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Association between parental exposure to metal mixture and preterm birth: A prospective birth cohort study

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ABSTRACT

Accumulating evidence suggests that maternal prenatal exposure to metals is associated with preterm birth. However, the relationship between paternal metals exposure and preterm birth remains unclear. In current study, we assessed the association of paternal exposure, maternal exposure and parental co-exposure to metals with the risk of preterm birth, using data from the Jiangsu Birth Cohort (JBC) study. Urine samples collected from 1680 couples during the first trimester were measured for 25 metals concentrations. In the multivariable logistic regression models, paternal and maternal urinary antimony (Sb) concentrations were associated with 45 % (paternal: Odds Ratio (OR), 1.45; 95 % Confidence Interval (95 %CI), 1.01–2.09) and 43 % (maternal: OR, 1.43; 95 % CI, 1.01–2.03) higher risk of preterm birth per ln-unit increase, respectively. Also, maternal urinary cobalt (Co) concentrations (OR, 1.45; 95 % CI, 1.02–2.06) and copper (Cu) concentrations (OR, 2.16; 95 % CI, 1.15–4.03) were significantly associated with an increased risk of preterm birth. In addition, maternal exposure to Cu and paternal exposure to Sb demonstrated a significant dose-response relationship, with trend test *P*-values of 0.037 and 0.015, respectively. These findings suggested that higher concentrations of Cu and Sb are associated with an increased risk of preterm birth. The Bayesian Kernel Machine Regression (BKMR) models revealed a positive joint effect on preterm birth that intensified across increasing quantiles of parental mixture concentrations. Our findings emphasize that metals influence the onset of preterm birth through both maternal and paternal exposure. These results lay a theoretical foundation for developing risk assessment models based on parental exposure characteristics, offering deeper insights into the etiology of preterm birth. Furthermore, they provide essential scientific evidence to support its prevention and control strategies.

Abbreviations: ATP, adenosine triphosphate; APRs, acute-phase reactants; BKMR, Bayesian kernel machine regression; BMI, Body mass index; DAG, directed acyclic graph; ICP-MS, Inductively coupled plasma mass spectrometry; IQR, interquartile range; Ln, natural logarithm; LOD, Limit of detection; MCMC, Markov chain Monte Carlo; MtDNAcn, mtDNA copy number; OR, Odds ratio; PIP, posterior inclusion probabilities; RCS, restricted cubic spline; SD, standard deviation; SG, specific gravity; TC, total cholesterol; TG, triglyceride; 95 % CI, 95 % Confidence interval; Ti, titanium; V, vanadium; Cr, chromium; Mn, manganese; Co, cobalt; Ni, nickel; Cu, copper; Zn, zinc; As, arsenic; Se, selenium; Rb, rubidium; Sr, strontium; Mo, molybdenum; Cd, cadmium; Sn, tin; Sb, stibium; Cs, cesium; Ba, barium; La, lanthanum; Ce, cerium; Re, rhenium; Hg, mercury; Tl, thallium; Pb, lead; U, uranium.

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1. Introduction

Preterm birth is defined as birth before 37 weeks' gestation (Romero et al., 2014). In China, about 752,900 preterm infants were born in 2020, accounting for 6.1 % (95 % credible interval, 5.1–7.4) of all newborns (Ohuma et al., 2023), and the number of preterm births in China is still on the rise (Deng et al., 2021). Compared to full-term infants, premature infants are at a higher risk of developing neonatal respiratory issues, vision and hearing impairments, neurodevelopmental disorders, and other complications, which often results in increased psychological and financial burdens for the families of preterm babies (Vogel et al., 2018). Therefore, it is imperative to identify the underlying causes of the increased preterm birth rate and implement control measures to promote the health of offspring.

With the rapid development of industrialization and the widespread use of materials, humans are constantly exposed to various metals through the air, as well as contaminated food and drinking water (Elder et al., 2015). Studies have shown that metal exposure can have adverse health effects on the general population (Alsubih et al., 2021; Kiani et al., 2021; Shamsollahi et al., 2019; Sadighara et al., 2023). Accumulating evidence suggests that maternal prenatal exposure to metals is associated with preterm birth, such as Cu, chromium (Cr) and arsenic (As) (Kim et al., 2018; Huang et al., 2021; Liu et al., 2022). However, due to variations in study design, study populations, and types of biological samples used for metal detection, findings remain inconsistent. As couples typically share the same living environment, dietary patterns, and lifestyle behaviors (Zhang et al., 2020, 2021), they are likely to exposure to similar environmental factors. In addition, preconception exposure to environmental chemicals may have an epigenetic impact on spermatogenesis (Sun et al., 2017), with potential effects that persist through embryogenesis and placentation, thereby increasing the susceptibility to adverse pregnancy outcomes, including a shortened gestational period (Cha et al., 2012; Li et al., 2012; Zong et al., 2015). Therefore, we hypothesized that paternal preconception exposure to metals may also affect the risk of preterm birth. A recent study found that paternal preconception exposure to phenol and phthalate mixtures was associated with an increased risk of preterm birth, partially supporting our hypothesis (Zhang et al., 2021; Mustieles et al., 2020). However, there is little epidemiological evidence on the association of paternal exposure to metals with the risk of preterm birth, and the effects of combined paternal and maternal metal exposure on preterm birth remain unclear.

