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Maternal essential and toxic metal mixtures in late pregnancy and neonatal birth weight

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A R T I C L E I N F O

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A B S T R A C T

Background: Prenatal exposure to toxic metals has been consistently associated with impaired fetal growth, yet pregnant individuals are simultaneously exposed to mixtures of essential and toxic metals. Evidence on how such complex metal mixtures in late pregnancy influence birth outcomes in European populations remains limited.
Methods: In a prospective study of 2,754 German mother–infant pairs, 37 metals were measured in maternal blood during late pregnancy. We used elastic net regression, restricted cubic splines, Bayesian kernel machine regression (BKMR), and quantile g-computation to evaluate individual and mixture effects on birth weight, adjusting for key sociodemographic and clinical covariates.
Results: Among 2,754 mother–infant pairs (median [IQR] maternal age, 30 [26–34] years; median [IQR] birth weight, 3368.0 [3025.0–3725.0] g), mixture analyses identified manganese (Mn), cobalt (Co), cadmium (Cd), and cesium (Cs) as key metals associated with birth weight. Mn ($\beta = 57.86$) and Co ($\beta = 30.11$) were positively associated with birth weight, whereas Cd ($\beta = -40.82$) and Cs ($\beta = -25.52$) were inversely associated. Bayesian kernel machine regression revealed that higher Mn concentrations were associated with weaker negative associations of Cs and Cd with birth weight. Quantile g-computation showed that mixtures dominated by Mn and Co were associated with higher birth weight (37.34 g [95% CI, 5.64 to 69.05 g]; 44.06 g [95% CI, 12.96 to 75.15 g]), while mixtures including Cd and Cs showed nonsignificant negative associations.
Conclusion: In this large European birth cohort, fetal growth was associated with the combined effects of essential and toxic metals rather than isolated exposures. The positive associations of manganese and cobalt with birth weight were weaker in the presence of co-exposure to cadmium and cesium, highlighting the importance of mixture-oriented environmental risk assessment. Integrated public health strategies that reduce toxic metal exposure while ensuring adequate maternal micronutrient status may be relevant for optimizing birth outcomes.

1. Introduction

Maternal exposure to environmental metals during pregnancy represents a complex real-world exposure scenario in which toxic and essential elements co-occur through diet, drinking water, air pollution, and consumer products (Christian, 2010; Vigeh et al., 2025). These metals include toxic elements such as lead and arsenic, as well as essential trace elements including zinc, copper, and selenium, which are required for normal biological function but may become harmful when present at insufficient or excessive levels (Qiu et al., 2024; Caserta et al., 2013).

During gestation, metals can cross the placental barrier via metal-specific transporters and accumulate in fetal tissues, potentially disrupting oxidative balance, endocrine signaling, and mitochondrial

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activity (Gundacker and Hengstschläger, 2012; Issah et al., 2024). Toxic metals have been associated with impaired placental function and fetal development, whereas deficiencies or excesses of essential elements may interfere with enzymatic activity and antioxidant defense mechanisms (Caserta et al., 2013).

Birth weight is a key marker of fetal health that reflects intrauterine growth and is associated not only with perinatal outcomes, including neonatal morbidity and preterm complications, but also with long-term cardiometabolic risk (Okwaraji et al., 2024). Numerous epidemiological studies have linked low birth weight to increased risks of type 2 diabetes, cardiovascular disease, and hypertension in adulthood, consistent with the developmental origins of health and disease (DOHaD) hypothesis (Reichetzeder et al., 2016; Bianchi and Restrepo, 2022; Tian et al., 2019). Insulin resistance has been proposed as one potential mechanism linking impaired fetal growth to adverse cardiometabolic outcomes later in life (Callan et al., 2013; Orzeł et al., 2024; Li and Yang, 2018).

Despite growing evidence, most previous studies have focused on a limited number of metals, often in relatively small cohorts, and have primarily assessed exposures during early pregnancy (Ashley-Martin et al., 2018; Hu et al., 2022). Data on metal exposure during late pregnancy—a critical period characterized by rapid fetal growth and intensified placental transport—remain limited, particularly in European populations (Wei et al., 2023).

To address these gaps, we conducted a prospective cohort study in a large German birth cohort to examine associations between maternal whole-blood concentrations of essential and toxic metals measured in late pregnancy and neonatal birth weight. We hypothesized that metal mixtures would show non-linear and interactive associations with birth weight, and that essential elements may modify or buffer the adverse effects of toxic metals.

2. Methods

2.1. Study population

This prospective cohort study included 5612 mother–infant pairs from a German birth cohort. Participants were enrolled at the Department of Obstetrics, Charité University Hospital, Berlin. The study was approved by the Ethics Committee of Charité – Universitätsmedizin Berlin (approval number: EA1/229/14). We included women with singleton pregnancies who had available data on maternal whole blood metal concentrations and neonatal birth weight. The final analytical sample comprised 2754 mother–infant pairs (eFig. 1).

2.2. Exposure assessment: maternal whole blood metals

Maternal whole blood samples were collected during late pregnancy, immediately upon admission to the delivery room in preparation for delivery, aliquoted, and stored in liquid nitrogen until analysis. EDTA whole-blood tubes were used for sample collection. Metals were measured in whole blood, reflecting concentrations in both plasma and cellular components.

