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Associations between prenatal multiple metal exposure and preterm birth: Comparison of four statistical models

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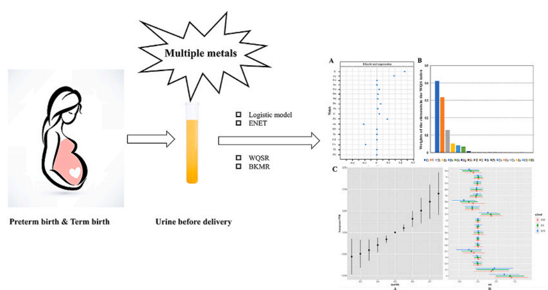
HIGHLIGHTS

- The individual and mixture effects of 18 metals on PTB were examined by several models.
- Urinary concentration of metal mixture was associated with a higher risk of PTB.
- V was identified as the most important risk factor among co-exposed metals for PTB.
- The potential interaction between Zn and Cu was identified by BKMR model.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Exposure to some heavy metals has been demonstrated to be related to the risk of preterm birth (PTB). However, the effects of multi-metal mixture are seldom assessed. Thus, we aimed to investigate the associations of maternal exposure to metal mixture with PTB, and to identify the main contributors to PTB from the mixture.
Methods: The population in the nested case-control study was from a prospective cohort enrolled in Wuhan, China between 2012 and 2014. Eighteen metals were measured in maternal urine collected before delivery. Logistic regression, elastic net regularization (ENET), weighted quantile sum regression (WQSR), and Bayesian kernel machine regression (BKMR) were used to estimate the overall effect and identify important mixture components that drive the associations with PTB.
Results: Logistic regression found naturally log-transformed concentrations of 13 metals were positively associated with PTB after adjusting for the covariates, and only V, Zn, and Cr remained the significantly positive associations when additionally adjusting for the 13 metals together. ENET identified 11 important metals for PTB, and V ($\beta = 0.23$) had the strongest association. WQSR determined the positive combined effect of metal mixture on PTB (OR: 1.44, 95%CI: 1.32, 1.57), and selected Cr and V (weighted 0.41 and 0.32, respectively) as the most weighted metals. BKMR analysis confirmed the overall mixture was positively associated with PTB, and the independent effect of V was the most significant. Besides, BKMR showed the non-linear relationships of V and Cu with PTB, and the potential interaction between Zn and Cu.

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Conclusion: Applying different statistical models, the study found that exposure to the metal mixture was associated with a higher risk of PTB, and V was identified as the most important risk factor among co-exposed metals for PTB.

1. Introduction

Preterm birth (PTB), defined as 37 weeks of completed gestation or less according to the World Health Organization (WHO) standard (1977), is a crucial global health issue. Preterm neonates suffer a greater risk of adverse outcomes, including newborn deaths, complications of prematurity, and long-term neurodevelopmental impairment (Vogel et al., 2018). China has the second greatest number of premature births (Estimated number of preterm births : 3,519,947 in 2014), which have been a severe burden for public health (Chawanpaiboon et al., 2019).

In addition to advanced maternal age, maternal obesity, multiple pregnancy, depression, and pregnancy complications, which are well-established risk factors for PTB, the impact of environmental chemicals on PTB has caused widespread concern (Ferguson et al., 2013; Ferguson and Chin, 2017; Etzel, 2020). Metals are ubiquitous chemicals in the environment, and some studies have elaborated the association of PTB with prenatal exposure to several heavy metals, including lead (Pb) (Cheng et al., 2017), cadmium (Cd) (Wang et al., 2016a), and arsenic (As) (Rahman et al., 2018), etc.

However, many studies mainly focused on the relationship between the typical toxic metals (e.g., Cd, Pb, and As) and PTB, while some epidemiologic studies suggested several trace metals (e.g., chromium (Cr) and vanadium (V)) may also increase the risk of adverse birth outcomes recently (Freire et al., 2019; Zhou et al., 2019). Moreover, the disordered homeostasis of essential metals such as copper (Cu) and zinc (Zn) can also lead to abnormal pregnancy outcomes (Wang et al., 2020). It is therefore required to study the effects of exposure to metallic elements on PTB. Furthermore, previous studies of the association between metal exposures and PTB generally considered only single-metal effect or investigated the association with each metal individually in a single-pollutant model (Hu et al., 2017; Tsuji et al., 2018; Yu et al., 2019). Since people are simultaneously exposed to multiple chemicals, the effects of combined exposures may deviate from the sum of single pollutants. The single-pollutant analysis model is prone to confounding due to the existence of co-exposure to pollutants and does not allow evaluating the potential interactions between exposures (Braun et al., 2016). Addressing the challenges in studying the health effects of mixture exposure has been a vital work recently (Dominici et al., 2010; Taylor et al., 2016). It is of particular importance to examine the potential effects of simultaneous exposure to metal mixtures on preterm delivery, which could help make public health interventions.