In this prospective cohort study, we aimed to investigate the potential associations between paternal and maternal exposure to metals, as well as parental co-exposure to metal mixtures, and the risk of preterm birth in liveborn infants. By addressing these aspects, we seek to fill significant gaps in the current literature, enhance understanding of the complex interplay between metal exposure and preterm birth risk, and provide valuable insights for developing targeted prevention strategies.

2. Methods

2.1. Study design

This study was carried out within the Jiangsu Birth Cohort (JBC) study, an ongoing prospective longitudinal research initiative that recruits women in the first trimester of spontaneous pregnancy at the Women's Hospital of Nanjing Medical University or the Suzhou Affiliated Hospital of Nanjing Medical University. The detailed design of the JBC study has been described previously (Du et al., 2023). The inclusion eligibility criteria were as follows: 1) couples who delivered a singleton live birth; 2) urine samples collected from both parents during the first trimester of pregnancy. From 2014–2019, a total of 1685 recruited couples conceived singleton spontaneously and provided their urine samples. We excluded 3 couples with induced labor and 2 couples with stillbirths. Finally, a total of 1680 couples were included in the study. The study protocol was reviewed and approved by the institutional review board of Nanjing Medical University. All participants have provided written informed consents at recruitment.

2.2. Exposure assessment

Metal concentrations were measured using urine samples collected from couples on their recruitment day, with the gestational age at sample collection ranging from 8 to 14 weeks. Urine samples were collected in sterile polypropylene specimen cups and subsequently stored in sterile polypropylene tubes at −20℃ for the sequent measurements. For sample preparation, urine samples were first thawed at room temperature and then diluted at a 1:20 ratio with nitric acid (300 μL samples with 5700 μL 2 % HNO_3 diluent solution), allowing the mixture to sit overnight. Twenty-five metals (Table 2) were measured using inductively coupled plasma mass spectrometry (ICP-MS) (Thermo Fisher Scientific, Germany) in kinetic energy discrimination mode. The operating conditions of ICP-MS were Radio Frequency (RF) power 1550 W, plasma cool flow 14.00 L/min, auxiliary gas flow 0.8 L/min, nebulizer flow 1.05 L/min, collision cell gas at 4.3 mL/min, resolution (peak high 10 %) 0.75 amu, dwell times 0.03 s. Seronorm ™ trace elements urine samples (Seronorm ™ Trace Elements Urine L-1, LOT1706877, Norway) were used as quality control materials to ensure the accuracy of laboratory measurement procedures. The ICP-MS was calibrated using a blank sample along with a minimum of five standards for each target element. A minimum R^2value of > 0.995 was required for an acceptable calibration curve. Metal measurement variations were determined based on repeated measurements. For most metals, intraday variations were under 15 %, with the exceptions of cerium (Ce), rhenium (Re) and mercury (Hg). Inter-day variations were all below 25 %, except for manganese (Mn) and Co (Table S1). The limit of detection (LOD) values for the metals were presented in Table S1. More than 95 % of urine samples had metal concentrations above the LOD. For measurements below the LOD, values were replaced with half the LOD. Urinary specific gravity (SG) was measured with digital hand-held refractometer (Atago PAL-10S, Co., Ltd., Tokyo, Japan) to adjust for urinary dilution. The formula used was: Pc = P [(SGm - 1)/ (SG - 1)], where Pc is the SG-corrected concentration, P is the unadjusted concentration, and SGm is the median concentration of SG.

2.3. Outcome and covariates

Preterm birth is defined as the delivery of a live infant before 37 completed weeks of gestation, and full-term birth refers to a baby born at or after 37 weeks of gestation. It can be further subdivided into three types on the basis of gestational age: extremely preterm (<28 weeks), very preterm (28–32 weeks) and moderate or late preterm (32–37 weeks) (Ohuma et al., 2023). Gestational age for determining preterm birth was obtained from medical records and calculated based on the last menstrual period, with verification by ultrasound and confirmation from two maternal-fetal medicine specialists. At recruitment, face-to-face interviews were conducted to collect parental information on sociodemographic characteristics during follow-up visits throughout pregnancy. All potential confounders were respectively selected a priori using directed acyclic graph (DAG) (Textor et al., 2011). The minimum sufficient adjustment sets for estimating the effects of maternal exposures on preterm birth included maternal age, education, Body Mass Index (BMI), maternal tobacco use, maternal passive smoking, household income, area of residence and parity. For estimating the effects of paternal exposures, the adjustment sets included paternal age, education, BMI, parental tobacco use, household income, area of residence, and parity (Figure S1). We implemented standardized quality control

Table1
Basic characteristics of study population.