Concentrations of 37 metals, including both essential and toxic elements, were measured in whole blood using a validated whole-blood metal assay based on inductively coupled plasma tandem mass spectrometry (ICP-MS) at the Institute of Medical Diagnostics (IMD), Berlin, Germany. All analyses were performed in an accredited clinical laboratory operating under certified procedures in Germany. The laboratory undergoes routine external quality assurance, including regular participation in Ringversuche (external proficiency testing). Because the measurements were performed as part of a standardized clinical assay by an external laboratory, only the methodological details directly available from the laboratory documentation are reported here. Limits of detection and detection rates for all analyzed elements are provided in the Supplementary Material. Values below the limit of detection (LOD) were imputed as LOD divided by the square root of 2. All metal concentrations were natural log–transformed to reduce skewness prior to analysis.

2.3. Assessment of outcome and covariates

The primary outcome was neonatal birth weight (grams), abstracted from medical records. Potential confounders were selected a priori based on biological plausibility and prior literature. Gestational age at delivery and infant sex were included based on biological plausibility, as they are fundamental determinants of fetal growth and birth weight. Maternal age, pre-pregnancy body mass index (BMI), smoking during pregnancy, and hypertension during pregnancy were included based on prior epidemiological evidence demonstrating their associations with birth weight and/or environmental exposures.(Kent et al., 2013; Stillman et al., 1986; Lei et al., 2018) The primary adjustment set therefore included gestational age, maternal age, pre-pregnancy BMI, smoking during pregnancy (yes/no), hypertension during pregnancy (yes/no), and infant sex (male/female). We used a parsimonious set of covariates to avoid overadjustment and loss of precision. Variables with substantial missingness (e.g., income) were not included in the primary model. Maternal height and ethnicity were additionally evaluated in sensitivity analyses.

2.4. Statistical analysis

Descriptive statistics were used to summarize participant characteristics. Continuous variables are presented as median (interquartile range, IQR), and categorical variables as number (percentage). We employed a multi-step approach to evaluate both individual and joint effects of metal mixtures on birth weight. Spearman correlation coefficients were used to assess crude correlations between individual metal concentrations and birth weight. An elastic net regression model with 10-fold cross-validation was then used to identify the subset of metals most predictive of birth weight from the full set of 37. Based on the initial analyses, we focused on four key metals: Manganese (Mn), Cobalt (Co), Cadmium (Cd), and Cesium (Cs). These selected metals were evaluated in potential nonlinear dose–response relationships between each key metal and birth weight using restricted cubic splines.

To assess mixture effects, we applied several advanced mixture modeling approaches. Bayesian kernel machine regression (BKMR) evaluated pairwise interactions while accounting for correlated exposures. And generalized additive models (GAMs) tested for three-way interactions. Quantile g-computation estimated the overall joint association (and direction) of increasing all metals in a specific mixture by one quartile simultaneously.

To assess the robustness of our findings, we conducted several sensitivity analyses addressing potential sources of bias. We applied three hierarchical adjustment models with increasing covariate inclusion to evaluate residual confounding. The influence of missing data was examined by comparing results from multiple imputation with complete-case analyses. Robustness to outcome definition was assessed using gestational age- and sex-standardized birth-weight z scores. Potential selection bias due to loss to follow-up was addressed using inverse probability weighting (IPW), with weights estimated from logistic regression models including maternal age, BMI, ethnicity, and maternal height. The distribution of weights was examined to ensure no extreme values. Covariate balance before and after weighting was assessed using standardized mean differences (SMD). Weighted analyses were combined with multiple imputation to address missing covariate data. (eTables 4–7).

Missing covariate data were multiply imputed using chained equations (MICE), assuming missing at random. Full methodological details (eMethods), model specifications, and sensitivity analyses are provided in the Supplement. All analyses were conducted using R version 4.4.1.

3. Results

3.1. Study population characteristics

The table presents the demographic characteristics of the 2754 mother–infant pairs included. (Table 1) The median maternal age was 30 years (26–34), and pre-pregnancy BMI was 22.32 kg/m^2 (20.42–25.65). The median maternal height and pre-pregnancy weight were 167.0 cm (163.0–172.0) and 61.0 kg (55.4–69.00), respectively. Before pregnancy, 1026 (37.25%) pregnant individuals smoked, and 361 (13.11%) continued smoking during pregnancy. The median systolic and diastolic blood pressures in the third trimester were 115.83 mmHg (109.17–123.33) and 70.00 mmHg (65.00–75.50), respectively. Hypertensive disorders occurred in 262 (9.51%) of pregnancies, and 120 (4.36%) had diabetes either before or during pregnancy. Regarding socioeconomic status, 236 (8.57%), 233 (8.46%), and 140 (5.08%) were classified as low, medium, and high income, respectively. Most participants were Caucasian 2559 (92.92%).

As for the newborns, the median birth weight was 3368.00 g (3025.00–3725.00), birth length was 51.00 cm (49.00–53.00), and head circumference was 35.00 cm (34.00–36.00). The median gestational age at delivery was 39.00 weeks (38.00–40.00). Median APGAR scores at 5 and 10 min were both 10.00 (9.00–10.00). The proportion of male and female infants was 1459 (53.00%) to 1270 (46.11%).

Table 1
Maternal and Neonatal Characteristics (N = 2754).

