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Inverse association between maternal serum concentrations of trace elements and risk of spontaneous preterm birth: a nested case–control study in China

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Abstract

Few studies have evaluated the joint effect of trace elements on spontaneous preterm birth (SPTB). This study aimed to examine the relationships between the individual or mixed maternal serum concentrations of Fe, Cu, Zn, se, Sr and Mo during pregnancy, and risk of SPTB. Inductively coupled plasma MS was employed to determine maternal serum concentrations of the six trace elements in 192 cases with SPTB and 282 controls with full-term delivery. Multivariate logistic regression, weighted quantile sum regression (WQSR) and Bayesian kernel machine regression (BKMR) were used to evaluate the individual and joint effects of trace elements on SPTB. The median concentrations of Sr and Mo were significantly higher in controls than in SPTB group ($P < 0{\cdot}05$). In multivariate logistic regression analysis, compared with the lowest quartile levels of individual trace elements, the third- and fourth-quartile Sr or Mo concentrations were significantly associated with reduced risk of SPTB with adjusted OR (aOR) of 0·432 (95 CI < 0·05). In multivariate logistic regression analysis, compared with the lowest quartile levels of individual trace elements, the third- and fourth-quartile Sr or Mo concentrations were significantly associated with reduced risk of SPTB with adjusted aOR of 0·432 (95 % CI 0·247, 0·756), 0·386 (95 % CI 0·213, 0·701), 0·512 (95 % CI 0·297, 0·883) and 0·559 (95 % CI 0·321, 0·972), respectively. WQSR revealed the inverse combined effect of the trace elements mixture on SPTB (aOR = 0·368, 95 % CI 0·228, 0·593). BKMR analysis confirmed the overall mixture of the trace elements was inversely associated with the risk of SPTB, and the independent effect of Sr and Mo was significant. Our findings suggest that the risk of SPTB decreased with concentrations of the six trace elements, with Sr and Mo being the major contributors.

Keywords: **Trace elements: Spontaneous preterm birth: Weighted quantile sum regression: Bayesian kernel machine regression: Joint effect**

Preterm birth (PTB), defined by WHO as birth before 37 weeks' gestation, is one of the common adverse pregnancy outcomes[1,2]. Approximately 10·6 % of neonates worldwide are born prematurely in 2014, equating to an estimated 14·84 million live PTB[3]. In china, the overall PTB rate increased from 5·9 % in 2012 to 6·4 % in 2018[4], and the annual number of premature infants has reached 1·17 million, ranking second among all countries[3]. The majority of PTB cases in China are attributable to spontaneous preterm birth (SPTB), including preterm premature rupture of membranes and spontaneous preterm labour with intact membranes[5,6]. Complications of PTB are the leading cause of neonatal deaths and the largest direct cause of deaths of children younger than 5 years[5,7]. In addition, the treatment of premature infants is still challenging, and a large number of medical resources need to be invested, which not only brings heavy economical and psychological pressure to families but also causes a huge burden for public health of the country[3].

Many maternal and fetal characteristics have been reported to be associated with the risk of PTB, including pregnancy

Abbreviations: aOR, adjusted OR; BKMR, Bayesian kernel machine regression; ICP-MS, inductively coupled plasma MS; PTB, preterm birth; SPTB, spontaneous preterm birth; WQSR, weighted quantile sum regression.

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spacing, multiple pregnancy, maternal chronic diseases, infection, lifestyle, undernutrition, maternal psychological health and genetic factors[8,9]. In addition, exposures to environmental chemicals, including organic pollutants, metals and metalloids, as well as air pollutants, have the potential to increase the risk of PTB through multiple pathways[10,11]. However, we have an incomplete understanding of the factors that lead to PTB currently. Moreover, the research focusing on SPTB has been complicated by aetiological, pathophysiological and genetic heterogeneities[12].

It is known that essential trace elements (ETE), such as Fe, Cu, Zn, se, Sr and Mo, are crucial for the fundamental metabolic processes, maintenance of cell proliferation and function, and play critical role in supporting successful pregnancy[13–16]. Some studies have reported significant associations between the deficiency of trace elements and increased risk of PTB, or in other words, associations between the supplement of trace elements and decreased risk of PTB, including Fe[17–21], Cu[22], Zn[21,23,24], se[25–28] and Sr[24]. However, some studies have revealed that the intake of trace elements were significantly associated with increased risk of PTB, including Fe[29–31], Cu[31–35] and Zn[35–37]. In addition, other others have found no association between the levels of these elements and PTB, including Fe[24,33,38], Cu[24,37,38], Zn[31–33,39], se[21,31–33,37,38,40], Sr[31,35,38] and Mo[24,31,32,38]. Thus far, previous studies examining the association between prenatal exposure to essential trace minerals and PTB have yielded inconsistent results, and most of them have focused on overall PTB. Several studies have classified PTB and analysed SPTB separately, but the sample size is relatively small[20,21,31–33,37].

In the real-world environment, humans are exposed simultaneously to multiple ETE, which, upon acting together, may have additive, synergistic, antagonistic and/or potentiating effects on health[41]. Therefore, mixture exposure models are imperative to evaluate the overall effects and interactions of multiple ETE on SPTB. However, most of previous studies on the association between trace elements and SPTB have used traditional statistical methods that examined one element at a time, and only few studies have evaluated the joint effects of multi-element mixtures on risk of SPTB[21,36].Weighted quantile sum regression (WQSR) is a statistical model for multivariate regression in high-dimensional datasets by constructing a weighted index estimating the mixed effect of all predictor variables on an outcome[42,43]. In addition, Bayesian kernel machine regression (BKMR) is a hierarchical variable selection approach to estimate the health effects of complex mixtures using a kernel function[44,45].