In China, environmental pollution has long been the main issue of public concern (Han et al., 2016; Zou et al., 2020). However, few studies have investigated the relationship between maternal multiple metal exposure and PTB. In the present study, we explored the associations of maternal exposure to 18 metal elements measured in urine samples with preterm delivery based on a nested case-control study involving 1,124 pregnant women (including 281 PTB cases and 843 matched controls) in Wuhan, China. We used several advanced statistical models, such as elastic net regression (ENET) (Zou and Hastie, 2005), weighted quantile sum regression (WQSR) (Carrico et al., 2015), and Bayesian kernel machine regression (BKMR) (Bobb et al., 2015) to explore the associations of metal exposure with PTB, to estimate the cumulative effects of metal mixture, and to identify potentially toxic metals.

2. Materials and methods

2.1. Study population

The population in this nested case-control study was from a cohort that recruited pregnant women between September 2011 and October 2014, from Wuhan Medical and Health Center. The recruitment criteria were as follows: (1) with a singleton gestation and live birth; (2) living in Wuhan; (3) willing to provide urine samples before delivery. During the period, 7,359 pregnant women were enrolled. We excluded those who kept drinking ($n = 7$) or smoking during pregnancy ($n = 2$), delivered an infant with a birth defect ($n = 57$), and lacked the complete assessment for 18 element concentrations ($n = 59$). There were 27 pregnant women with missing data on pre-BMI ($n = 24$) and education level ($n = 3$) were further excluded, leaving a total of 7,187 mother-infant pairs.

Among them, 281 PTB cases were selected. PTB was defined as a live birth before 37 weeks. Controls were those who gave neonate at term ($\geq$37 weeks). Three controls were randomly selected for every case which was matched by infant sex and maternal age (within a 1-year interval).

All participants signed a written informed consent at enrollment. Ethical approval for the study was passed by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology, and Wuhan Women and Children's Medical Care Center.

2.2. Information collection

Face-to-face interviews were conducted by well-trained interviewers with participants before or after delivery to collect basic demographic data, socioeconomic status and lifestyle factors, including maternal age, education, household income, smoking and drinking, passive smoking and dietary supplements consumption, etc. Information on pregnancy complications (gestational diabetes mellitus and hypertension disorders), parity, and date of delivery were obtained from the electronic medical records. Gestational age at birth was estimated based on the last menstrual period (LMP). The pre-pregnancy body mass index (BMI) of mothers was calculated by self-reported body weight and height before pregnancy in the first prenatal visit.

2.3. Metal measurement

Urine analysis, as the most widely used and accepted method for biological monitoring of environmental pollutants, was applied to reflect the recent metal exposure in this study (Aguilera et al., 2010; Castaño et al., 2012; Hao et al., 2015; Wang et al., 2016b). Urine samples from participants were collected before delivery, and then divided into 5mL polypropylene tubes and stored at -18 °C until further analysis.

For sample pretreatment, 1 mL of urine was equilibrated to room temperature to 15 mL polypropylene tubes together with 4 mL 3% HNO_3 for overnight nitrification, then was further digested by ultrasound at 40 °C for 1 h. Eighteen elements, including V, Cr, cobalt (Co), nickel (Ni), Cu, gallium (Ga), silver (Ag), barium (Ba), thorium (Th), uranium (U), Zn, As, rubidium (Rb), strontium (Sr), Cd, cesium (Cs), thallium (Tl), and Pb, were measured using inductively coupled plasma mass spectrometry (ICP-MS) (Agilent 7700, Agilent Technologies, Santa Clara, CA, USA). Limits of detection, intra-assay and inter-assay coefficient of variations (CVs) for all urinary metals are shown in Table S1.

The urinary creatinine concentrations were measured by the Sarcosine Oxidase Method with Mindray BS-180 CREA Kit (Shenzhen Mindray Bio-medical Electronics CO., LTD., Shenzhen, China). Urinary metal concentrations were adjusted for creatinine and used in the subsequent statistical analyses.

2.4. Statistical analyses

Metal concentrations below the limit of detection (LOD) were replaced by LOD/ $\sqrt{2}$. Distributions of creatinine-adjusted urinary metal concentrations, tested by the Kolmogorov-Smirnov normality test, were skewed. Thus, the natural logarithmic transformation of urinary creatinine-corrected metal concentrations was performed to reduce the impact of extreme values for all analyses. The correlations among the 18 ln-metal concentrations were calculated by Pearson and presented via a correlation-matrix heat map.

