted the univariate linear regression models and RCS models with the additional covariate (GDM), as shown in Table S5 and Fig. S12, and observed similar results to the main analyses. Additionally, we conducted additional stratified analyses by infant sex, as shown in Table S6 and Table S7. For PDI scores, As and Sr had a significant negative effect on PDI scores in the whole analysis sample. However, upon sex-stratification, As was not associated with PDI scores for either boys or girls. In contrast, Sr had a significantly negative effect on PDI scores for boys, with a β value of −4.028 (95 % CI: −7.44, −0.62), while no significant effect was observed for girls. Furthermore, Fe showed a significantly negative impact on PDI scores for boys after sex-stratification, with a β value of −3.502 (95 % CI: −6.79, −0.22). For MDI scores, Sr had a significant negative effect on MDI scores in the whole analysis sample. After sex-stratification, this negative impact was significant only for boys, with a β value of −3.919 (95 % CI: −7.79, −0.04). Additionally, Al had a significantly negative effect on MDI scores for boys after sex-stratification, with a β value of −4.028 (95 % CI: −7.98, −0.07). These results suggest that the impact of metals exposure on infant neurodevelopment may vary by sex, with boys potentially being more susceptible to these effects than girls.

4. Discussion

In this study, we measured the concentrations of a range of metals in cord blood serum in order to assess the effects of prenatal exposure of these metals and their mixtures on neurodevelopment in one-year-old infants. Our results provide some evidence that individual metals, such as As and Sr, are significantly associated with lower PDI scores, while Sr is also associated with lower MDI scores. Additionally, our findings revealed potential additive interactions between metals, such as positive interactions between Mn and Zn on PDI, and between Fe and Zr, and Zn and As on MDI. In contrast, Rb and La demonstrated a negative additive interaction on MDI. Furthermore, we observed nonlinear relationships between Ca and Mn with PDI, and between Mn, As, and Zr with MDI. Using WQS and BKMR models to assess the combined effects of metal mixtures, we found that co-exposure to metals was associated with an increased risk of delayed psychomotor and mental development. The BKMR model also identified interactions between Mn and other metals (e.g., Cs, Co, and Y) on PDI, and between Fe and Zr on MDI. These findings highlight the complex relationship between prenatal metal mixture exposures and neurodevelopmental outcomes and the need for further research in this field.

As is a prevalent element in the environment, primarily found in soil and water, often resulting from natural erosion as well as human activities such as industrial and agricultural processes (Garza-Lombó et al., 2019). In regions such as Bangladesh, India, Mexico, Chile, and certain areas of the United States, drinking water is the main route of As exposure. In areas with lower levels of As in water, such as Spain, the primary sources of exposure are certain foods, particularly rice, as well as other products like shellfish and legumes (Soler-Blasco et al., 2022). In China, studies have indicated that rice is a significant source of As intake, particularly in the southern regions where it constitutes the majority of total As consumption (Li et al., 2011). A cohort study in Wuhan indicated that prenatal As exposure, particularly during early pregnancy, is negatively associated with neurodevelopment in two-year-old children, even at low levels of exposure (H. Chen et al., 2023). Furthermore, the same study also found a nonlinear relationship between Dimethylarsinic Acid Percentage (DMA%) and MDI (nonlinear term P-value = 0.049), which is consistent with the results of our RCS model that revealed a nonlinear relationship between As and MDI. Similar conclusions have been observed in studies from other countries, with research in Norway and Bangladesh indicating that prenatal As exposure is a risk factor for neurodevelopment in offspring, potentially contributing to the development of Autism Spectrum Disorder (ASD) and impacting cognitive development as measured by Intelligence Quotient (IQ) (Hamadani et al., 2011; Skogheim et al., 2021). Our study reached a similar conclusion, finding that prenatal As exposure is significantly associated with psychomotor developmental delays in one-year-old infants. Studies have shown that As easily crosses the blood-brain barrier, accumulating in brain regions such as the striatum and hippocampus, leading to neurotoxicity. The brain is highly sensitive to oxidative stress due to its high energy demand, making it more susceptible to damage. Exposure to As exacerbates oxidative stress by reducing the activity of antioxidant enzymes in the brain, thereby contributing to damage in the brain. As a result, increased oxidative stress is a key mechanism in As-induced neurotoxicity (Thakur et al., 2021). Additionally, animal studies suggest that As may further induce neurotoxicity by causing thiamine deficiency and decreasing acetylcholinesterase activity, thus affecting neurodevelopment (Mochizuki, 2019).