Characteristics, No. (%)	Mothers (n = 1680)	Fathers (n = 1680)
Age, year		
mean ± SD	29.35 (3.75)	30.73 (4.41)
< 25	154 (9.2)	86 (5.1)
25–30	909 (54.1)	781 (46.6)
30–35	461 (27.4)	550 (32.8)
> 35	156 (9.3)	260 (15.5)
Education, year		
≤12	163 (9.7)	162 (9.7)
> 12	1517 (90.3)	1513 (90.3)
BMI, kg/m^2		
mean ± SD	21.25 (2.92)	24.15 (3.16)
< 18.5	248 (14.8)	37 (2.3)
18.5–23.9	1169 (69.6)	781 (48.7)
24–27.9	206 (12.3)	623 (38.8)
> 28	56 (3.3)	164 (10.2)
Nationality		
Han	1640 (97.6)	1647 (98.0)
Other	40 (2.4)	33 (2.0)
Alcohol intake		
No	1644 (97.9)	912 (59.2)
Yes	36 (2.1)	628 (40.8)
Tobacco use		
No	1665 (99.1)	1085 (67.3)
Yes	15 (0.9)	526 (32.7)
Passive smoking		
No	1108 (70.2)	-
Yes	471 (29.8)	-
Study center		
Nanjing	1102 (65.6)	-
Suzhou	578 (34.4)	-
Household income, CNY		
<50,000	99 (5.9)	-
50,000–200,000	1169 (69.6)	-
> 200,000	411 (24.5)	-
Area of residence		
Rural	449 (26.7)	-
Urban/sub-urban	1231 (73.3)	-
Hypertensive disorders in pregnancy		
No	1625 (96.7)	-
Yes	55 (3.3)	-
Diabetes in pregnancy		
No	1253 (74.6)	-
Yes	427 (25.4)	-
Parity		
Nulliparous	1307 (77.8)	-
Multiparous	372 (22.2)	-
PTB		
No	1615 (96.1)	-
Yes	65 (3.9)	-

Abbreviation: BMI, body mass index; CNY, China yuan; SD, standard deviation.
[a] Hypertensive disorders in pregnancy includes chronic, gestational hypertension and pre-eclampsia.
[b] Diabetes in pregnancy includes chronic and gestational diabetes.
Missing data: Age (fathers, n = 3); Education (fathers, n = 5); Tobacco use (fathers, n = 69); Household income (n = 1); BMI (mothers, n = 1; fathers, n = 75); Passive smoking (n = 101); Parity (n = 1).

procedures to ensure the accuracy and reliability of all data used in the study.

2.4. Statistical analysis

Among parental characteristics, continuous variables were summarized as means and standard deviation (SD), and categorical data as absolute numbers and percentages (%). Descriptive statistics were calculated for the SG-corrected concentrations. As the parental SG-corrected urinary metal concentrations were log-normally distributed, all values were transformed using the natural logarithm (Ln) for subsequent analyses. Pearson correlation coefficients were then calculated separately between maternal and paternal metals, as well as between parental metals.

To assess the association between parental exposure to individual metals and preterm birth, logistic regression models were used to estimate Odds Ratio (OR) with 95 % confidence interval (CI), adjusted for covariates. The metals involved in the following analyses were significantly associated with preterm birth. The potential non-linear relations between parental urinary metal concentrations and the risk of preterm birth were accessed using restricted cubic spline (RCS) models, with four knots at the 5th, 35th, 65th and 95th percentiles of the Ln-transformed concentrations. Dose-response effects were then estimated for an interquartile range (IQR) increase in exposure, treating the metals as ln-transformed continuous variables. Quartile differences were also assessed, with the lowest quartile serving as the reference for maternal copper (Cu) exposure and paternal antimony (Sb) exposure, and the lower quartile as the reference for maternal cobalt (Co) and Sb exposure, based on the results from the RCS analysis. The trend tests were performed by modeling quartiles of metals as ordinal categorical variables. Subsequently, Bayesian Kernel Machine Regression (BKMR) model was developed to evaluate the effects of multiple metals on the risk of preterm birth. BKMR uses kernel regression to handle high-dimensional parameter spaces, account for non-linearity and non-additivity, and estimate both individual and joint effects of compound mixtures (Bobb et al., 2015). Metals and all continuous covariates were then centralized and standardized. The BKMR model, assuming a probit link, was fitted with h () interpreted as the exposure-response relationship between metals exposure and a binary outcome as latent continuous (>0, preterm birth; <0, full-term birth). The Markov Chain Monte Carlo (MCMC) sampler was run for 10,000 iterations and the posterior inclusion probability (PIP) was extracted to indicate a relative importance of each exposure in predicting the outcome within the model. The analytical procedures included the followings: 1) the interactions between any two metals were visualized by investigating the exposure-response function of a single metal while fixing the second metal at various quantiles and keeping all other metals at the 50th percentile; 2) the overall effect of the mixture of metals were visualized by comparing the estimated change in preterm birth when metals concentrations were at specific percentiles to when all metals are all at the 50th percentile. Besides, in order to explore possible synergistic and antagonistic relationships between the metals, NLinteraction R package was applied, which use Bayesian semi-parametric regression and sparsity-inducing priors to generate PIPs for pairwise interactions (Howe et al., 2020; Joseph Antonelli et al., 2020). The MCMC sampler was ran for 10,000 iterations, and half scans were dropped as burn-in, with other options set as default. Based on the Watanabe-Akaike information criterion, 2 degree of freedom was selected (Joseph Antonelli et al., 2020).