2.4.1. Single-pollutant model

To evaluate the association between single metal concentration and the risk of PTB, we conducted conditional logistic regression analysis with the ln-transformed, creatinine-corrected concentration of each metal as continuous variables by calculating crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) for PTB. The single-metal models were adjusted for the covariates, including pre-pregnancy BMI (<18.5, 18.5–23.9, and ≥ 24 kg/m^2), passive smoking during pregnancy (yes or no), maternal age (≤25, 25–30, ≥30 years), hypertensive disorders in pregnancy (yes or no), parity (nulliparous, multiparous), and educational level (lower than high school, high school or equivalent, college or above).

2.4.2. Mixture analysis models

Three methods, including ENET, WQSR and BKMR, were used to evaluate the associations between exposures of multiple metals and PTB.

Due to the strong correlation of metals, traditional regression models may produce inaccurate estimates and are not suitable for the analysis of exposures with strong correlations. ENET (Zou and Hastie, 2005), a combination of Lasso (Tibshirani, 1996) and Ridge (Hoerl and Kennard, 2012), can deal with high dimensional data via choosing a smaller set of the exposure variables with the most predictive performance and has higher prediction accuracy than Lasso and Ridge regression in the presence of correlated variables (Bühlmann and Geer, 2011). There are two penalty parameters (λ, α) in ENET model. λ, a non-negative value, is the shrinkage parameter to control the overall shrinkage strength. With the increase of λ, the coefficients of variables are shrunk more strongly. The parameter α between 0 and 1 can optimize ENET model by balancing the penalty between Lasso and Ridge regression. When α is towards 1, ENET is close to the Lasso, which pushes the coefficients of irrelevant variables all way to 0. Setting α close to 0 makes the ENET similar to Ridge regression, which tends to shrink the coefficients to approximately but not equal to 0. For the ENET regression, the optimal value of α and λ were selected via 10-fold cross-validation based on minimum misclassification error (Huang et al., 2019). Here, we only penalized the metal variables and incorporated the covariates (same as the single-pollutant model) into the model to adjust for potential confounders. The variables with non-zero coefficients determined by the ENET model represent the dominant metals that drive the associations with PTB.

WQSR is a useful method for risk analysis to assess the combined effects of multiple predictors with high dimensionality and inherent correlations. (Carrico et al., 2015; Czarnota et al., 2015). WQSR estimated a weighted linear index based on dividing metals into different quantiles (deciles were used here), which represented the combined effects of the overall mixture (Gennings et al., 2010). Because WQSR is limited to the correlation between the outcome and mixture in one direction (Carrico et al., 2015), we constrained the direction of the model to be positive. The corresponding weight of each metal which was determined through the use of bootstrap sampling (b = 1000) showed its contribution to WQSR index, illustrating the importance of its association with PTB.

We finally used BKMR to evaluate the joint effect of metals on PTB, capture the potential nonlinear relationships, and identify the interactions between the components of the mixture (Bobb et al., 2015). BKMR uses a Gaussian kernel function to estimate the exposure-response function flexibly, while allows for identifying the nonlinear and nonadditive relationships. BKMR can be used to analyze the association between mixture exposure and the binary outcome with a probit link function, which could quantify the relationship between the metal exposures and the risk of PTB (Bobb et al., 2018). In addition, this approach allows either component-wise or hierarchical variable selection to obtain the posterior inclusion probabilities (PIP), which can measure the importance of each exposure variable, and the variables with PIP greater than 0.5 are usually considered significant (Coker et al., 2018). Here, we implemented component-wise variable selection for eighteen metals to initially select the important variables and assess the overall effect and independent effects with 50 000 iterations of the Markov chain Monte Carlo (MCMC) sampler. Since hierarchical variable selection can improve association detection capability for highly correlated exposures, then we performed the hierarchical variable selection for the selected metals before based on their correlations to further identify the most important metals and explore the exposure-response relationships and the potential interactions (Ashrap et al., 2020).

The χ^2 test was used to analyze categorical variables, and Wilcoxon rank-sum test was used to analyze the creatinine-adjusted concentrations of urinary metals. All significance levels were set to a two-sided p value of <0.05 in this study. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., NC, USA) and R-3.6.3 (R Core Team, Austria). WQSR, ENET, and BKMR were performed with the R package “gWQS” (version 4.0.5), “glmnet” (version 4.0.2), and “bkmr” (version 0.2.0), respectively.