Characteristics	Total(n = 2754) No. (%) with data	Median (IQR)
Pregnant participants		
Age, y	2735 (99.31)	30.0 (26.0–34.0)
Missing	19 (0.69)	NA
Height, cm	2634 (95.64)	167.00 (163.00–172.00)
Missing	120 (4.36)	NA
Weight at the beginning of pregnancy, kg	1750 (63.54)	61.00 (55.40–69.00)
Missing	1004 (36.46)	NA
BMI at the beginning of pregnancy, kg/m^2	2691 (97.71)	22.32 (20.42–25.65)
Missing	63 (2.29)	NA
Smoking before pregnancy		
Yes	1026 (37.25)	NA
No	1499 (54.43)	NA
Missing	229 (8.32)	NA
Smoking during pregnancy		
Yes	361 (13.11)	NA
No	1807 (65.61)	NA
Missing	586 (21.28)	NA
Systolic BP 3rd trimester of pregnancy, mm Hg	2688 (97.60)	115.83 (109.17–123.33)
Missing	66 (2.40)	NA
Diastolic BP 3rd trimester of pregnancy, mm Hg	2681 (97.35)	70.00 (65.00–75.50)
Missing	73 (2.65)	NA
Hypertension during pregnancy		
Yes	262 (9.51)	NA
No	1503 (54.58)	NA
Missing	989 (35.91)	NA
Diabetes before/during pregnancy		
Yes	120 (4.36)	NA
No	2625 (95.32)	NA
Missing	9 (0.32)	NA
Income		
Low	236 (8.57)	NA
Medium	233 (8.46)	NA
High	140 (5.08)	NA
Missing	2145 (77.89)	NA
Ethnicity		
Caucasian	2559 (92.92)	NA
Other	178 (6.46)	NA
Missing	17 (0.62)	NA
Newborn		
Birth weight, g	2754 (100.00)	3368.00 (3025.00–3725.00)
Birth length, cm	2722 (98.84)	51.00 (49.00–53.00)
Missing	32 (1.16)	NA
Head circumference, cm	2242 (81.41)	35.00 (34.00–36.00)
Missing	512 (18.59)	NA
Gestational age, week	2680 (97.31)	39.00 (38.00–40.00)
Missing	74 (2.69)	NA
APGAR 5 min	2361 (85.73)	10.00 (9.00–10.00)
Missing	393 (14.27)	NA
APGAR 10 min	2356 (85.55)	10.00 (9.00–10.00)
Missing	398 (14.45)	NA
Child sex		
Male	1459 (53.00)	NA
Female	1270 (46.11)	NA
Missing	25 (0.89)	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; NA, not applicable.

3.2. Maternal whole blood metal concentrations

The concentrations of 37 maternal metals in whole blood samples are presented in eTable 1, showing the geometric mean, median with IQR, and the limit of detection (LOD). These values provide an overview of the central tendency, dispersion, and analytical sensitivity of the measurements. Among the detected metals, selenium (Se) exhibited the highest mean concentration (58.174 μg/L), whereas several trace elements, including iridium (Ir), platinum (Pt), uranium (U), and gold (Au), showed low concentrations, all below 0.01 μg/L. The LODs varied across metals, reflecting differences in detection capabilities.

3.3. Associations between exposure to individual metals and birth weight

Spearman correlation analysis was conducted to evaluate the relationship between birth weight and metal concentrations (eFig. 2). Cobalt (Co) exhibited the strongest positive correlation (ρ = 0.103), followed by manganese (Mn) (ρ = 0.101), strontium (Sr) (ρ = 0.067), tin (Sn) (ρ = 0.067), barium (Ba) (ρ = 0.065), and molybdenum (Mo) (ρ = 0.038). Conversely, cadmium (Cd) (ρ = -0.070) showed the strongest negative correlation, followed by niobium (Nb) (ρ = -0.064), cesium (Cs) (ρ = -0.047), and tantalum (Ta) (ρ = -0.045). Additionally, the Spearman correlation coefficients of each pair of metals, indicating interactions, ranged from −0.21 to 0.61 (eFig. 3).

3.4. Associations between mixed metals exposure and birth weight

To identify key metals associated with birth weight, we employed Elastic Net regression models (Fig. 1). Among these, 27 metals were retained with non-zero coefficients. The top contributors included Mn (β = 57.86), Cd (β = -40.82), Co (β = 30.11), Cs (β = -25.52), and selenium (Se) (β = -25.32), which were identified as the most important metals associated with birth weight.

3.5. Identification of key metals and their nonlinear associations with birth weight

We identified four key metals associated with birth weight—Mn, Co, Cs, and Cd—using a combined approach of Spearman correlation analysis and Elastic Net regression. Notably, Mn and Co exhibited positive associations with birth weight, whereas Cs and Cd showed negative associations. Furthermore, the Spearman correlation matrix revealed weak to moderate inter-metal correlations (eFig. 2), indicating minimal multicollinearity concerns.

We further evaluated exposure–response relationships between each of the 4 selected metals and birth weight using restricted cubic spline (RCS) models (Fig. 2). After covariate adjustment, Mn was positively and linearly associated with birth weight (p for overall $<$ 0.001; p for nonlinear = 0.398). Co showed a positive and nonlinear association with