Stratification analyses were further conducted to investigate the associations between parental metal exposure and different types of preterm births. As the number of extremely preterm is one, the groups included very preterm (n = 6) and moderate to late preterm (n = 58). Sensitivity analyses were performed to examine the results' robustness. In order to differentiate the effects of maternal and paternal metal exposure on preterm birth, partner's specific metal concentrations were additionally adjusted. As diabetes in pregnancy or hypertensive disorders in pregnancy have been reported to be risk factors for premature birth (Vogel et al., 2018), they were also adjusted. Based on etiology, preterm birth can be classified into spontaneous preterm birth and iatrogenic preterm birth, the latter referring to the induction of labor or elective cesarean delivery prior to 37 completed weeks of gestation for maternal or fetal indications, as well as other non-medical reasons (Goldenberg et al., 2008). Thus, iatrogenic preterm births (n = 10) were excluded in order to investigate the associations between parental metal exposure and spontaneous preterm birth.

All the statistical analyses were conducted in R Software Version 4.3.2 (The R Foundation). A two-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of participants

This cohort study included 1680 couples, with a mean age of 29.35 (SD = 3.75) years for mother and 30.73 (SD = 4.41) years for father at the time of recruitment. The demographic characteristics and follow-up information of couples were displayed in Table 1. A majority of participants were residents of urban or sub-urban areas and had completed at least a high school level education (12 years). Compared to mothers, fathers were more likely to be overweight or obese before pregnancy and engage in tobacco consumption. Among mothers, 77.8 % of them were nulliparous. About 25.4 % mothers were diagnosed with chronic or gestational diabetes and 3.3 % with chronic or pregnancy- induced hypertension. Of the 1680 singleton neonates, 3.9 % were born preterm.

3.2. Distribution of urinary metal levels

Table 2 and Table S1 presented the median concentrations and detection frequencies of metals in the urine of parents after adjusted for SG. The urinary detection frequency of each metal was similar for both maternal and paternal samples, ranging from 95.70 % to 100 %. The median concentrations of metals in mothers were slightly higher than those in fathers, except for nickel (Ni), zinc (Zn), arsenic (As), strontium (Sr), molybdenum (Mo), barium (Ba), rhenium (Re) and thallium (Tl). Ln-transformed metal concentrations were with low-to-high correlations within mothers and fathers, and with low-to-moderate correlations between couples. The Pearson correlation coefficients ranged from −0.28 (Ba and tin (Sn), cerium (Ce) and Sn) to 0.74 (titanium (Ti48) and strontium (Sr)) for maternal concentrations, −0.56 (Ba and Sn) to 0.72 (Ti48 and Sr) for paternal concentrations, and −0.31 (maternal Ce and paternal Sn) to 0.36 (maternal Ce and paternal Ce, maternal Sn and paternal Sn) for couples' concentrations (Figure S2).

3.3. Associations between individual metals and preterm birth

Both paternal and maternal urinary exposure to Sb were associated with the increased risk of preterm birth in models adjusted for covariates. The ORs for preterm birth per Ln unit increase in Sb concentrations were 1.45(95 % CI: 1.01–2.09) for paternal exposure and 1.43 (95 % CI: 1.01–2.03) for maternal exposure. In the adjusted models, maternal urinary concentrations of Cu and Co were associated with a higher risk of preterm birth. The ORs were 2.16 (95 % CI: 1.15–4.03) for Cu and 1.45 (95 % CI: 1.02–2.06) for Co (Table S2 and Fig. 1). In general, the increased risk of preterm birth was positively associated with both paternal and maternal Ln-transformed urinary concentrations of Sb, as well as with maternal Ln-transformed urinary concentrations of Cu and Co.

Non-linear relationships of parental Sb concentrations and maternal Co and Cu concentrations with the risk of preterm birth were further assessed (Figure S3). Maternal Cu concentrations and paternal Sb concentrations showed linear relationships with the risk of preterm birth, while maternal Co and Sb concentrations showed non-linear relationships with the risk of preterm birth. Furthermore, mothers with Co concentrations below or above 0.307 μg/L and with Sb concentrations below or above 0.127 μg/L had a higher risk of preterm birth. Logistic regression was applied to further evaluate the effects of parental urinary concentrations of metals at different levels on preterm birth (Table 3). The dose-response effects, estimated for an IQR increase in exposure, revealed a significantly positive association between paternal and maternal Sb exposure (paternal Sb exposure, OR: 1.35 per IQR increase, 95 % CI: 1.01–1.81; maternal Sb exposure, OR: 1.30 per IQR increase, 95 % CI: 1.00–1.69), as well as maternal Co (OR: 1.42 per IQR increase, 95 % CI: 1.01–1.98) and Cu (OR: 1.47 per IQR increase, 95 % CI: 1.07–2.00) exposure, with the risk of preterm birth. Compared with the lowest quartile, the highest level of paternal Sb (OR: 3.65, 95 % CI: 1.42–9.36) and maternal Cu (OR: 2.34, 95 % CI: 1.05–5.22) were both positively associated with preterm birth. The highest level of maternal Co (OR: 2.70, 95 % CI: 1.23–5.92) and Sb (OR: 2.59, 95 % CI: 1.13–5.95) also presented the significantly positive association with preterm birth compared with lower quartile. Linear trend was observed in the association of maternal Cu concentrations ($P = 0.037$) and paternal Sb concentrations ($P = 0.015$) with preterm birth.