3. Results

3.1. Characteristics of the study population

General characteristics of the cases and controls are summarized in Table 1. There were 636 male infants and 488 female infants. The mean maternal age at delivery was 29.08 ± 4.48 years. Compared to term birth, the PTB case mothers had a lower level of education (less than high school, 32.38% vs. 26.81%). There were a higher proportion of case mothers with parity two or more (32.74% vs. 18.15%) and hypertension during pregnancy (12.81% vs. 3.91%) compared to term birth. No significant differences were found in passive smoking, pre-pregnancy body mass index, and gestational diabetes incidence.

3.2. Urinary metal concentrations

Most of the elements had detection rates above 90%, except for Ag (84.8%) and Th (79.4%). The distribution of these metals was shown in Table S2. The creatinine-adjusted concentrations of most urinary metals (except for Co, Rb, Sr, and Cs) in the case group were significantly different from these in the term birth. Pearson correlation coefficients of the ln-transformed metal concentrations were correlated from weakly to highly, ranging from 0.03 to 0.77 (Figure. S1).

3.3. Metal exposure and PTB based on the logistic model

In the multivariable logistic regression analysis, after adjusting for all the covariates, 13 metals showed positive associations with PTB in the single-metal model (Table 2). After additional adjustment for 13 metals in the multi-metal model, only V, Zn, and Cr kept the significantly positive associations, among which the OR of V for PTB was the largest [OR: 2.20, 95%CI: (1.88, 2.58) in the single-metal model and OR: 2.01, 95% CI: (1.51, 2.68) in the multi-metal model]. Conversely, Pb showed a significantly negative association with PTB in the multi-metal model [OR: 0.63, 95% CI: (0.48, 0.83)].

Table 1
Basic characteristics of preterm birth cases and controls [n (%)].

Characteristics	PTB case	Term birth	*p*-Value
N	281	843	
Matched parameters			
Maternal age (years)			
≤25	62 (22.06)	186 (22.06)	
25–30	101 (35.94)	303 (35.94)	
≥30	118 (41.99)	354 (41.99)	
Infant gender			
Male	159 (56.58)	477 (56.58)	
Female	122 (43.42)	366 (43.42)	
Demographic and delivery parameters			
Pre-pregnancy BMI (kg/m^2)			0.76
Underweight (<18.5)	59 (21.00)	195 (23.13)	
Normal (18.5–23.9)	185 (65.84)	538 (63.82)	
Overweight (≥24)	37 (13.17)	110 (13.05)	
Parity			<0.001
Primiparous	189 (67.26)	690 (81.85)	
Multiparous	92 (32.74)	153 (18.15)	
Education levels			<0.001
Lower than high school	91 (32.38)	124 (26.81)	
High school	50 (17.79)	172 (20.40)	
Collage or higher	140 (49.82)	547 (64.89)	
Passive smoking during pregnancy			0.81
No	213 (75.8)	633 (75.09)	
Yes	68 (24.2)	210 (24.91)	
Folic acid supplementation during pregnancy			0.98
No	44 (15.7)	133 (15.78)	
Yes	237 (84.3)	710 (84.22)	
Gestational diabetes			0.27
No	249 (88.61)	766 (90.87)	
Yes	32 (11.39)	77 (9.13)	
Hypertension during pregnancy			<0.001
No	245 (87.19)	810 (96.09)	
Yes	36 (12.81)	33 (3.91)	

Abbreviation: BMI, body mass index; PTB, preterm birth.
* *p*-Values were tested by χ^2 test.

Table 2
The association between metal concentrations and the risk of preterm birth.

Metal concentration (Ln-μg/g creatine)	OR (95%CI)		
	Crude model[a]	Single metal model[b]	Muti-metal model[c]
V	2.14 (1.85, 2.48)	**2.20 (1.88, 2.58)**	**2.01 (1.51, 2.68)**
Cr	1.79 (1.59, 2.01)	**1.89 (1.65, 2.15)**	**1.36 (1.09, 1.70)**
Co	1.20 (1.00, 1.44)	1.08 (0.89, 1.32)	/
Ni	1.21 (1.09, 1.35)	**1.18 (1.05, 1.32)**	1.01 (0.89, 1.14)
Cu	1.55 (1.32, 1.82)	**1.40 (1.18, 1.65)**	1.09 (0.906, 1.31)
Ga	1.17 (1.10, 1.25)	**1.19 (1.12, 1.28)**	0.97 (0.86, 1.10)
Ag	1.21 (1.12, 1.31)	**1.25 (1.14, 1.36)**	1.09 (0.92, 1.30)
Ba	1.26 (1.16, 1.36)	**1.29 (1.19, 1.40)**	1.10 (0.98, 1.25)
Th	1.17 (1.08, 1.27)	**1.20 (1.10, 1.31)**	1.00 (0.87, 1.15)
U	1.46 (1.29, 1.64)	**1.54 (1.35, 1.76)**	0.83 (0.67, 1.02)
Zn	1.80 (1.50, 2.16)	**1.84 (1.51, 2.24)**	**1.37 (1.00, 1.89)**
As	0.83 (0.68, 1.02)	0.83 (0.67, 1.03)	/
Rb	1.11 (0.89, 1.38)	1.21 (0.96, 1.53)	/
Sr	1.12 (0.95, 1.32)	1.08 (0.91, 1.30)	/
Cd	1.58 (1.32, 1.89)	**1.39 (1.15, 1.67)**	0.85 (0.64, 1.12)
Cs	0.85 (0.66, 1.10)	0.95 (0.73, 1.23)	/
Tl	1.36 (1.12, 1.64)	**1.37 (1.12, 1.69)**	0.84 (0.66, 1.06)
Pb	1.25 (1.06, 1.49)	**1.26 (1.05, 1.50)**	**0.63 (0.48, 0.83)**