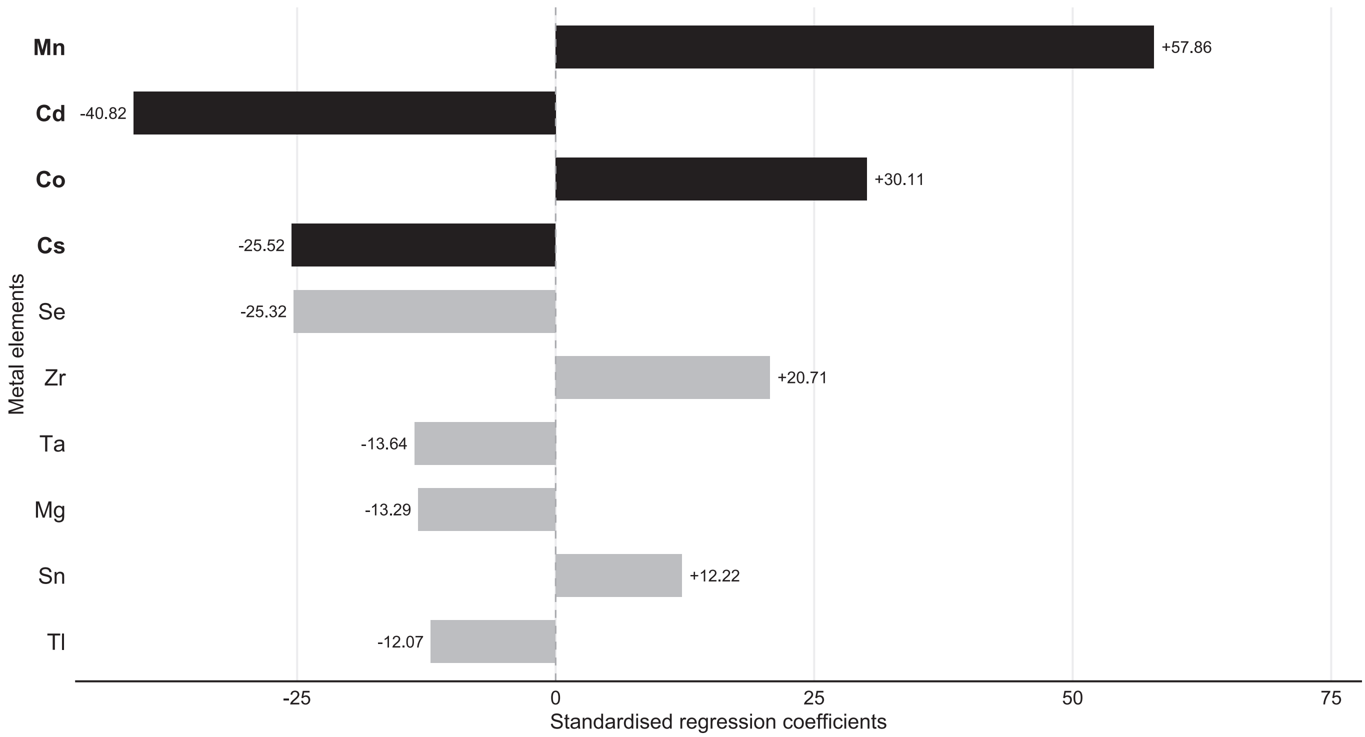

Fig. 1. Elastic Net Regression coefficients for Top 10 mixed metals and birth weight. Bars represent standardized regression coefficients per log-transformed unit increase in maternal whole blood metal concentration. The full dataset of 37 metals was analyzed, only the top 10 metals with non-zero coefficients are displayed. Models were adjusted for gestational age, maternal age, maternal BMI, smoking during pregnancy, hypertension, and infant sex.

birth weight, whereas Cs and Cd exhibited a significant nonlinear association with reduced birth weight. All nonlinear trends were statistically significant (p for nonlinear < 0.05).

3.6. *Interactions of key metals in relation to birth weight*

Pairwise interactions among Mn, Co, Cd, and Cs were assessed using BKMR. As shown in Fig. 3, bivariate association results from BKMR revealed potential interactions. The separation of curves was most pronounced for Mn and Co when conditioned on Cd or Cs, whereas the Cd–Cs pair showed comparatively weaker separation. For example, when Co and Cd concentrations were fixed at the 50th percentile, the exposure–response curve of Cs shifted upward as Mn increased from the 10th to the 90th percentile, indicating that the association between Cs and birth weight depended on Mn levels.

3.7. *Three-way interactions of key metals in relation to birth weight*

Generalized additive models (GAMs) identified statistically significant three-way interactions between metal mixtures and birth weight in all four models (all FDR-adjusted $p < 0.001$; eTable 2). To further characterize the direction and magnitude of these effects, we applied quantile g-computation.

In Model A (Mn × Co × Cs), the total mixture effect was significantly positive ($\beta = 37.34$ g, 95% CI: 5.64 to 69.05, $p = 0.021$), and in Model B (Mn × Co × Cd) the effect was similarly positive ($\beta = 44.06$ g, 95% CI: 12.96 to 75.15, $p = 0.0055$). In contrast, Models C (Cd × Cs × Mn) and D (Cd × Cs × Co) showed negative but non-significant total mixture effects ($\beta = -10.89$ g, $p = 0.507$; $\beta = -15.55$ g, $p = 0.354$, respectively).

Taken together with the stratified GAM plots (Fig. 4), these findings indicate that mixtures dominated by Mn and Co are associated with a higher birth weight, whereas combinations involving Cd and Cs attenuate these protective effects (eTable 3). Importantly, while GAM confirmed statistically significant interactions for all models, the non-significant qgcomp estimates for Models C and D suggest that the direction and strength of their effects may vary across exposure quantiles, highlighting possible heterogeneity in the mixture response.

3.8. *Sensitivity analyses*

Using three tiered adjustment models (Model 1: gestational age and infant sex; Model 2: additionally maternal age, maternal BMI, smoking during pregnancy, and hypertension; Model 3: further maternal height and ethnicity), the direction of associations for Mn, Co, Cs, and Cd with birth weight was consistent across all models. Similar patterns were observed when analyses were restricted to participants with complete data. Specifically, Mn and Co showed positive associations and Cs showed inverse associations with birth weight, while the association for Cd was attenuated and became non-significant after further adjustment (eTable 4). These findings indicate that the direction of the associations was generally consistent across different approaches for handling missing data.