3.4. Associations between metal mixture and preterm birth

In BKMR, the PIPs of maternal metals ranked higher than paternal

Table 2
The distributions of parental urinary metal concentrations.

Exposure (ug/L)	Maternal exposure (n = 1680)		Paternal exposure (n = 1680)	
	number of <LOD (100 %)	SG_adjusted-median (IQR)	number of <LOD (100 %)	SG_adjusted-median (IQR)
Ti48	0(0 %)	145.46(94.96,209.91)	0(0 %)	143.89(102.01,196.42)
V	0(0 %)	0.22(0.16,0.30)	0(0 %)	0.19(0.14,0.24)
Cr	1(0.1 %)	0.73(0.41,1.19)	0(0 %)	0.64(0.41,1.03)
Mn	72(4.3 %)	0.63(0.34,1.21)	34(2 %)	0.58(0.35,1.02)
Co	1(0.1 %)	0.43(0.27,0.73)	0(0 %)	0.27(0.20,0.40)
Ni	0(0 %)	3.46(2.30,5.41)	0(0 %)	3.95(2.65,6.35)
Cu	1(0.1 %)	17.69(13.66,22.56)	0(0 %)	13.49(10.54,17.67)
Zn	0(0 %)	436.93(288.30,667.58)	0(0 %)	583.02(428.26,806.89)
As	0(0 %)	27.29(18.63,41.84)	0(0 %)	34.48(23.84,53.42)
Se	0(0 %)	10.98(8.39,14.39)	0(0 %)	10.39(8.30,13.47)
Rb	0(0 %)	2290.96(1791.00,2886.38)	0(0 %)	1944.76(1494.16,2477.00)
Sr	0(0 %)	146.97(93.56,212.21)	0(0 %)	178.14(127.80,238.95)
Mo	0(0 %)	58.61(45.70,74.97)	0(0 %)	64.09(48.02,91.74)
Cd	0(0 %)	0.58(0.37,0.98)	0(0 %)	0.55(0.37,0.86)
Sn	0(0 %)	1.11(0.55,3.09)	6(0.4 %)	0.93(0.46,3.41)
Sb	0(0 %)	0.13(0.09,0.19)	0(0 %)	0.12(0.08,0.18)
Cs	4(0.2 %)	12.24(9.87,15.45)	0(0 %)	10.31(8.48,12.69)
Ba	0(0 %)	19.96(4.89,56.60)	0(0 %)	21.72(4.46,50.70)
La	35(2.1 %)	0.02(0.01,0.07)	36(2.1 %)	0.02(0.01,0.05)
Ce	0(0 %)	0.19(0.02,0.65)	3(0.2 %)	0.13(0.02,0.42)
Re	0(0 %)	0.05(0.03,0.07)	0(0 %)	0.05(0.04,0.08)
Hg	0(0 %)	0.39(0.24,0.58)	1(0.1 %)	0.35(0.26,0.50)
Tl	0(0 %)	0.41(0.31,0.55)	0(0 %)	0.47(0.37,0.61)
Pb	0(0 %)	1.89(1.06,3.28)	0(0 %)	1.63(1.09,2.61)
U	29(1.7 %)	0.01(0.01,0.02)	33(2 %)	0.01(0.00,0.01)

Abbreviation: LOD, limit of detection; SG, urine specific gravity; IQR, interquartile range.