[a] Crude model was expressed by crude odds ratio (95% confidence interval).
[b] Single metal model was adjusted for pre-pregnancy BMI, passive smoking during pregnancy, maternal age, hypertensive disorders, parity, and educational level.
[c] Multi-metal model included thirteen urinary metals into analysis and was adjusted for pre-pregnancy BMI, passive smoking during pregnancy, maternal age, hypertensive disorders, parity, and educational level.

3.4. Multi-metal exposures and PTB

3.4.1. Elastic net regression

In the ENET model, λ and α were determined as 0.12 and 0.1, respectively, obtained from 10-fold cross-validation. As shown in Fig. 1, the ENET model produced non-zero coefficients ($\beta \neq 0$) for 11 metals after adjusting for confounders. Nine metals (V, Cr, Zn, Ba, Cu, U, Ga, Ag, and Th) were positively associated with PTB ($\beta > 0$), and V exhibited the largest magnitude β coefficient ($\beta = 0.23$), which represented the change in log-odds of PTB per increment in standardized ln-transformed metal concentrations.

3.4.2. WQSR

As shown in Fig. 2, the positive WQSR index was significantly associated with PTB (p-value < 0.001). A decile increase in the WQSR index resulted in 1.44 (95% CI: 1.32, 1.57) for the OR of PTB. The highest weighted metal in the index was Cr (weighted 0.41), followed by V (weighted 0.32), which indicated Cr and V were the largest contributors to the mixture effect.

3.4.3. BKMR

We first fitted the BKMR model with variable selection including 18 elements to initially identify the important mixture components, and evaluate the joint and independent effects on PTB. Table S3 shows the PIP of each metal. Eight metals, including V, Cu, Zn, Rb, As, Cr, Pb, and Cr were selected as important variables because their PIPs were higher than 0.5. Fig. 3A shows the joint effect of the metal mixture composed of 18 metals on the latent continuous binary outcome of PTB, and the results indicated that the joint effect on PTB increased as the cumulative level across all metal exposures increased. The latent continuous outcome of PTB increased by 0.45 units when all metals were at their 75th percentile compared to when they were fixed at their median value. Fig. 3B shows the independent effects of metals, and it reflects the effect change (95%CI) of PTB when a single metal was at the 75th percentile compared to its 25th percentile, when all of the remaining metals were fixed at either the 25th, 50th, or 75th percentile. Visually, Zn and V were significantly associated with increased risk of PTB when the concentrations of other metals were fixed at their 25th, 50th, and 75th percentiles.

In the secondary analysis, we implemented BKMR model with hierarchical variable selection only including the eight metals that were preliminarily selected in component-wise variable selection, to further identify the important metals and explore the potential non-linear relationships and interactions between variables. Based on Pearson correlation coefficients, we grouped Cr and V into group 1, Pb and Zn into group 2, and Cu, As, Rb, and Cd into group 3. The model estimated the group posterior inclusion probability (groupPIP) which represented the probability of including an exposure group, and conditional posterior inclusion probabilities (condPIP) which represented the probability of involving a particular metal within the group. The groupPIPs of three groups and the condPIPs for each metal were summarized in Table S3. All three groupPIPs were higher than 0.5, and V (condPIP = 1.00), Cu (condPIP = 1.00), Zn (condPIP = 0.95) were the highest ranking within