In this study, we found that elevated Sr levels in UCB serum were significantly associated with lower PDI and MDI scores. Sr, as an alkaline earth metal, naturally occurs in the human body and is considered a trace element (Xu et al., 2015). As an element in the same group as Ca, Sr's effects are considered to be similar to those of Ca (X.C. Liu and Skibsted, 2022; Pors Nielsen, 2004). In our analysis, Ca did not exhibit a significant linear relationship with infant neurodevelopment; however, a significant nonlinear dose-response relationship between Ca and PDI was observed in the RCS model, which aligns with previous findings from the NHANES study showing a U-shaped nonlinear association between dietary Ca intake and peripheral neuropathy (Wu et al., 2023). Although we did not identify a significant nonlinear relationship between Sr levels and neurodevelopmental outcomes in this study, previous research has suggested that Sr may demonstrate a dose-dependent biphasic effect: low doses can stimulate beneficial biological processes such as osteogenesis, while high doses may lead to apoptosis and adverse effects (Aimaiti et al., 2017). This biphasic nature could explain why we observed a linear negative association between Sr and neurodevelopmental outcomes, as the Sr levels in our study may have exceeded the "optimal" range for neurodevelopment, potentially resulting in harmful effects. However, the optimal dose of Sr for neurodevelopment remains unclear, and further studies are required to determine its specific dose-response relationship and potential neurotoxicity. Moreover, other studies have reported differing conclusions. For example, a cohort study conducted in Wuhan indicated a positive association between urinary Sr levels and MDI scores, and Sr was suggested to have a slightly nonlinear relationship with MDI in the BKMR model (C. Li et al., 2020). Another study by Jia et al. found that Sr levels in breast milk at 42 days postpartum were positively correlated with attention and MDI scores in 8-month-old infants, and their RCS regression analysis also revealed a nonlinear association between Sr levels in breast milk and PDI scores (K. Jia et al., 2022). The beneficial effects of Sr are hypothesized to stem from its role in reducing lipid peroxidation and providing protection against oxidative damage (Barneo-Caragol et al., 2018). These conflicting findings could be attributed to several factors: (1) differences in sample selection and data collection methods. Sr levels in UCB might not directly correspond to those in urine or breast milk, which could affect the observed relationships. (2) Environmental and geographical factors. The uneven distribution of Sr in nature may lead to regional differences in dietary Sr intake, thereby influencing its impact on neurodevelopment (Cabrera et al., 1999). (3) The relatively small sample size in our study may have limited the statistical power to detect nonlinear relationships. Furthermore, most current studies on Sr focus on its effects on bone metabolism, while research on its influence on neurodevelopment remains limited (Marie et al., 2001; Pors Nielsen, 2004; Querido et al., 2016). Therefore, further research is needed to clarify the complex role of Sr in neurodevelopment, particularly its potential nonlinear dose-response relationship.

Mn is an essential trace element in the human body, serving as a cofactor for enzymes involved in various biological processes (Baj et al., 2023). These processes include, but are not limited to, macronutrient metabolism, bone formation, the antioxidant defense system, ammonia clearance in the brain, and neurotransmitter synthesis (Erikson and Aschner, 2019). However, excessive exposure to Mn is toxic, particularly to the central nervous system, as Mn accumulates in the brain, leading to the gradual destruction of neurons and resulting in cognitive, behavioral, and motor deficits (Kim et al., 2022). Mn is widely distributed on the Earth's surface, naturally occurring in rocks, soil, water, and food, making daily dietary intake the primary source of Mn for humans (Studer et al., 2022). In our study, we found a significant nonlinear dose-response relationship between Mn exposure and infants' PDI and MDI scores. This finding aligns with several international cohort studies that have also reported a U-shaped association between Mn exposure and neurodevelopmental indicators (Bauer et al., 2017; Gunier et al., 2015; Muñoz-Rocha et al., 2018). Additionally, some studies have found an inverted U-shaped relationship between Mn and neurodevelopment (Chung et al., 2015; Claus Henn et al., 2010; Muñoz-Rocha et al., 2018). These curves suggest that there may be an "optimal" concentration range for Mn, where levels below or above this range could negatively impact neurodevelopment (W. Zhang et al., 2023). In addition, the neurotoxic mechanisms of Mn have been extensively studied, including its interference with epigenetics, oxidative stress, mitochondrial dysfunction, glutamate excitotoxicity, protein misfolding, inflammation, autophagy, mitosis, endoplasmic reticulum stress, and apoptosis (Lindner et al., 2022; Pajarillo et al., 2022).