In this study, we measured the concentrations of ETE in maternal serum samples during the second trimester of pregnancy and aimed to examine the individual and joint associations between prenatal exposure to six ETE, including Fe, Cu, Zn, se, Mo, Sr, and the risk of SPTB.

Methods

Study population and epidemiological data collection

This nested case–control study was part of a multi-centre birth cohort that recruited pregnant women between August 2018 and December 2021. Pregnant women in this study were recruited from Maternal and Child Healthcare Hospital of Guangxi, Zhuang Autonomous Region, and Fujian Provincial Maternal and Child Healthcare Hospital. The recruitment criteria were as follows: (1) attending their first antenatal appointment between 6 and 14^{+6} weeks of gestation and (2) planning to establish their health record and deliver in the same hospitals. The exclusion criteria included: (1) having mental health diseases and could not cooperate with questionnaire investigation and (2) pregnancies resulting in two or multiple births.

During pregnancy, each participant completed three times of self-administered questionnaires under face-to-face instruction from a trained investigator three times, once in the first trimester, once in the second trimester and once in the third trimester.

Maternal venous blood samples (4 ml) were collected in the first and second trimester ($22–26^{+6}$w), respectively. After standing for 30 min, serum samples were obtained by centrifuging and stored in the − 80°C refrigerator until analysis. Gestational age was calculated based on reported last menstrual period and confirmed with ultrasound dating. If there was a discrepancy between the two, ultrasound dating was used for final determination of gestational age. A total of 212 cases with SPTB were selected. SPTB was defined as a live birth at < 37 weeks gestational age without iatrogenic causes, including spontaneous preterm labour with intact membranes and preterm premature rupture of membranes referring the previous study[5]. Among them, twenty cases without maternal blood samples of second trimester were excluded. Two hundred and eighty-two women with full-term delivery (≥ 37 weeks) and maternal blood samples of second trimester were randomly selected. Ultimately, a total of 192 cases with SPTB and 282 controls were included in our nested case–control study.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Ethics Committee of Sichuan University (no. K2017045), Maternal and Child Healthcare Hospital of Guangxi, Zhuang Autonomous Region (no. 20174-2), and Fujian Provincial Maternal and Child Healthcare Hospital (no. 2017KR-030). Written informed consent was obtained from all subjects.

Measurement of serum essential trace elements

Maternal serum samples in the second trimester were provided for inductively coupled plasma MS (ICP-MS), using the Agilent 7500cx ICP/MS system (Agilent Techologies, Wilmington, DE) equipped with a G3160B I-AS integrated autosampler. The quantitative analysis of six ETE, including Fe, Cu, Zn, se, Mo and Sr, was performed at the West China School of Public Health in Sichuan University. Specifically, 250 µl of maternal serum sample was added with 1 ml of nitric acid and digested on microwave digestion apparatus. After digestion, the remaining nitric acid was removed at 80°C. The digestion tank was washed several times with ultrapure water and transferred to a graduated tube to a constant volume of 5 ml, and a digestion blank was made at the same time. The above samples were injected into the ICP-MS instrument for determination and quantified by internal standard curve method, which ^{72}Ge serves as the internal standard for

^{96}Mo, ^{64}Cu, ^{66}Zn, ^{78}Se, ^{88}Sr and ^{45}Sc as the internal standard for ^{56}Fe. The conditions for ICP-MS instrument were as follows: radio frequency (RF) power 1550 W, carrier gas flow rate 1·05 l/min, sampling depth 8·0 mm, atomiser pump speed 0·10 rps, atomisation chamber temperature 2°C, extraction lens 200·0 V, the fourth stage rod deflection voltage 3·0 V, the eighth stage rod RF power 150 V and energy discrimination 5·0 V. All elements were measured using He collision mode, with He air velocity 1·0 l/min.

The ICP-MS analytical method was verified in the laboratory, including detection limits, precision and accuracy. The limit of detection (LOD) and the limit of quantification (LOQ) were determined by three and ten times the standard deviation of the mixed serum measurement values (online Supplementary Table S1). Intra-day and inter-day precisions of 1·08–5·68 % and 2·33–8·79 % were determined by analysing eight replicate samples within the same day and over three separate days. Recoveries of 82·2–121·5 % were calculated by detecting five replicate samples per concentration spiked at three levels of LOQ, 2 LOQ and 5 LOQ. ClinChek R-Control serum control for trace elements, level I (Recipe, German) was analysed by ICP-MS method, and the measured value is within the quality control range (online Supplementary Table S2). On the basis of recommendations in IUPAC: Harmonised Guidelines for Internal Quality Control in Analytical Chemistry Laboratories, a spiked sample, a serum control and a procedural blank as quality control materials were inserted for determination at an approximate frequency of one per ten test materials, and repeat measurement for random materials was done every no more than five test materials.

Statistical analyses

The composition ratio of baseline characteristics between case and control groups was compared by χ^2 test. These characteristics included maternal age (at the time of the last menstrual period, ≤ 24, 24–34, ≥ 35 years), maternal ethnicity (Han, others), maternal education level (primary or lower, junior high, high school, college or higher), maternal gravidity (none, once or more), maternal pre-pregnancy BMI before known pregnancy (BMI = weight/(height × height) (kg/m^2) (≤ 18·5, 18·5–24·9, ≥ 25 years), medication use (whether took the medication after pregnancy, yes or no), parental smoking or environmental tobacco smoke exposure (whether one/both of the parents smoked or was exposed to environmental tobacco smoke during the 3 months prior to the first trimester, yes or no), maternal alcohol consumption (whether drunk during the 3 months prior to the first trimester, yes or no), maternal folic acid supplement (whether supplemented with folic acid after pregnancy, yes or no) and infant sex (male of female).

Normality of parameters was assessed by Shapiro–Wilk test. As the distributions of Fe, Cu, Zn, se, Mo and Sr concentrations did not meet the normality assumption, they were described as median (interquartile range) and compared with Mann–Whitney *U* test.