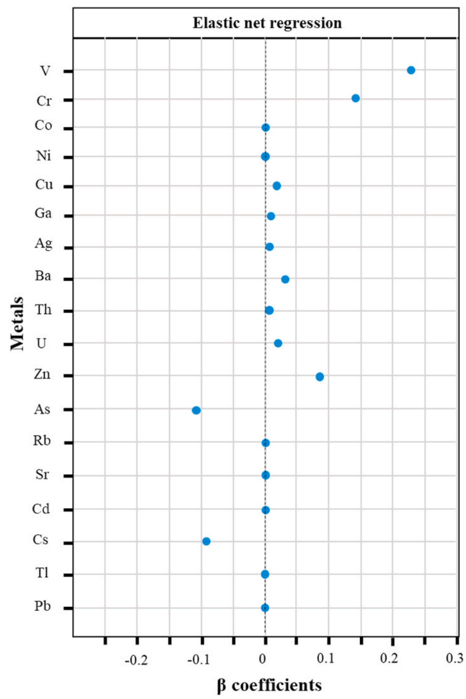


Fig. 1. Elastic net regression models (β coefficients for 18 metals) for the estimation of the association between multiple metals and preterm birth. Model was adjusted for pre-pregnancy BMI, passive smoking during pregnancy, maternal age, hypertensive disorders, parity and educational level.

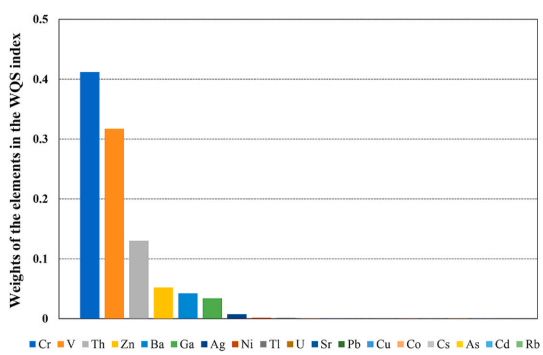


Fig. 2. Variable weights from the WQSR index. Model was adjusted for pre-pregnancy BMI, passive smoking during pregnancy, maternal age, hypertensive disorders, parity, and educational level.

the groups respectively.

To investigate potential non-linear relationships, the univariate exposure-response functions were estimated in Figure S2. As the plot shows, Zn had a positive approximately linear relationship with PTB, and V and Cu exhibited non-linear relationships (the wide confidence intervals at high concentration due to sparse data) when each of other metals was fixed at their median value. Further, the bivariate exposure-response functions for every two metals on PTB are visually displayed in Figure S3. When Cu was fixed at the 25th quantile, the slope between Zn and PTB was different from that when Cu was fixed at the 50th or 75th quantile, indicating the existence of potential interactions between Zn and Cu.

4. Discussion

In the present study, we applied conditional logistic regression, ENET regression, WQSR, and BKMR model to investigate the associations between the concentrations of 18 metals in maternal urine and PTB. All these methods found positive associations between several metals, especially V. WQSR and BKMR confirmed the positively combined effect of the metal mixture on PTB. Additionally, BKMR depicted the non-linear dose-response relationships of Cu and V with PTB and implied the potential interactions between Zn and Cu. These methods addressed different aspects of questions in mixture exposure study and had their own pros and cons.

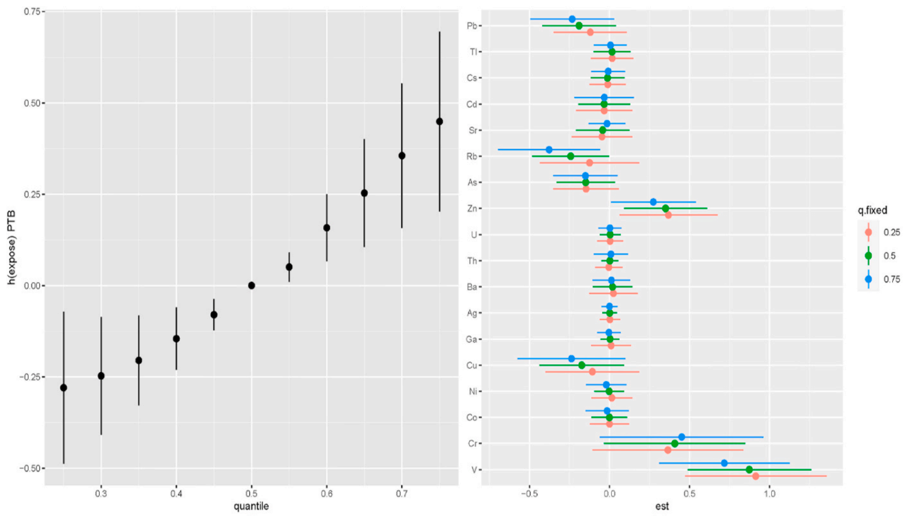
Conventional statistical approaches (such as logistic regression model) are simple and easy to explain so that they are widely used in the assessment of health effects of chemicals. However, limited to multiple comparisons, multicollinearity, and high dimensionality, they could draw misleading conclusions. The logistic model found 13 metals (V, Cr, Ni, Cu, Ga, Ag, Ba, Th, U, Zn, Cd, Tl, and Pb) were positively associated with PTB. V, Zn, and Cr still had significant positive associations with PTB after adjusting for 13 metals, whereas Pb showed a negative association. Several metals were moderately to highly correlated, thus including these metals in one logistic regression model could cause fallacious coefficient estimates and unreasonable interpretations due to producing unstable *p*-values for predictors and biased standard errors (Weisskopf Marc et al.; Sun et al., 2013; Vatcheva et al., 2016). In the multi-metal model, some metals were correlated to Pb, such as V (correlation coefficient of V and Pb: $r_s = 0.47$) and Zn (correlation coefficient of Zn and Pb: $r_s = 0.57$). Hence, the significantly negative association between Pb and PTB obtained from the multi-metal logistic model should be treated with caution. Additionally, the significant association between Pb and PTB was not captured by ENET and BKMR. The results indicated the challenges for conventional statistic models on studying the effects of chemical mixtures and highlighted the necessity of using diverse statistic approaches to explain the results together.