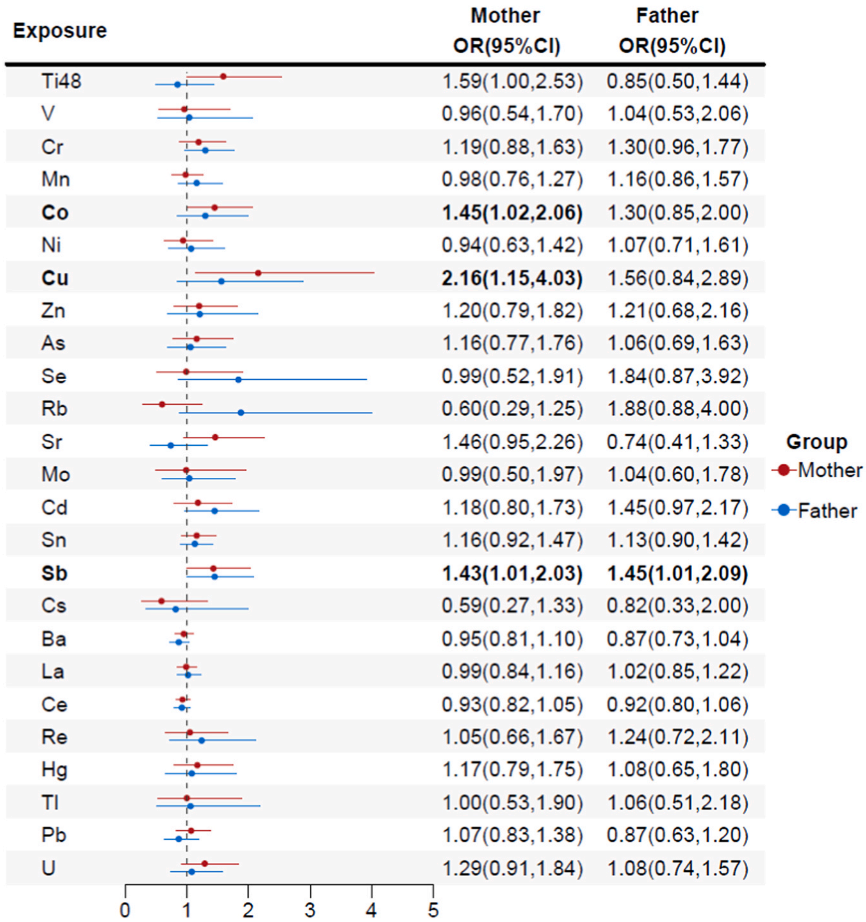

Fig. 1. Effects of parental exposure to metals on risk of preterm birth by logistic regression. Analyses for maternal exposures were adjusted for maternal age, maternal education, maternal BMI, maternal tobacco use, maternal passive smoking, household income, area of residence and parity. Analyses for paternal exposures were adjusted for paternal age, paternal education, paternal BMI, paternal tobacco use, household income, area of residence and parity.

metals, with Co exhibiting the highest PIP among the maternal metals (Table S3). Post-hoc bivariate interaction analysis suggested a synergistic toxic effect of paternal Sb exposure combined with maternal Sb exposure, as well as a synergistic toxic effect between maternal Co exposure and paternal Sb exposure, on the risk of preterm birth (Figure S4a). With the simultaneous increment of maternal Co, Cu, Sb and paternal Sb concentrations from the 25th to 75th percentile, the risk of preterm birth increased steadily; parental concentrations of these metals in the upper 75th percentile had 1.11 times increased risk of preterm birth (95 %CI: 1.04–1.19) compared to them in the 50th percentile (Figure S4b). To investigate the association between maternal Co and paternal Sb, as well as between paternal and maternal Sb, the NLinteraction method was applied. The PIPs for pairwise interactions between parental Sb (PIP=0.67) ranked the highest among all possible pairs (Table S4).

3.5. Stratification analyses

After stratifying preterm birth into very preterm birth and moderate to late preterm birth, we found that maternal exposure to Co was significantly associated with an increased risk of very preterm birth, while maternal exposure to Cu significantly increased the risk of moderate to late preterm birth. Additionally, the effect of paternal exposure to Sb on preterm birth maintained (Table S5).

3.6. Sensitivity analyses

When additionally adjusting for the partner's specific metal concentrations, the associations persisted, indicating that paternal and maternal metal exposures independently contributed to the risk of preterm birth. After adjusting for diabetes in pregnancy and hypertensive disorders in pregnancy in the models, the results were still robust. Additionally, when iatrogenic preterm births were excluded, the main findings did not change substantially (Table S6).

4. Discussion

In this birth cohort study conducted in Jiangsu, China, we found that both paternal and maternal urinary Sb exposure and maternal urinary Co and Cu exposure in the first trimester were significantly associated with increased risks of preterm birth. These findings were further substantiated through analyses of preterm birth subcategories and sensitivity analyses, with the effect remaining consistent. Importantly, our findings indicated that parental exposure to mixtures of Co, Cu, and Sb was related to an increased risk of preterm birth, highlighting the potential joint effects of parental metal exposure on preterm birth.

The effects of parental exposure to Sb on preterm birth have been minimally explored in prior research. Concerning the observed association between paternal urinary Sb exposure and increased risk of preterm birth, factors such as sperm quality and its impact on embryonic development and healthy live births may offer plausible explanations (Colaco and Sakkas, 2018). A study using a murine model demonstrated that Sb exposure could lead to reproductive toxicity in mice, significantly reducing both sperm survival rate and sperm viability (Wu et al., 2021). In addition, prior studies have shown that environmental factors can modify paternal epigenetic markers, which may potentially exert

Table 3
Risk of preterm birth across quartiles of maternal and paternal urinary metal concentrations.