We performed natural $\log_{10}$ transformation to account for chemicals' right-skewed distributions and to ensure positive minimum values in following analyses. Pearson's correlation was used to identify the correlation between concentrations of every two trace elements in maternal serum sample. The concentrations of the trace elements were further divided into four categories according to the quartile which they fell into. The multivariate logistic regressions were used to estimate the OR, adjusted OR (aOR) and 95 % CI for the associations of the levels of single ETE with SPTB comparing each quartile to the lowest quartile.

WQSR was used to evaluate the combined effects of ETE on SPTB. This approach takes into account all measured trace elements and assumes that all trace elements in the model have the same direction of action in relation to SPTB. The concentrations of each trace element were transformed into ordinal variables (quartiles), and a weighting index representing trace elements was calculated by the WQSR model, and the corresponding weights of each trace element represented the degree of contribution of specific trace elements to the WQSR index. In this study, the coefficient of WQSR index was set as negative constraint coefficient to determine whether there was a correlation in this direction

In addition, BKMR was also employed to investigate the association between mixed exposure to the six trace elements and SPTB risk. In the present analyses, a Gaussian kernel was applied, and 10 000 iterations were ran in the model. Component-wise variable selection for trace elements was implemented to obtain the posterior inclusion probabilities and measure the importance of each exposure variable. The joint effect of the mixture exposure was displayed by evaluating the expected change in SPTB risk, when all six elements were in certain percentiles (i.e. from 20th to 80th percentile, with an interval of 10 percentile) compared with the SPTB risk when all six elements were in their 50th percentile). The risk for SPTB for a change in a concentration of trace element from 25th to 75th percentiles was also plotted for each trace element when the remaining five were fixed at their 25th, 50th or 75th percentile. The exposure–response function for one trace element was presented by holding all other five trace element at their medians. The bivariate exposure–response function for one trace element when the second element was at its 10th, 50th or 90th percentile was showed by remaining four elements at their medians.

All of the statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 22.0 software (SPSS Inc., IBM) and R-4.1.0 (R Core Team). WQSR and BKMR were performed with the R package 'gWQS' (version 4.0.5) and 'bkmr' (version 0.2.0), respectively. Two-tailed values of $P < 0·05$ and 95 % CI excluding 1·00 were considered to be statistically significant.

Results

Descriptive characteristics of the study participants

According to the inclusion and exclusion criteria, 474 pregnant women were available for the analysis, including 282 normal controls and 192 SPTB. The baseline characteristics of the participants are presented in Table 1. The differences between the control group and SPTB group were statistically significant for maternal ethnicity, parental smoking or environmental

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Table 1. Characteristics of women who had SPTB (cases) and those who had normal delivery at ≥ 37 gestational weeks (controls) in this study

Variable/characteristic	Controls (*n* 282) No.	%	SPTB (*n* 192) No.	%	χ^2	*P*
Maternal age (years)					0·564	0·754
≤ 24	25	8·87	15	7·81		
25–34	204	72·34	136	70·83		
≥ 35	53	18·79	41	21·35		
Maternal ethnicity					5·008	0·025
Han	170	60·28	135	70·31		
Others	112	39·72	57	29·69		
Maternal education level					0·554	0·907
Primary or lower	2	0·71	1	0·52		
Junior high	16	5·67	12	6·25		
High school	46	16·31	27	14·06		
College or higher	218	77·30	152	79·17		
Gravidity					0·125	0·724
None	110	39·01	78	40·63		
Once or more	172	60·99	114	59·37		
Pre-pregnancy BMI (kg/m^2)					4·575	0·101
≤ 18·5	47	16·67	35	18·23		
18·5–24	208	73·76	127	66·15		
≥ 24	27	9·57	30	15·63		
Maternal medication use*					2·748	0·097
Yes	81	28·72	69	35·94		
No	201	71·28	123	64·06		
Parental smoking or ETS exposure*					15·672	< 0·001
Yes	82	29·08	26	13·54		
No	200	70·92	166	86·46		
Maternal alcohol consumption*					5·696	0·017
Yes	68	24·11	29	15·10		
No	214	75·89	163	84·90		
Folic acid supplements*					0·366	0·545
Yes	209	74·11	147	76·56		
No	73	25·89	45	23·44		
Infant sex					3·069	0·080
Male	137	48·58	109	56·77		
Female	145	51·42	83	43·23		

SPTB, spontaneous preterm birth; ETS, environmental tobacco smoke.
* The exposure was defined from the 3 months before pregnancy to the first trimester.

tobacco smoke exposure and maternal alcohol consumption. The other variables, including maternal age, maternal education level, gravidity, pre-pregnancy BMI, maternal medication use, folic acid supplements and infant sex did not show statistical differences between the two groups.

Levels of trace elements in maternal serum

The LOD, detection rate and distributions of trace elements in maternal serum samples are presented in Table 2. The LOD for Fe, Cu, Zn, se, Sr and Mo was 12·20 ng/ml, 4·96 ng/ml, 15·90 ng/ml, 9·88 ng/ml, 0·72 ng/ml and 0·42 ng/ml, respectively. The concentrations of Fe, Cu, Zn, se and Sr were all higher than the LOD, with a detection rate of 100 %, while Mo had a detection rates of 91·35 %. The levels of Sr (26·34 and 29·18 ng/ml in cases and controls) and Mo (0·84 and 0·96 ng/ml in cases and controls) in case maternal serum samples were significantly lower than those in the controls ($P = 0·008$ for Sr and $P = 0·014$ for Mo), but no significant differences were found for Fe, Cu, Zn and se ($P > 0·05$).

The correlation matrix for the concentrations of trace elements is shown in online Supplementary Fig. S1. Fe and Cu were found to be mildly and positively correlated with each other with rho values 0·36. No correlations were observed between the other trace elements.