ENET can choose the variables with the best predictive performance and allow for the inclusion of collinear predictors in the final model. ENET identified 9 metals (V, Cr, Zn, Ba, Cu, U, Ga, Ag, and Th) were positively associated with PTB, and V had the strongest association. However, the selected variables are the most statistically relevant rather than biologically meaningful for the outcome and there are no *p*-values for coefficients.

WQSR can quantify the joint effect of the mixture and identify the important contributors to the effect, but it could lose exposure information owing to the use of quantiles and could not provide beta coefficients for individual variables. By using WQSR model, we found a positive combined effect of the metal mixture on PTB [OR: 1.44, 95% CI: (1.32, 1.57)], and selected Cr and V as the most weighted chemicals. Besides, confined to the premise of linear association in the same direction, WQSR may not accurately identify the vital variables with a non-linear relationship.

BKMR is a useful method to estimate non-linear exposure-response surface, potential interactions, single-exposure effect, and overall mixture effect. In the present study, BKMR model identified the overall mixture effect was positively associated with PTB, which confirmed the findings found in WQSR. With the hierarchical variable selection, BKMR further selected V, Zn, and Cu as the most important metals. Besides, BKMR identified the non-linear dose-response relationships of Cu and V with PTB, and found the potential interactions between Zn and Cu, which were unavailable from other models. However, as a nonparametric method, it is unable to quantify effects, and the Markov chain Monte Carlo (MCMC) method for Bayesian inference makes BKMR computationally expensive and costs more time compared with other methods. Thus, diverse methods are needed to assess the health effects of a chemical mixture.

This present study identified V as the most important risk factor among the metal mixtures for PTB, which confirmed our previous finding that V was associated with an increased risk of PTB based on the large cohort (Hu et al., 2017). Recently, V exposure prenatally was also found to be associated with other adverse birth outcomes (e.g., spontaneous abortion and worse fetal growth) in other population studies



A B

Fig. 3. (A) Overall effect of metal mixture on preterm birth (estimates and 95%CI). The plot depicted the estimated change in a latent continuous outcome (continuous marker of the binary preterm birth) when all the metals at fixed percentiles were compared to all the metals at their 50th percentile. h(expose) can be regarded as a latent continuous marker of preterm birth. (B) Independent effect of metals on preterm birth. Estimates and 95% CI for the association of preterm birth with single metal at the 75th vs. 25th percentile when all the other metals were fixed at either the 25th, 50th, or 75th percentile.

(Zhou et al., 2019; Wang et al., 2020; Li et al., 2021). As a transition metal in nature, V has been discharged into the environment considerably by human activities, such as burning of fossil fuel, mining, and industrial activities, which has become an emerging environmental concern (Imtiaz et al., 2015). V in daily diet and atmosphere are the main sources of V exposure for the general population (Moreno et al., 2010). Some foods such as fish, grains, parsley, and mushrooms contain a higher level of V (Mukherjee et al., 2004). V loaded in $PM_{2.5}$ (Rojas-Lemus et al., 2021) might cause its additional exposure for the women in our study. A recent study showed the median $PM_{2.5}$-bound V concentration for 24-h personal exposure was 2.30 ng/m^3 in Wuhan, China (Wang et al., 2021), which was higher than that in Montreal, Canada (median: 1.61 ng/m^3) (Godri Pollitt et al., 2016). The pregnant women in the present study had higher urinary V concentration (median: 1.53 μg/g creatinine) than the black pregnant women from the United States (median: 0.16 μg/g creatinine) (Han et al., 2020), and the general adult population of Northern France (median: 0.33 μg/g creatinine) (Nisse et al., 2017), but lower than an adult population in Spain (median: 2.12 μg/g creatinine) (Domingo-Relloso et al., 2019a). Exposure to high level of V has been demonstrated to cause irreversible damage to the body (Liu et al., 2012; Li et al., 2013; Wilk et al., 2017). V can cross the placental barrier and then accumulate in the fetal membrane, bringing potential risks to mothers and fetus (Zhou et al., 2019). Their ability to induce oxidative stress and membrane injury (Deng et al., 2012; Zwolak, 2020), which may explain the potential mechanism of V affecting adverse birth outcomes.