Exposure	Case/N	OR (95 %CI)	*P*	*P* for trend
Maternal exposure				
Co				
per IQR	-	1.42(1.01,1.98)	0.041	
Q1	18/414	1.84(0.79,4.28)	0.157	0.098
Q2	11/413	reference		
Q3	11/413	1.14(0.46,2.84)	0.782	
Q4	24/414	2.70(1.23,5.92)	0.013	
Cu				
per IQR	-	1.47(1.07,2.00)	0.016	
Q1	10/415	reference		0.037
Q2	15/415	1.55(0.66,3.65)	0.318	
Q3	16/415	1.54(0.65,3.61)	0.324	
Q4	22/415	2.34(1.05,5.22)	0.037	
Sb				
per IQR	-	1.30(1.00,1.69)	0.046	
Q1	18/415	1.90(0.79,4.55)	0.151	0.158
Q2	9/415	reference		
Q3	16/415	1.90(0.79,4.56)	0.149	
Q4	22/415	2.59(1.13,5.95)	0.025	
Paternal exposure				
Sb				
per IQR	-	1.35(1.01,1.81)	0.043	
Q1	6/416	reference		0.015
Q2	22/415	2.90(1.12,7.53)	0.028	
Q3	14/415	2.32(0.87,6.20)	0.093	
Q4	22/416	3.65(1.42,9.36)	0.007	

Abbreviation: IQR, interquartile range. OR, Odds ratio; 95 %CI, 95 % Confidence Interval.
Analyses for maternal exposures were adjusted for maternal age, education and BMI, maternal tobacco use, maternal passive smoking, household income, area of residence and parity. Analyses for paternal exposures were adjusted for paternal age, education and BMI, paternal tobacco use, household income, area of residence and parity.

significant effects on the health of offspring (Champroux et al., 2018). The paternal genome also plays a crucial role in placental development, with paternally expressed imprinted genes predominating in the placenta (Wang et al., 2013).

The positive association between maternal Sb exposure and preterm birth was also observed. A prospective cohort study conducted in Guangdong found that Sb concentrations in cord blood were associated with an increased risk of preterm birth. The exposure-response relationship for Sb showed a rise at lower concentrations in cord blood, followed by a notable decline as concentrations increased (Wang et al., 2022). The linear relationship between maternal Sb exposure and preterm birth in our study is consistent with the findings of the aforementioned study. However, a different expose-response relationship was observed in our study, where both higher or lower concentrations of maternal Sb were associated with an increased risk of preterm birth. The inconsistencies in the findings may be due to differences in the biological samples used for metal detection, variations in the study populations, and disparities in sample size. Sb is considered a metalloestrogen (Choe et al., 2003), and a review illustrated that prolonged exposure to xenoestrogens can induce peripheral insulin resistance and glucose intolerance (Hectors et al., 2011). This disruption increases the risk of gestational diabetes mellitus and may potentially lead to preterm birth (Goldenberg et al., 2008; Hectors et al., 2011). It has also been reported that exposure to Sb can induce oxidative stress, leading to the depletion of antioxidants. This impairs the placental antioxidant capacity and its protective systems, potentially contributing to the risk of preterm birth (Sultana et al., 2017; Xiao et al., 2018). Additionally, environmental exposures can cause epigenetic inheritance during oogenesis and pregnancy, which is essential for the proper development of the embryo (Gluckman et al., 2008).

Co is an essential trace element for humans, playing a crucial role in the synthesis of nucleic acids, amino acids, and the formation of erythrocytes (Stoica et al., 2004). We observed a U-shaped relationship between maternal Co exposure and preterm birth. Only one cohort study conducted in Ma'anshan reported that lower maternal serum Co levels were associated with a higher risk of preterm birth, supporting our findings (Li et al., 2019). Previous studies have demonstrated that maternal serum Co levels were associated with antioxidant and anti-inflammatory properties. Higher concentrations of Co, within the normal range, could enhance blood flow to the placenta thereby reducing damage caused by inflammatory and oxidative factors (Liang et al., 2018). This may be the reason why the lower Co levels were associated with increased risk of preterm birth. Additionally, we also found that higher maternal urinary Co concentrations were associated with the increased risk of preterm birth. A study revealed that Co can accumulate in the placenta, with higher concentrations of Co in the placenta being associated with a reduced placental mitochondrial deoxyribonucleic acid (DNA) copy number (mtDNAcn). This reduction in mtDNAcn leads to decreased adenosine triphosphate (ATP) production, which can impair placental growth (Grundeken et al., 2024; Hantson, 2019). Additionally, maternal Co exposure is associated with elevated levels of estriol (E3), which may lead to adverse birth outcomes, such as preterm birth (Rivera-Núñez et al., 2021; Noyola-Martínez et al., 2019).

The positive relationship between maternal Cu exposure and preterm birth was consistent with findings from most prior studies (Kim et al., 2018; Liu et al., 2022). Our study also observed a linear relationship between Cu concentrations and preterm birth, with the risk of preterm birth increasing consistently among mothers in higher quartiles of Cu. The cohort study conducted in Shanxi Province (Hao et al., 2019) and a Meta-analysis obtaining data from 18 geographically diverse study cohorts (Monangi et al., 2024) both support our findings. The potential mechanism may involve Cu contributing to increasing plasma levels of total cholesterol (TC) and triglycerides (TG) (Hao et al., 2019), which are related to placental dysfunction or microvascular damage (Kelly et al., 2009). A study has found a relationship between increased Cu levels and biomarkers of oxidative stress, which suggested that Cu may impact preterm birth through pathways including oxidative damage (Ashrap et al., 2021). In addition, the Malawi cohort study found that higher maternal Cu levels increased the risk of preterm birth, possibly because Cu concentrations were positively correlated with the levels of certain acute-phase reactants (APRs), thereby triggering an inflammatory response that leads to preterm birth (Monangi et al., 2024).