Association between the concentration of single-trace element and the risk of spontaneous preterm birth

The relationships between the concentrations of single-trace element and the risk of SPTB are summarised in Table 3. Compared with the first-quartile $\log_{10}$-transformed Sr concentration, the third- and fourth-quartile concentrations were associated with decreased risks of SPTB, the aOR were 0·432 (95 % CI 0·247, 0·756) and 0·386 (95 % CI 0·213, 0·701), respectively. In addition, when the first-quartile $\log_{10}$-transformed Mo concentration was used as the reference, 0·512-fold (95 % CI 0·297, 0·883) and 0·559-fold (95 % CI 0·321, 0·972) decreased risks of SPTB were observed for the third and fourth concentration quartiles, respectively. No statistically significant association were found between concentrations of Fe, Cu, Zn and se, and risk of SPTB.

Effect of multi-trace elements on the risk of spontaneous preterm birth: weighted quantile sum regression

The relationship between WQSR index and SPTB and the weights of each trace element are shown in Fig. 1. After adjusting for all covariates, the WQSR model showed that the negative WQSR index was significantly associated with SPTB (*P*-value < 0·001. An interquartile increase in the WQSR index resulted in 0·368 (95 % CI 0·228, 0·593) for the aOR of SPTB. The highest weighted element in the index was Sr (weighted 0·420), followed by Mo (weighted 0·324), which indicated that Sr and Mo were the largest contributors to the mixture effect.

Effect of multi-trace elements on the risk of spontaneous preterm birth: Bayesian kernel machine regression

The posterior inclusion probability of each metal is shown in online Supplementary Table S3. Sr and Mo were selected as important variables because their posterior inclusion probabilities were higher than 0·9. Figure 2(a) showed the joint effect of multi-trace elements on the risk of SPTB, and the results indicated that when the median concentration (50th percentile) of all elements was used as the reference, a significant negative association of the mixtures of the trace elements with the risk of SPTB was evident if the concentration of the mixtures was fixed at different percentiles. Figure 2(b) showed the single-exposure effect of individual trace element on SPTB, and reflected that between the 25th and 75th percentile values, an increasing concentrations of Sr or Mo were associated with decreased SPTB risk when the concentrations of the other trace elements were fixed at their 25th, 50th, 75th percentile values, without the credible interval across zero. The univariate exposure–response functions were estimated to investigate potential non-linear relationships. As shown in Fig. 2(c), Zn exhibited positive approximately linear relationship with SPTB, and Fe, Cu, Sr and Mo displayed negative approximately linear relationships when

Table 2. The levels and distributions of trace elements in maternal serum samples of case and control groups

Elements	LOD (ng/ml)	Concentration ≥ LOD		Total participants (*n* 474)		Controls (*n* 282)		Cases (*n* 192)		
		n	%	Median	IQR	Median	IQR	Median	IQR	*P**
Fe	12·20	474	100	1301·24	1051·51–1562·64	1308·93	1056·68–1571·67	1295·39	1049·33–1554·99	0·934
Cu	4·96	474	100	1816·91	1618·61–2009·42	1823·69	1637·69–2023·12	1795·27	1590·85–1990·95	0·249
Zn	15·90	474	100	818·29	752·93–902·6	813·05	745·53–894·91	829·88	764·02–920·13	0·093
se	9·88	474	100	98·48	79·62–117·82	96·82	79·15–117·55	99·75	79·71–117·95	0·551
Sr	0·72	474	100	27·86	22·09–34·35	29·18	22·73–35·23	26·34	20·92–32·87	0·008
Mo	0·42	433	91·35	0·93	0·68–1·22	0·96	0·72–1·23	0·84	0·61–1·18	0·014

LOD, limit of detection.
* Mann–Whitney *U* test for case and control.

Table 3. Logistic regression analyses of the association between essential trace elements in maternal serum and the risk of SPTB

Elements	Concentration levels†	Cases		Controls					
		No.	%	No.	%	OR	95 % CI	aOR‡	95 % CI
Fe	First quartile	47	24·48	66	23·40	Reference		Reference	
	Second quartile	44	22·92	74	26·24	0·835	0·492, 1·416	0·866	0·498, 1·507
	Third quartile	53	27·60	62	21·99	1·200	0·711, 2·027	1·126	0·650, 1·949
	Fourth quartile	48	25·00	80	28·37	0·843	0·502, 1·414	0·856	0·496, 1·477
Cu	First quartile	54	28·13	67	23·76	Reference		Reference	
	Second quartile	45	23·44	73	25·89	0·765	0·456, 1·282	0·642	0·372, 1·108
	Third quartile	46	23·96	67	23·76	0·852	0·507, 1·431	0·778	0·449, 1·346
	Fourth quartile	47	24·48	75	26·60	0·778	0·466, 1·296	0·616	0·355, 1·068
Zn	First quartile	42	21·88	87	30·85	Reference		Reference	
	Second quartile	46	23·96	53	18·79	1·798	1·048, 3·085	1·613	0·916, 2·839
	Third quartile	53	27·60	86	30·50	1·277	0·772, 2·111	1·264	0·749, 2·131
	Fourth quartile	51	26·56	56	19·86	1·886	1·112, 3·201	1·565	0·900, 2·723
se	First quartile	46	23·96	71	25·18	Reference		Reference	
	Second quartile	41	21·35	72	25·53	0·879	0·516, 1·499	0·876	0·504, 1·523
	Third quartile	55	28·65	69	24·47	1·230	0·737, 2·055	1·108	0·650, 1·889
	Fourth quartile	50	26·04	70	24·82	1·102	0·656, 1·852	0·986	0·573, 1·696
Sr	First quartile	55	28·65	58	20·57	Reference		Reference	
	Second quartile	55	28·65	64	22·70	0·906	0·541, 1·518	0·868	0·502, 1·502
	Third quartile	45	23·44	86	30·5	0·552	0·329, 0·924	0·432	0·247, 0·756**
	Fourth quartile	37	19·27	74	26·24	0·527	0·307, 0·905	0·386	0·213, 0·701**
Mo	First quartile	58	30·21	60	21·28	Reference		Reference	
	Second quartile	51	26·56	71	25·18	0·743	0·446, 1·237	0·729	0·427, 1·246
	Third quartile	42	21·88	80	28·37	0·543	0·323, 0·913	0·512	0·297, 0·883*
	Fourth quartile	41	21·35	71	25·18	0·597	0·353, 1·012	0·559	0·321, 0·972*