When replacing birth weight with gestational age- and sex-standardized birth-weight z scores in the primary adjustment set (gestational age, infant sex, maternal age, maternal BMI, smoking during pregnancy, and hypertension), Mn and Co remained positively associated and Cs and Cd remained inversely associated (eTable 5). These findings show that the observed associations were consistent across alternative covariate specifications and outcome definitions. In addition, inverse probability weighting analyses combined with multiple imputation yielded results highly consistent with the main analyses, with similar directions and magnitudes of associations across all models (eTable 7), suggesting that loss to follow-up is unlikely to materially affect the findings.

4. Discussion

In this large German birth cohort, we systematically evaluated associations between multiple essential and toxic metals measured in maternal whole blood during late pregnancy and neonatal birth weight.

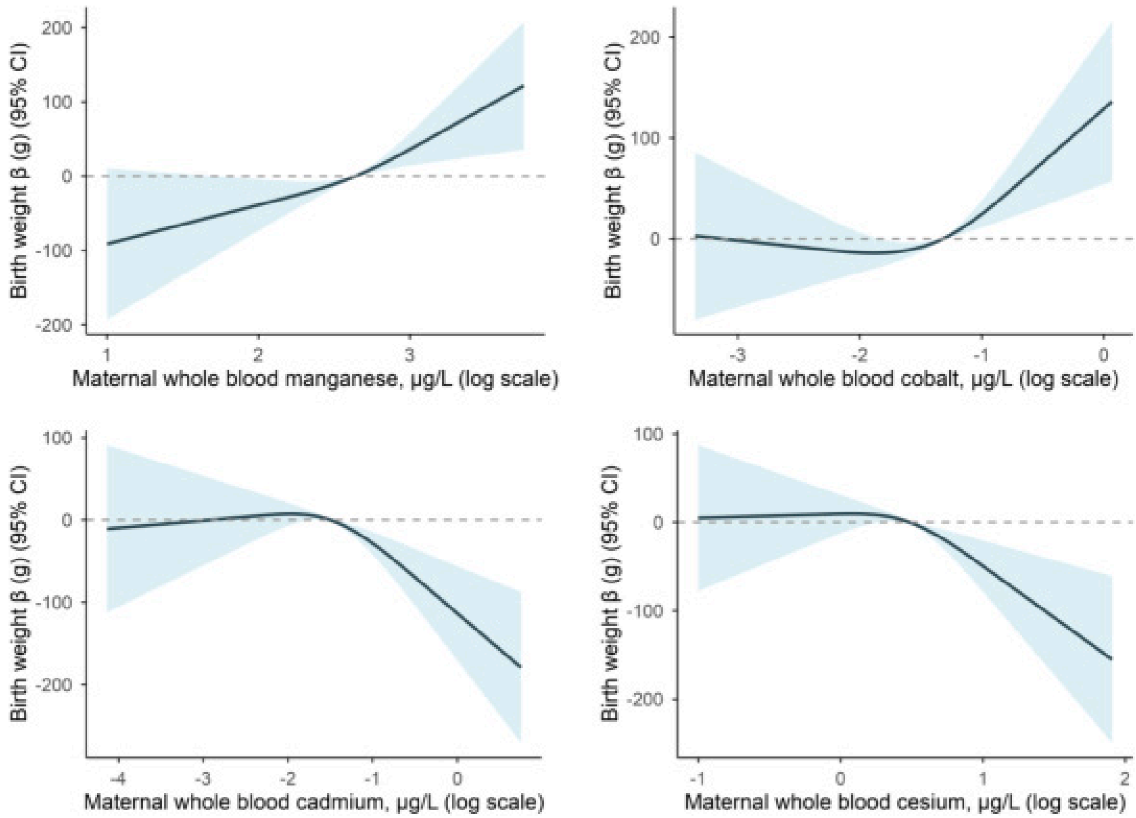

Fig. 2. Restricted cubic spline models between Mn, Co, Cs, Cd and birth weight. Abbreviations: CI, confidence interval. Restricted cubic spline models were used to estimate nonlinear associations between maternal whole blood concentrations of manganese (Mn), cobalt (Co), cesium (Cs), and cadmium (Cd) and neonatal birth weight (grams).Metal concentrations were log-transformed prior to analysis. Shaded areas represent 95% confidence intervals. All models were adjusted for gestational age, maternal age, maternal BMI, smoking during pregnancy, hypertension, and infant sex. P values for both overall and nonlinear associations are annotated in each plot.

Several essential elements, including manganese, cobalt, and molybdenum, as well as strontium and barium, were positively associated with birth weight, whereas potentially toxic or non-essential elements such as cadmium, cesium, niobium, tantalum, and tin were inversely associated. Mixture analyses further showed that essential elements were associated with less negative associations of toxic metals, whereas co-exposure to multiple harmful elements was associated with less favorable patterns. This study represents one of the largest European investigations to date examining late-pregnancy exposure to complex metal mixtures in relation to fetal growth.