Two prior studies have examined the associations between metal compounds and PTB using mixture analysis methods, but the results were inconsistent. Kim et al. (2018) used ENET regression to examine the associations between 17 urinary metal concentrations corrected by specific gravity and PTB and found Cu as the important predictor. Ashrap et al. (2020) identified blood Pb and Zn as critical metals that might adversely affect PTB using ENET and BKMR models. In our study, the positive associations of Cu and Zn with PTB were also captured by logistic regression, ENET, and BKMR. Additionally, BKMR model also implied the potential interactions between Zn and Cu. The urinary Cu (median = 18.8 μg/g creatinine) observe in this study was higher than that of 20–39 years women involved in the Canadian Health Measures Survey (median = 10.72 μg/g creatinine) (Canada, 2010), the pregnant women from Australia (median = 10.4 μg/g creatinine, two weeks before delivery) (Callan et al., 2013), and Spain (median = 15 μg/g creatinine at the third trimester) (Fort et al., 2014). The pregnant women in our study also had higher urinary Zn concentrations (median = 542 μg/g creatinine) compared to the concentrations reported in the studies from Canada (median = 229.69 μg/g creatinine, 20–39 years healthy women) (Canada, 2010), Australia (median = 396 μg/g creatinine, two weeks before delivery) (Callan et al., 2013), and Spain (median = 290 μg/g creatinine, the third trimester) (Fort et al., 2014). Cu and Zn are essential elements for biological processes in the human body, and deficiency of Cu and Zn is associated with adverse birth outcomes (Grzeszczak et al., 2020). However, excessive Cu and Zn can produce reactive oxygen species (ROS) and involve in oxidative stress (Lee, 2018; Sebio et al., 2019). Previous studies suggested that increasing urinary Cu or Zn levels were associated with higher oxidative stress biomarkers (Domingo-Relloso et al., 2019b; Kim et al., 2019), which might represent an important etiology for PTB. The higher concentrations of Cu and Zn in serum were reported to be related to a higher risk of PTB in a case-control study from Malawi (Chiudzu et al., 2020). A nested case-control study in Shanxi, China also found that higher maternal serum Cu level in the first trimester was associated with an increased risk of spontaneous preterm birth (Hao et al., 2019).

There were several strengths of our study. First, multiple metal exposure was assessed in a large population of pregnant women, thereby reducing the influence of confounding metals. Second, different mixture modeling methods were used to explore the metal mixtures in relation to PTB, which may help to address different research questions and make the conclusion more reliable. Third, the cases and controls from the cohort which excluded those with smoking history and drinking during pregnancy, were matched with potentially important factors (infant gender and maternal age). The detailed information on demographic and socioeconomic characteristics, reproductive and medical histories was collected to adjust for the potential confounders.

Nevertheless, there were also some limitations in the study. Many metals involved in the present study have relatively short half-lives in urine, which could be regarded as reliable biomarkers of recent exposure (Domingo-Relloso et al., 2019b; Lozano et al., 2022). However, a previous study on variability of 7 metals in urine samples in healthy adult Chinese men showed that urinary As, Cd, and Co concentrations corrected by creatinine were fairly stable (ICCs = 0.41, 0.64, and 0.41, respectively) in five sampling days, while Cu, Pb, and Ni were observed with relatively poor reproducibility (ICCs = 0.01–0.18) (Wang et al., 2016b). Thus, future studies should consider multiple repeated urine sample measurements, which can improve exposure assessment and reduce exposure misclassification. Additionally, the concentration of each metal measured in this study is the total concentration rather than their individual forms. Different forms of Cr and As have different toxic effects, thus future studies are needed to assess the exposure to individual forms of metals. Moreover, although detailed data on potential confounding factors were collected, there could be still some potential confounding due to unmeasured factors, such as maternal dietary information.

5. Conclusions

Our study suggested the importance of applying different methods to assess the health effects of mixture exposure. The results consistently revealed that there was a significantly positive joint effect of metal mixture on PTB and V might be the most important toxic agent. Our findings may help to develop more targeted public health interventions to reduce the incidence of PTB. The mechanism of V leading to PTB needs further research to confirm our findings.

Competing financial interests

The authors have no competing financial interests to declare.

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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 data

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