SPTB, spontaneous preterm birth; ETS, environmental tobacco smoke.
Significant differences were indicated by:
* $P < 0·05$.
** $P < 0·005$.
† Data were divided by overall maternal serum quartiles log10-transformed concentrations.
‡ aOR, adjusted OR. Logistic regression was used to calculate OR and 95 % CI; all models were adjusted for maternal age (continuous), maternal ethnicity, maternal education level, gravidity, pre-pregnancy BMI (continuous), maternal medication use, parental smoking or ETS exposure, maternal alcohol consumption, folic acid supplements and infant sex.

each of other metals was fixed at their median value. The cross-sectional analysis of the exposure response plane in high dimension was performed to investigate whether there is an interaction between trace elements. As shown in Fig. 2(d), no significant interactions between each of these trace elements with others were observed.

Discussion

In this nested case–control study, we examined the associations between the concentrations of Fe, Cu, Zn, se, Sr and Mo in maternal serum and the risks for SPTB. Multivariate logistic regression analysis demonstrated that the higher concentrations of Sr and Mo were associated with the decreased risks for SPTB. WQSR and BKMR models confirmed the inverse joint effects of trace elements mixture on SPTB. In addition, Sr and Mo were the major elements that contributed to the joint effects of the multi-trace elements.

Sr is considered as potential essential elements, not only plays a scavenging role in lipid peroxidation, preventing oxidative damage[46,47], but also has effects on skeletal formation[48]. Due to its ability to cross the placental barrier, Sr affects fetal growth and development[49]. In the current study, we found that higher maternal serum concentrations of Sr were associated with decreased risk of SPTB. To our knowledge, only a few reports have analysed the association between Sr status and the risk of

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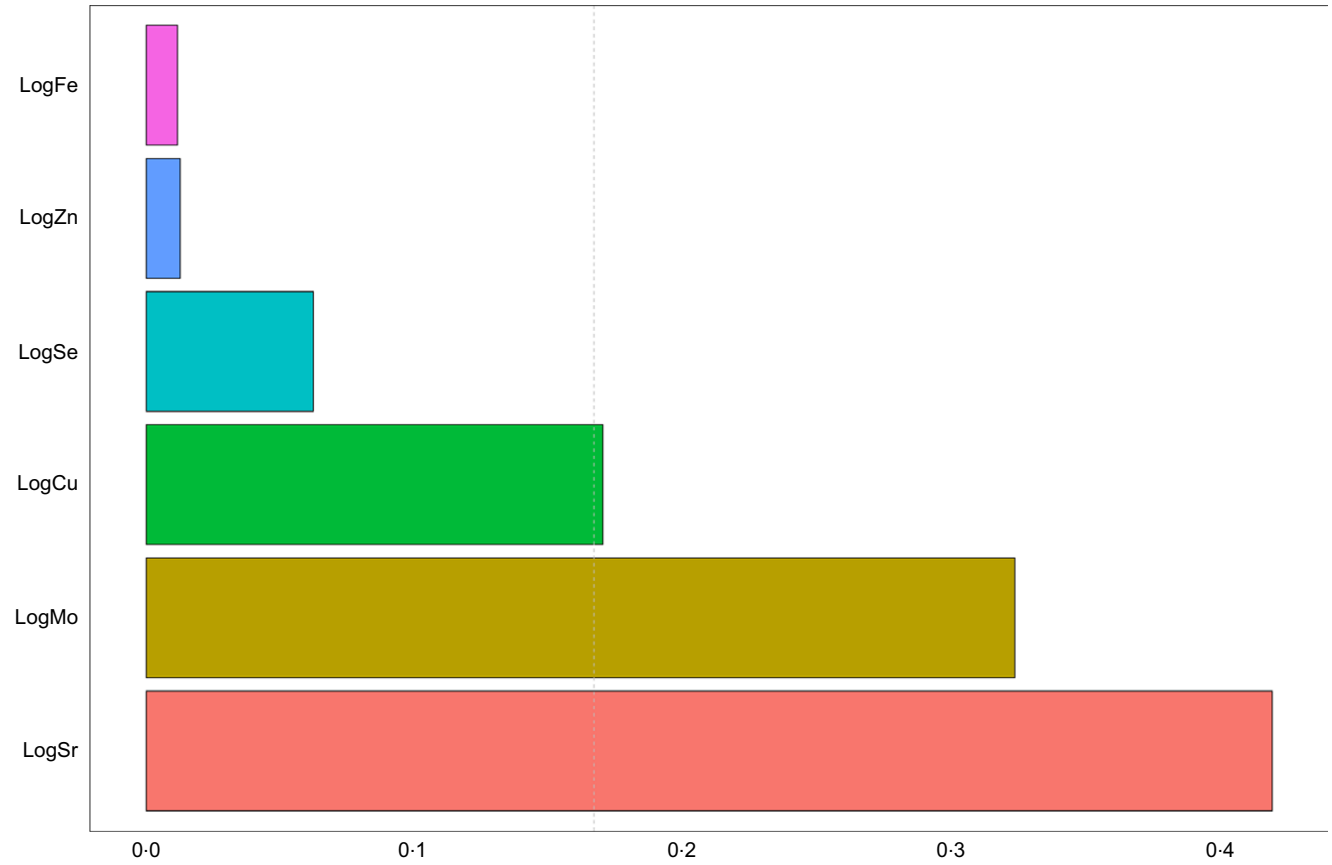

Fig. 1. Variable weights from the WQSR index. Model was adjusted for maternal age (continuous), maternal ethnicity, maternal education level, gravidity, pre-pregnancy BMI (continuous), maternal medication use, parental smoking or ETS exposure, maternal alcohol consumption, folic acid supplements and infant sex. ETS, environmental tobacco smoke; WQSR, weighted quantile sum regression.