Assessing maternal metal concentrations in late pregnancy is biologically meaningful, as this period represents a critical window of accelerated fetal growth and heightened placental transfer (Wei et al., 2023). However, maternal metal concentrations were assessed only once, immediately before delivery, which limits inference regarding critical windows of susceptibility across pregnancy. Because metals were measured in whole blood, including both plasma and cellular components, these measurements likely reflect integrated exposure over the preceding several weeks (approximately 4–6 weeks), rather than only very short-term exposure at sampling. In addition, previous studies suggest that metal concentrations in blood during pregnancy may be relatively stable and may reflect cumulative exposure burden (Taylor et al., 2014), and major exposure changes are unlikely in our cohort, as participants generally remained in the same residential environment and maintained broadly similar dietary and lifestyle habits. Therefore, late-pregnancy whole-blood concentrations may reasonably approximate habitual exposure during the final phase of pregnancy. Nevertheless, a single measurement does not allow differentiation between cumulative exposure and specific gestational windows of susceptibility, and interpretation should therefore remain cautious.

Distinct metals are likely to influence fetal growth through different biological pathways. In the present study, manganese and cobalt were consistently associated with higher birth weight across multiple analytic approaches. Manganese is an essential cofactor for numerous enzymes involved in mitochondrial function and antioxidant defense, and adequate maternal manganese status has been linked to improved fetal growth in several cohorts (Ashley-Martin et al., 2018; Hu et al., 2022). Cobalt, as the central component of vitamin B12, plays a role in DNA synthesis and cellular proliferation. The observed non-linear association between cobalt and birth weight is broadly consistent with some previous reports suggesting an optimal exposure range (Amegah et al., 2021). However, despite these biologically plausible mechanisms and supportive findings, the associations of manganese and cobalt with birth weight have not been entirely consistent across studies. For example, previous studies have reported non-linear or U-shaped associations between maternal manganese levels and birth weight, with higher exposure potentially associated with restricted fetal growth (Zota et al., 2009). Similarly, evidence regarding cobalt remains heterogeneous. Previous mixture-based analyses have reported non-linear associations with fetal growth, with effects varying across populations and exposure profiles (Howe et al., 2022). These discrepancies may reflect the biological duality of essential elements—where both deficiency and excess can be harmful—, as well as differences in exposure levels, timing of assessment during pregnancy, and methodological approaches across studies.

In contrast, cadmium is a well-established placental toxicant that can impair vascularization, induce oxidative stress, and disrupt nutrient transport, thereby restricting fetal growth (Huang et al., 2017; Inadera et al., 2020). Numerous studies have consistently linked prenatal cadmium exposure to lower birth weight and increased risk of small-for-