Zr is a transition metal widely found in nature and present in almost all biological systems. Current information indicates that it is neither an essential element nor a toxic element, with no known biological function in plant or animal metabolism, and humans are primarily exposed through water and food (Lee et al., 2010; Shahid et al., 2013). The distribution of Zr within animal bodies is closely related to their mode of contact and the environmental concentration. It typically accumulates initially in soft tissues and then gradually transfers to the bones. Moreover, Zr can penetrate the blood-brain barrier, leading to deposits in the brain, and is also capable of crossing the placental barrier, subsequently entering milk (Ghosh et al., 1992). In this study, we found a nonlinear dose-response relationship between Zr and MDI. However, no similar findings have been reported in other studies to date. A study in Kentucky, USA, indicated that children with internalizing behavior had higher concentrations of Zr in their fingernails than non-pica children (Zierold et al., 2022). Ryu et al. (2014) reported in 2014 a case of a woman with systemic Zr poisoning presenting with acute intermittent parkinsonism and skin discoloration. These researchers have expressed that the understanding of neurological issues or symptoms potentially caused by Zr is currently insufficient, and further research is needed to clarify whether these presumed health effects are indeed caused by Zr.

There is increasing evidence that exposure to individual chemicals rarely occurs in isolation but rather as part of complex mixtures (Claus Henn et al., 2014; Merced-Nieves et al., 2021). Components within a mix can interact, altering their toxicokinetics and toxicodynamics, leading to enhanced toxic effects (synergism) or reduced effects (antagonism) (Andrade et al., 2017). The findings of this study further support the existence of such metal interactions, particularly the additive positive effects of Mn and Zn on PDI, as well as Fe and Zr, and Zn and As on MDI, suggesting that these metals may jointly influence infant neurodevelopment through co-exposure. Conversely, the negative additive effect observed between Rb and La indicates that certain metals may exhibit toxic synergism under co-exposure, potentially in association with adverse developmental outcomes. BKMR analysis revealed that neurodevelopmental scores showed a significant downward trend as metal mixture concentrations increased. The BKMR model, with its ability to capture complex nonlinear exposure-response relationships, can simultaneously evaluate the combined effects of multiple metals as well as their potential interactions. In our study, interactions effects were observed between Mn and Cs, Co, and Y on PDI scores, as well as between Fe and Zr on MDI scores. These results further support the hypothesis that co-exposure may significantly influence neurodevelopment, potentially via mechanisms such as oxidative stress, immune regulation, or metabolic function. For example, previous studies have shown that Mn and Zn metabolism are closely linked in various cellular processes (Nishito et al., 2024). Zn may mitigate the toxicity of Mn to HepG2 cells by reducing its bioavailability (Michaelis et al., 2023). This protective mechanism could explain the positive additive effect observed between Mn and Zn in our study. Similarly, the study by

Dashner-Titus et al. (2023), found that Zn could protect the body from As toxicity by modulating metal transporters and inhibiting oxidative stress which may also explain the positive additive effect observed between Zn and As, further suggesting that Zn may play a protective role in metal mixture exposure. As a key element for brain development, Fe plays a critical role in synaptogenesis, myelination, energy metabolism, and neurotransmitter production (German and Juul, 2021), and its interaction with other metals such as Pb, Mn, Cu, and Zn during intake and metabolism affects neurodevelopment (Schildroth et al., 2022). Therefore, understanding the impact of iron's interaction with other metals on neurodevelopment is crucial for public health interventions. K. Jia et al. (2022) demonstrated that under certain thresholds, higher Rb intake is beneficial for infant neurocognitive development, while exposure to La has been shown to cause central nervous system damage and dysfunction in children (Yan et al., 2022; Zheng et al., 2020).