PTB or SPTB. A nested case–control study in Wuhan, China, did not find significant association between maternal urine Sr levels before delivery and the risk of PTB[35]. In addition, a nested case–control study in Shanxi, China, also found no significant association between maternal serum Sr levels during early pregnancy and the risk of SPTB[31]. Furthermore, no statistically significant association was found between umbilical cord serum concentrations of Sr and the risk of PTB from a prospective birth cohort in rural Bangladesh[38]; however, the same research team found that higher maternal serum concentrations of Sr in the first trimester were significantly associated with PTB risk (aOR = 0·39; 95 % CI 0·20, 0·74)[24], and this protective effect of Sr on PTB was consistent with our results. Moreover, one study found that Sr deficiency in the soil, food and water might pose the risk of birth defects[50]. Another study suggested that maternal intake of alkaline earth elements (including Sr) from food might significantly prevent neural tube defects in offspring[51].

Mo, an ETE that is naturally present in many foods, is a necessary component of sulfite oxidase, xanthine oxidase, aldehyde oxidase and the mitochondrial amidoxime-reducing component in the human body, which catalyse multiple reactions in the metabolism of purines, aldehydes and sulphur-containing amino acids[52]. Mo is required by the body for various physiological processes.

During pregnancy, Mo plays an important role in supporting the development and growth of the fetus[53]. In the current study, we observed that higher maternal serum concentrations of Mo were associated with decreased risk of SPTB. So far, there have only few reports on the relationship between Mo concentrations during pregnancy and PTB or SPTB, and most studies have not found significant associations. A birth cohort study from USA showed that there were no statistically significant association between maternal urine Mo concentrations and the risk of PTB or SPTB[32]. In addition, two studies from a prospective birth cohort in rural Bangladesh also did not find significant associations between Mo levels in maternal serum or cord blood serum and the occurrence of PTB[24,38]. Furthermore, no significant associations were observed between maternal serum Mo concentrations and risk for SPTB in a nested case–control study from Shanxi, China[31]. However, a cohort study in the Tibetan Plateau suggested that Mo played a dominant role in the 'beneficial' metal(loid)s mixture in prolonging gestational age and reducing the risk of PTB. Specifically, maternal urinary Mo levels were negatively and linearly associated with PTB[54], and this was similar with our results. In addition, Mo has protective effects on other adverse pregnancy outcomes. One study observed that increased concentrations of Mo in maternal serum were associated with reduced risk of neural tube defects with an OR 0·87 (95 % CI 0·90, 0·94)[55]. Another study demonstrated that