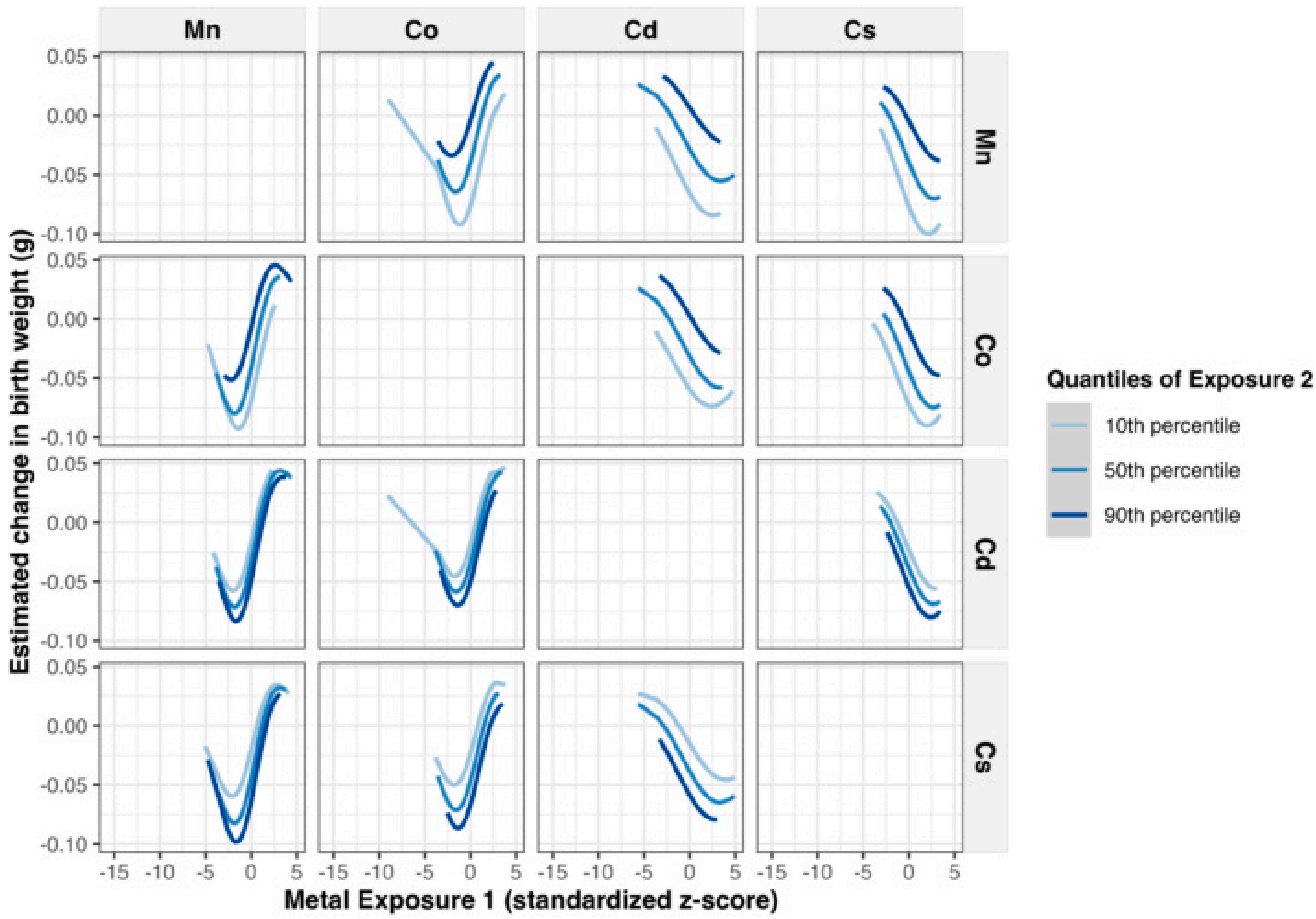

Fig. 3. Two-way interactions estimated by Bayesian kernel machine regression. Estimation of the bivariate association between each pair of metals and birth weight. Lines represent predicted effects at the 10th (light blue), 50th (blue), and 90th (dark blue) percentiles of the conditioning metal. Divergence of curves indicates evidence of interactions. All metal concentrations were measured in maternal whole blood (μg/L), log-transformed, and standardized. Models were adjusted for gestational age, maternal age, maternal BMI, smoking during pregnancy, hypertension, and infant sex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

gestational-age birth (Amegah et al., 2021). Cesium has been less extensively studied in pregnancy. In the general population, exposure is dominated by stable cesium, while radioactive cesium may contribute in specific environmental contexts. Previous ecological and cohort studies have suggested associations between cesium exposure and low birth weight (Scherb and Hayashi, 2020). In our study, higher maternal cesium concentrations were directly associated with lower birth weight, with non-linear exposure–response patterns suggesting potential thresholds of fetal sensitivity.

Because pregnant individuals are simultaneously exposed to multiple metals, evaluating interactions is essential. Our quantile g-computation analyses demonstrated that mixtures dominated by manganese and cobalt were associated with higher birth weight, consistent with Bayesian kernel machine regression results indicating that higher manganese levels were associated with weaker negative associations of cadmium and cesium with birth weight. A biologically plausible explanation for the buffering effect of Mn on Cd may involve oxidative stress and metal handling. Prenatal Cd exposure has been associated with reduced uteroplacental blood flow and impaired nutrient transport, contributing to restricted fetal growth (Khoshhali et al., 2020). In contrast, Mn may modulate these processes through its role in redox regulation and metal handling. Experimental evidence from in vitro studies has shown that Mn can attenuate Cd-induced cytotoxicity and reduce intracellular Cd accumulation, possibly through competition for shared metal transport proteins (Fujie et al., 2024). For Cs, however, the mechanism underlying the Mn–Cs pattern remains unclear. Although cesium may interfere with ion transport as a potassium analogue, evidence for Mn–Cs interaction during pregnancy is lacking; thus, this finding should be interpreted cautiously as hypothesis-generating. Such nutrient–toxicant antagonism has been reported in both experimental and epidemiological studies (Peraza et al., 1998; Liu et al., 2025). Conversely, cadmium appeared to attenuate the beneficial effects of essential elements, highlighting how toxic exposures may undermine nutritional protection. Together, these findings emphasize the importance of mixture-based approaches, which capture interactive and non-linear effects that would be missed by single-metal analyses (Lu et al., 2022; Takatani et al., 2022).

From a clinical and public health perspective, our findings underscore the need for integrated strategies during pregnancy. Reducing exposure to toxic metals remains essential, but ensuring adequate intake of essential trace elements may also support optimal fetal growth. Prenatal care may therefore benefit from combined attention to environmental exposure reduction and maternal nutritional status. At the population level, policies addressing environmental contamination of food and water, together with nutritional interventions, may offer synergistic benefits for perinatal health.

This study has several strengths, including the large, well-characterized European cohort, comprehensive profiling of essential and toxic metals in whole blood, and application of complementary mixture-modeling approaches. To better understand the complex relationships between metal mixtures and birth weight, we applied these