In addition, this study revealed a unique phenomenon: the metals Mn, As, and Zr, that demonstrated interaction effects, also exhibited nonlinear dose-response relationships with the study outcomes. Research by Belzak and Bauer (2019) suggests that what appears to be interaction effects may actually be disguised nonlinear effects. In this study, we were unable to distinguish between these two effects. The presence of this phenomenon highlights the importance of exploring the fundamental differences between interaction effects and nonlinear effects in future research. Although our current analysis does not definitively delineate the relationship between the two, we recommend that future studies employ more sophisticated statistical models or experimental designs to better separate and identify these effects. The work of Belzak et al. provides valuable insights into understanding this potential confusion, emphasizing the need to consider not only interaction effects but also the possibility of nonlinear effects during analysis.

Sensitivity analyses revealed that boys' neurodevelopment may be more susceptible to the effects of metal exposure than girls. This difference could be explained by several factors. First, sex hormone differences: estrogens play a crucial role in regulating neuronal structure and brain function, and the gender-specific toxic effects may be influenced by the protective properties of estrogens (Jedrychowski et al., 2009; Vahter et al., 2007). Second, differences in developmental timing: neurodevelopment occurs during multiple critical periods, and males and females may show different sensitivities to environmental factors during these periods. Joo et al. (2018) observed that Pb exposure has different effects on neurobehavioral development depending on sex, with males being more sensitive to prenatal exposure, while females are more affected by postnatal exposure.

There are three main strengths of the current study. First, we comprehensively applied a variety of statistical analysis methods to conduct an in-depth multidimensional exploration of the effects of prenatal metals exposure, which not only includes traditional linear relationships but also extends to more complex nonlinear patterns. Second, the study goes beyond assessing the impact of a single metal and also investigates the potential combined effects of metal mixtures, thereby more accurately simulating the multiple exposure situations that pregnant women may encounter in real life. Third, by examining the interactions between metals, this study provides a new perspective for revealing the complex mechanisms by which metal mixtures affect children's health. However, our study has some limitations: First, the study is based on a relatively small sample size, which may limit the generalizability and statistical power of the results. Specifically, in the analysis using RCS, the CI for PDI and MDI scores at extreme levels of metal exposure are consistently wider, indicating reduced precision in these estimates. Second, not all potential confounding factors, such as the dietary intake and nutritional status of pregnant women, were fully controlled. Third, the study only assessed metals exposure in serum from cord blood samples, more biomarkers were not measured, which may not accurately represent cumulative in utero and early postnatal exposure levels. Therefore, future research should focus on expanding the sample size (particularly individuals exposed to extreme levels of metal), comprehensively assessing a variety of biomarkers, delving into the interactions of genetic and environmental factors, conducting longitudinal studies to track children's long-term health outcomes, and exploring biological mechanisms and evaluating the effectiveness of potential intervention measures. Additionally, we hope to accumulate more theoretical and empirical foundations in future research to further substantiate and differentiate between interactive and nonlinear effects.

5. Conclusion

Our study indicates that the relationship between prenatal exposure to metals and neurodevelopment is complex, with specific metals, such as As and Sr, having an adverse impact on neurodevelopmental outcomes. Additionally, we observed nonlinear dose-response relationships and interactions among metal mixtures, with Mn showing the most prominent effect. Our findings further highlight the importance of effective preventive strategies to reduce prenatal exposure to metals and underscore the need for future research to explore the complex mechanisms through which metal mixtures impact children's health.

CRediT authorship contribution statement

Jia-Jia Tang: Writing – original draft, Methodology. **Philip Baker:** Writing – review & editing, Supervision. **He-Bin Chi:** Writing – original draft, Validation. **Richard Saffery:** Writing – review & editing, Supervision. **Han-Wen Zhang:** Data curation. **Feng Tang:** Validation, Methodology. **Xian-Shu Lin:** Methodology, Visualization, Writing – review & editing. **Bing-Rui Yang:** Methodology, Visualization, Writing – review & editing. **Toby Mansell:** Writing – review & editing. **Noora Kartiosuo:** Writing – review & editing. **Yin-Yin Xia:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Ting-Li Han:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Hua Zhang:** Supervision, Data curation. **Xiao-Yuan Fan:** Writing – original draft, Visualization, Software, Formal analysis, Conceptualization.

Declaration of competing interest

The authors confirm that there are no competing financial interests or personal affiliations that could be perceived as influencing the research presented in this publication.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.117860.

Data availability

Data will be made available on request.

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