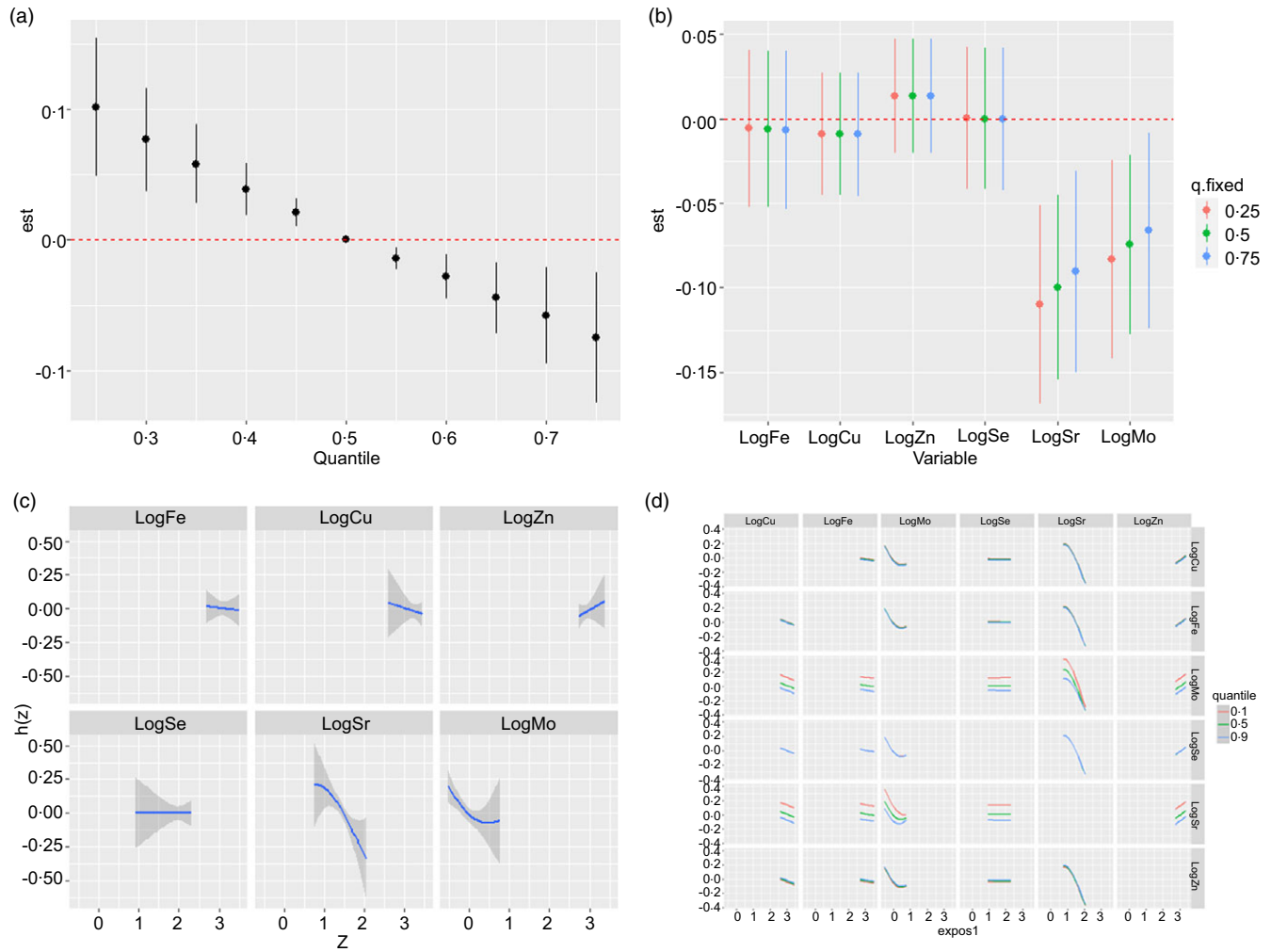

Fig. 2. BKMR association analysis. (a) Overall effect of the mixture (est and 95 % CI), defined as the difference in the response when all of the essential trace elements (ETE) exposures were fixed at a specific quantile (ranging from 20th to 80th), as compared with the SPTB risk when all of the overall ETE exposures were fixed at their median value. (b) Single-exposure effect of individual trace element on SPTB showing the effect of a change in log10-transformed concentrations of trace elements from the 25th percentile to the 75th percentile when the remaining elements were fixed at the 25th, 50th or 75th percentile. 'est' can be defined as the association between single ETE and a latent continuous outcome. (c) Univariate exposure–response functions and 95 % confidence bands (grey area) for each trace element, with other trace elements fixed at their median concentrations. (d) Bivariate exposure–response functions for every two elements on preterm birth. It shows the relationships between the trace element in column and SPTB, when the element in row fixed at its 10th, 50th, and 90th percentile, and the rest of the elements fixed at their 50th percentiles. Model was adjusted for maternal age (continuous), maternal ethnicity, maternal education level, gravidity, pre-pregnancy BMI (continuous), maternal medication use, parental smoking or ETS exposure, maternal alcohol consumption, folic acid supplements and infant sex. BKMR, Bayesian kernel machine regression; ETS, environmental tobacco smoke; SPTB, spontaneous preterm birth.

higher levels of Mo in maternal serum were linked with decreased risk for fetal orofacial clefts[56].

In the present study, no statistically significant association was found between maternal concentrations of Fe and the risk of SPTB, which was similar to an earlier report from a small birth cohort study in Australian women[33] and two studies from a prospective birth cohort in rural Bangladesh[24,38]. Besides, we did not observed a statistically significant association between the maternal concentrations of Cu and the risk of SPTB, which was consistent with four previous studies, a case–control study from Malawi about association analysis between maternal serum Cu and SPTB[37], a prospective birth cohort in rural Bangladesh about the relationship between cord serum or maternal serum Cu and PTB[24,38], and a nested case–control study in Beijing Birth Cohort (BBC), China, about association analysis between Cu concentrations in maternal hair and overall PTB as well as SPTB[21]. In addition, no statistically significant association was found between maternal concentrations of Zn and risk of SPTB, and this was similar to four previous study, including one analysis of maternal urine Zn concentrations and SPTB[32], one study on maternal plasma Zn concentrations and SPTB[33], one meta-analysis[39], and another study on maternal serum Zn concentrations and SPTB[31]. Moreover, no significant association was found between maternal se levels and SPTB, which was similar to a prospective birth cohort in rural Bangladesh on se levels in cord serum and the risk of PTB[38],and two nested case–control study from China on se levels in maternal hair or serum and PTB or SPTB risk[21,31].

It is worth noting that our results, including no significant associations between maternal concentrations of Fe, Cu, Zn, se

and SPTB, and the protective effects of Sr and Mo on SPTB, were differ from most of the previous studies. This inconsistency may be explained with two points. First, differences in sample collection time points may affect study findings. In our study, we collected maternal serum samples in the second trimester for trace element measurement and association analysis of SPTB risk. A nested case–control study in China found that compared with the lowest levels (quartile 1) of Fe and Cu in maternal serum during early pregnancy, the OR of SPB increased to 3·47 (95 % CI 1·07, 11·21) and 16·23 (95 % CI 3·86, 68·18) in the highest levels (Quartile 4), respectively[31]. A nested case–control study in Shanxi, China, reported that compared with the lowest serum Cu levels of maternal serum in the first trimester, the OR associated with SPTB increased to 2·02 (95 % CI 1·07, 3·82), 3·10 (95 % CI 1·54, 6·22) and 4·18 (95 % CI 2·11, 8·27) in the second, third and fourth quartiles, respectively[34]. It has been reported that metallic elements in maternal serum may change with gestational age[57]. Second, the types of samples used may influence the results of a study. Various types of biospecimens have been analysed to characterise trace element exposure in pregnant women, including maternal blood, urine and hair samples. In our study, maternal serum samples were used to assess maternal exposure to trace elements. A nested case–control study in China found that the higher Fe concentrations in maternal hair were associated with a reduced risk of total PTB (fourth quartile, aOR = 0·47, 95 % CI 0·23, 0·96) as well as SPTB (third quartile, aOR = 0·30, 95 % CI 0·11, 0·81; fourth quartile, aOR = 0·26, 95 % CI 0·09, 0·73)[21]. Another study in Australian women found that compared with a high Cu status (third tertile), a lower maternal plasma Cu status (second tertile) was associated with reduced risk of SPTB (adjusted relative risk = 0·52; 95 % CI 0·28, 0·98)[33]. A nested case–control study in Wuhan, China, found that a higher maternal urine Cu level before delivery was associated with an increased risk of PTB (aOR = 1·40, 95 % CI 1·18, 1·65)[35]. Assessment of exposure period might varies based on sample type.