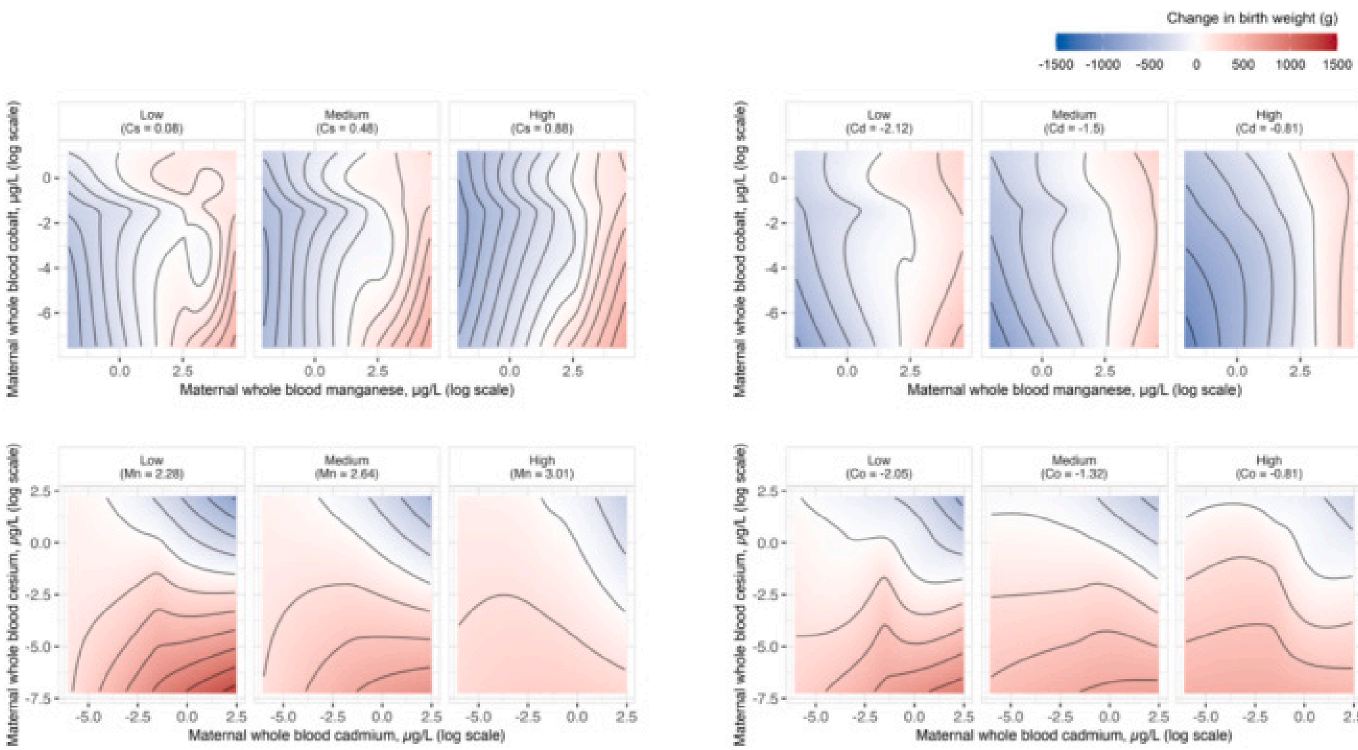

Fig. 4. Stratified GAM plots illustrating three-way interactions among metals on birth weight. Each panel displays the stratified partial effect surface of two metals across low, medium, and high levels of a third metal. Model A: Mn × Co × Cs; Model B: Mn × Co × Cd; Model C: Cd × Cs × Mn; Model D: Cd × Cs × Co. The color gradient reflects model-predicted birth-weight changes in grams. Darker red indicates a stronger positive association with birth weight, while darker blue reflects a stronger negative association. Stratification helps visualize potential moderating effects of the third metal. All models were adjusted for gestational age, maternal age, maternal BMI, smoking during pregnancy, hypertension, and infant sex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

approaches within a stepwise analytical framework. First, elastic net regression was used to identify a smaller set of key metals most strongly associated with birth weight from a large number of correlated exposures. Second, RCS models were used to examine whether these associations were linear or non-linear. Third, BKMR and GAMs were applied to explore potential interactions among metals, that is, whether associations varied across exposure levels. Finally, quantile g-computation was used to estimate the overall direction and magnitude of the combined mixture. Together, these methods provide a coherent and complementary framework for evaluating complex exposure mixtures.

Nevertheless, limitations should be acknowledged. Metal concentrations were measured at a single time point, limiting assessment of temporal variability and sensitive windows. Residual confounding by unmeasured factors should be considered. Although we adjusted for key maternal and clinical characteristics, unmeasured factors may influence both metal exposure and fetal growth. In particular, maternal diet and micronutrient supplementation, as well as co-exposure to other environmental contaminants (e.g., air pollution or organic pollutants), were not fully assessed. In addition, socioeconomic factors may contribute to residual confounding, as income data were missing for a substantial proportion of participants. As an observational study, causal inference is limited. Future research should incorporate repeated exposure measurements across pregnancy, integrate placental and molecular biomarkers to elucidate underlying mechanisms, and extend follow-up into later life to assess long-term health consequences. Advances in exposomics and mixture modeling will be critical for understanding the complex, interactive nature of prenatal environmental exposures.

5. Conclusion

In this large prospective cohort, we found that neonatal birth weight is shaped not by isolated toxic or essential metal exposures but by their combined presence in maternal circulation during late pregnancy. Manganese and cobalt were key elements associated with higher birth weight, whereas cadmium and cesium were associated with lower birth weight. Importantly, mixture analyses revealed that manganese was associated with weaker negative associations of cesium, while cadmium attenuated the benefits of essential elements. These results move beyond single-metal assessments to a mixture-based paradigm and highlight that maternal nutritional status may be related to variation in the associations between environmental exposures and birth outcomes. From a public health perspective, our findings support a dual approach: reducing toxic metal exposure while ensuring adequate intake of essential elements. Such integrated strategies may be more effective in improving perinatal outcomes and mitigating long-term health risks associated with low birth weight. Future studies with repeated measurements and mechanistic investigations are needed to further elucidate these interactions and guide targeted prenatal interventions.

6. Additional contribution

We would like to acknowledge members of the research team at the Department of Obstetrics, Charité University Hospital, who participated in participant recruitment, data collection, and data management.

7 Declaration of generative AI and AI-assisted technologies

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CRediT authorship contribution statement

Jiayi Xiang: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Xiaoli Zhang:** Data curation. **Katrin Huesker:**

Resources. **Yvonne Liu:** Resources. **Johann-Georg Hocher:** Resources. **Xin Chen:** Resources. **Zeyu Zhang:** Resources. **Huifang Zhang:** Resources. **Bernhard K. Krämer:** Writing – review & editing, Supervision, Resources. **Volker von Baehr:** Writing – review & editing, Supervision, Resources. **Berthold Hocher:** Writing – review & editing, Writing – original draft, Supervision, Project administration.

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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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2026.110244.

Data availability

The data that has been used is confidential.

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