The potential cumulative effects of parental metal mixture on preterm birth were observed in the BKMR model. Although there is a lack of evidence about the positive association between parental combined exposure to metal mixtures and preterm birth, a cohort study including 1675 couples and infants illustrated that parental co-exposure to metal mixture has significant joint effects on birth defects (Lv et al., 2024). This highlights the potential effects of parental metal mixture exposure and underscores the importance of mixture analysis to understand the impact of combined parental metal exposures. It also implies that preterm birth could be a pregnancy outcome influenced by both parents. Notably, paternally expressed imprinted genes typically promote the transfer of nutrients to the fetus, whereas maternally expressed imprinted genes generally reduce the resources allocated to the fetus (Piedrahita, 2011). Dysregulation in the balance of maternally and paternally expressed imprinted genes may contribute to fetal growth abnormalities (Piedrahita, 2011). One limitation of the BKMR models is its inability to quantify the significance of potential interactions. Through NLinteraction, we found that the interaction between parental Sb to ranked highest of all possible metal pairs. However, the underlying mechanisms of the interactions were less well-established, warranting further experimental studies to investigate them.

Our study has several strengths. Firstly, as most studies focus on maternal metal exposure, the availability of biological samples from both parents to assess not only maternal but also paternal exposure to metals in general population is a major strength of this study. Secondly, we considered the co-occurrence of parental exposure to multiple metals and assessed the combined effects of metal mixtures on preterm birth rather than the effects of single metals alone. Additionally, we accounted for the independent effects of maternal and paternal exposures by adjusting for each partner's specific metal concentrations, as well as considering the influence of parental exposure on spontaneous preterm birth.

Our study also has some limitations. Firstly, we measured metal concentrations only in the first trimester. However, early pregnancy has been recognized as a particularly sensitive window (Cheng et al., 2017) and can also effectively reveal the impact of metal exposure on preterm birth. Secondly, due to the limited number of preterm birth cases, the effects of parental metal exposure on extremely preterm could not be assessed. Thirdly, some unmeasured potential confounders may bias the final results, such as nutrient intake of mothers and parental mental health during pregnancy.

5. Conclusions

Our study reveals that both paternal and maternal urinary Sb exposure along with maternal prenatal urinary Co and Cu exposure were prospectively associated with the increased risk of preterm birth. Also, maternal exposure to Co and Sb show a nonlinear relationship with the risk of preterm birth. In contrast, maternal exposure to Cu and paternal exposure to Sb exhibited a significant dose-response relationship, with higher concentrations associated with an increased risk of preterm birth. In addition, our study observed potential joint effects of parental metal mixture on preterm birth. These findings suggest that metals play a role in the occurrence of preterm birth through both maternal and paternal exposure, highlighting the urgent need to reduce environmental metal pollution to mitigate reproductive health risks. Furthermore, these results provide strong scientific evidence to inform the development of more effective strategies for preventing and controlling preterm birth. Given the persistently high preterm birth rate and the detrimental effects of environmental pollutants, further research is crucial to elucidate the biological mechanisms underlying parental exposure to these pollutants. A deeper understanding of these mechanisms will be instrumental in guiding targeted interventions, shaping evidence-based public health policies, and ultimately improving maternal and infant health outcomes.

Ethics approval and consent to participate

The study protocol was reviewed and approved by the institutional review board of Nanjing Medical University. All participants have provided written informed consents at recruitment.

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CRediT authorship contribution statement

Yuxin Liu: Investigation, Data curation. **Bo Xu:** Investigation. **Haowen Zhang:** Writing – original draft, Formal analysis. **Yue Jiang:** Investigation. **Hong Lv:** Investigation, Data curation. **Cong Liu:** Investigation, Data curation. **Kun Zhou:** Investigation. **Jiangbo Du:** Writing – review & editing, Project administration, Conceptualization. **Yuanyan Dou:** Investigation, Data curation. **Yuan Lin:** Writing – review & editing, Project administration, Conceptualization. **Xin Xu:** Investigation, Data curation. **Yiyuan Chen:** Writing – original draft, Formal analysis. **Tianyu Sun:** Investigation, Data curation. **Zhibin Hu:** Writing – review & editing, Project administration, Conceptualization. **Bo Yang:** Writing – original draft, Formal analysis. **Kang Ke:** Investigation, Data curation. **Guangfu Jin:** Supervision, Project administration, Conceptualization. **Tao Jiang:** Validation, Investigation. **Jiaping Chen:** Investigation. **Hongbing Shen:** Supervision, Project administration, Conceptualization. **Shiyao Tao:** Investigation, Data curation. **Hongxia Ma:** Supervision, Project administration, Conceptualization. **Rui Qin:** Investigation, Data curation.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that they did not use any generative AI service during the preparation of this work.

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. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.118375.

Data availability

The data that has been used is confidential.

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