It is known that trace element exposures in humans never occur in isolation, so it is important to investigate multiple elements simultaneously. A few prior studies have examined the associations between element compounds and PTB and SPTB using mixture analysis methods, but the results were inconsistent. A birth cohort study from USA used elastic net (ENET) regression to examine the associations between seventeen urinary metal concentrations and PTB and found Cu as the important predictor of an increased risk of PTB[32]. A cohort study from Northern Puerto Rico identified blood Pb and Zn as critical metals that might adversely affect PTB using ENET and BKMR models[36]. A nested case–control study from China revealed that there was a significantly positive joint effect of metal mixture on PTB with V being possibly the most important toxic agent and also revealed an potential interaction between Zn and Cu using BKMR model[35]. Another nested case–control study from China found a negative association between mixed exposures to increased concentrations of nutritional trace metal(loid)s and a decreased SPTB risk, with Fe and Zn contributing the most strongly to the association[21]. In the present study, BKMR model identified that the overall mixture of the trace elements was inversely associated with SPTB, which confirmed the findings found in WQSR model, and demonstrated the significantly independent effect of Sr and Mo, but did not find potential interactions among the trace elements.

The molecular mechanisms through which prenatal exposure of trace elements may impact PTB are poorly understood. Oxidative stress, an imbalance between free radical generation and antioxidant defence, was recognised as a possible mechanism for PTB[58–60]. One study in pregnant women observed a statistically significant positive correlation between Sr and uric acid ($r = 0{\cdot}40$, $P = 0{\cdot}001$) and lipid peroxidation/total antioxidant activity ratio ($r = 0{\cdot}38$, $P = 0{\cdot}0002$). Additionally, Sr correlated negatively with total antioxidant activity ($r = -0{\cdot}40$, $P = 0{\cdot}0001$)[47]. Several studies which have not been performed in the context of pregnancy also found a relationship between Sr and oxidative stress[61,62]. These studies suggest that Sr has a scavenging effect on lipid peroxidation, playing a preventive role in oxidative damage. Two reports found maternal urinary Mo concentrations to be positively associated with lipid peroxidation biomarkers 8-isoprostaglandin F2α (8-isoPGF2α) and the oxidative DNA damage biomarker 8-hydroxydeoxyguanosine (8-OHdG) in the third trimester[63,64]. A review reported that Mo supplementation might ameliorate the oxidative stress and reduction in antioxidant enzymes that accompanied gestational diabetes mellitus[65]. It can therefore be suggested that Sr or Mo levels rise when some kind of oxidative damage exists, and this elevation attempts in some way to restore the balance between the organism's defence and its oxidative damage and reduce the risk of SPTB. Moreover, inflammation is thought to be another potential mechanism for PTB[66,67]. A large number of studies have found that Sr could suppress inflammation[68,69]. A review reported that the heightened inflammation that accompanies gestational diabetes mellitus might be ameliorated by a Mo supplementation[65]. Therefore, it is speculated that Sr and Mo could reduce the occurrence of SPTB by decreasing the inflammation during the pregnancy. Furthermore, epigenetics might play a role in connecting the environments to PTB[70]. A multi-omics study found that maternal Mo exposure during pregnancy was related to the methylation levels of 72 CpGs representing sixty-three loci, and thirteen of them have previously been related to gestational age[71]. Another study suggested that maternal Cd exposure was associated with a decrease in gestational age through an alteration in DNA methylation at a specific CpG site, cg21010642[72]. Therefore, the association between maternal Mo exposure and SPTB can also be explained from the DNA methylation levels of genes involved in gestational age. However, studies on the association of Sr or Mo with SPTB are limited, and more epidemiological and mechanistic studies are needed.

This study has several strengths. First, this study was nested in a prospective cohort, which allowed us to record exposure and outcome data prospectively and to minimise the potential for selection and recall bias. Second, in addition to investigating the single contribution of each trace element, we evaluated the joint effects of trace elements as a mixture on SPTB risk using WQSR and BKMR models, which are helpful for distinguishing the main contribution factor, and the consistency between the two models increases the robustness of our study findings. However, our study still had several limitations. First, we only measured trace elements from a single serum sample taken at the second

trimester, measuring these elements at multiple time points would give a better overall picture of exposure during pregnancy. Second, there were some other risk factors for SPTB which were not considered, such as genetic variation, psychological stress and conditions during pregnancy such as pregnancy-induced hypertension and gestational diabetes. Third, the present study did not explore the mechanism underlying the association between trace elements in maternal serum and SPTB.

In summary, the higher maternal serum levels of trace elements, including Fe, Cu, Zn, se, Sr and Mo, showed significantly inverse association with the risk of SPTB, and Sr and Mo were important contributors to the mixture effect. Thus, our results provide further evidence on the importance of the presence of ETE for SPTB prevention. Further research is necessary to confirm our findings and understand the mechanisms.

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Y. W. and J. Z. developed the study design. N. L. and P. Y. conducted the experiment and drafted the manuscript. Z. L. and J. T. assisted in analysing the data. L. L., M. W., H. W., Y. Z., Y. D., H. K. and Y. L. assisted in organising and collecting the samples. X. L. and J. L. participated in reviewing, editing and revising the manuscript. All authors have read and approved the final manuscript.

Authors declare that there is no conflict of interest.

Supplementary material

For supplementary materials referred to in this article, please visit https://doi.org/10.1017/S0007114523003070

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