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Prenatal exposure to metal mixtures and fetal growth outcomes: findings from the PIPA Project, Brazil

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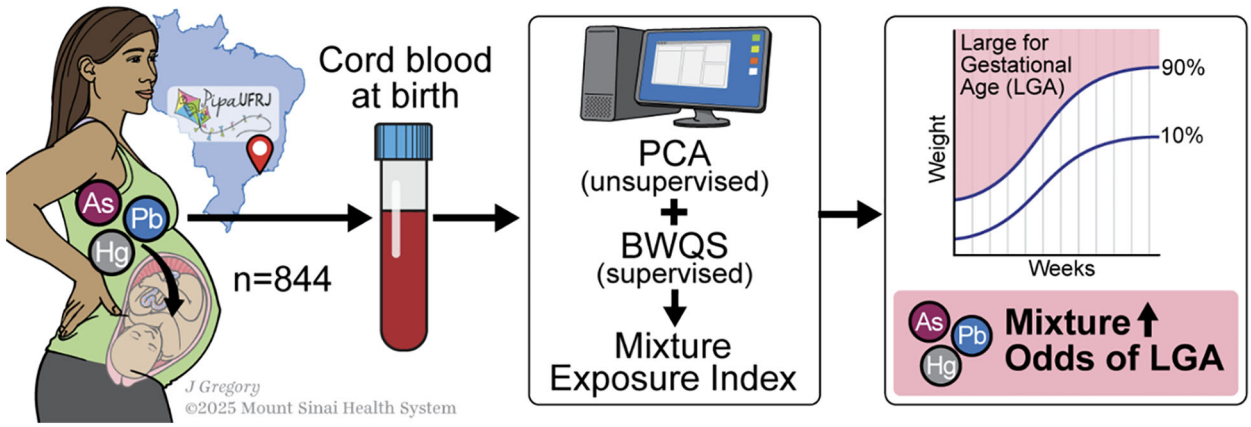
Introduction: Exposure to arsenic (As), lead (Pb), and mercury (Hg) can occur in utero, as these metals cross the transplacental barrier and may affect birth outcomes. This study aimed to investigate the associations between prenatal individual and mixture exposures to As, Pb, and Hg and fetal growth outcomes.

Methods: We conducted a cross-sectional analysis of 721 participants from the PIPA Project (Brazil). Umbilical cord blood samples were analyzed for metal concentrations. Outcomes included birth weight z-score (BWZ) and birth weight categories by gestational age: small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA). Associations between individual metals and outcomes were assessed using regression models. Mixture associations were evaluated using Principal Component Analysis (PCA) and Bayesian Weighted Quantile Sum (BWQS) regression.

Results: Individually, Pb and Hg concentrations were positively associated with BWZ (Pb β = 0.154, 95% CI: 0.04–0.262; Hg β = 0.072, 95% CI: 0.014–0.137). Pb was linked to higher odds of LGA (OR = 2.48, 95% CI: 1.53–4.02), whereas Hg was negatively associated with odds of SGA (OR = 0.27, 95% CI: 0.11–0.67). PCA identified a global exposure component (Hg, As, Pb) positively associated with BWZ (β = 0.090, 95% CI: 0.020–0.158) and LGA (OR = 1.44, 95% CI: 1.07–1.94). BWQS confirmed positive mixture associations with BWZ (β = 0.106, 95% CrI: 0.069–0.141) and LGA (OR = 1.45, 95% CrI: 1.12–1.89), and an inverse association with SGA (OR = 0.80, 95% CrI: 0.65–0.96). Pb was the main driver of the LGA mixture association (weight: 62%), while SGA associations were driven by both Pb (40%) and Hg (34%).

Discussion: Findings suggest that prenatal metal co-exposure is associated with an upward shift in fetal growth, with consistent results across single-pollutant and mixture statistical methods.

KEYWORDS
birth weight, child environmental health, cord blood, endocrine disruptors, fetal development, infant, large for gestational age, metal mixtures



GRAPHICAL ABSTRACT

Highlights

- Prenatal exposure to Pb, Hg, and As mixture is associated with higher birth weight z-scores.
- Lead and mercury co-exposure was associated with higher odds of LGA.
- Mercury exposure alone or combined with arsenic was inversely associated with SGA births.
- PCA identified global metal co-exposure and a Pb-As contrast driving fetal growth patterns.
- Supervised (BWQS) and unsupervised (PCA) mixture models yielded convergent results.

Introduction

Human exposure to arsenic (As), lead (Pb), and mercury (Hg) can occur *in utero*, considering the ability of these chemicals to cross the transplacental barrier (1), there is increased interest in examining the potential combined effects of these metals on fetal and infant development. Studies carried out on umbilical cord blood indicate high detection rates of these metals, and their concentrations are highly correlated with concentrations measured in the mother's blood (Figueiredo, 2020). Once reaching the fetus, these elements can accumulate in tissues, causing damage to developing organs and systems (1). The individual effects of these metals on fetal development have been well documented. They are among the most studied toxic metals in relation to fetal growth. They have been associated with adverse birth outcomes such as reduced birth weight, alterations in head circumference, and an increased risk of prematurity, predominantly showing negative associations (2).

Pb readily crosses the placenta and may interfere with calcium metabolism and placental function, potentially affecting fetal growth; prenatal Pb exposure has been associated with lower birth weight and an increased risk of small for gestational age (SGA) infants (3). Hg, particularly methylmercury, accumulates in fetal tissues and may affect placental function and fetal development, with studies reporting inverse associations between maternal Hg levels and birth weight (4). Prenatal As exposure has also been associated with oxidative stress, endocrine disruption, and impaired placental vascularization, mechanisms that may contribute to altered fetal growth and lower birth weight (5). Considering that these metals may co-occur in the environment, combined exposure may influence fetal growth through multiple and potentially interacting biological pathways (6).

Fetal growth, however, is a complex process determined by the interplay of maternal, fetal, placental, metabolic, nutritional, and socioeconomic factors. Maternal anthropometric and metabolic characteristics are particularly important determinants of fetal growth. Maternal diabetes, for example, is a well-established risk factor for excessive fetal growth and LGA, partly through alterations in maternal-fetal glucose and insulin homeostasis. Maternal BMI and hypertensive disorders may also influence fetal growth through metabolic and placental pathways. Therefore, associations between prenatal environmental exposures and birth weight should be interpreted within the broader context of established maternal and fetal determinants of growth. Accounting for these factors is particularly relevant when investigating LGA, an outcome that may reflect a different pattern of fetal growth disturbance from the growth restriction traditionally considered in studies of prenatal metal exposure.

A recent systematic review (2) highlighted that environmental exposure to As, Hg, and Pb is generally associated with lower birth weight. Some studies have also reported associations between prenatal metal exposure and an increased risk of SGA, whereas others have found no significant associations. However, relatively few studies have examined whether prenatal exposure to metals is associated with excessive fetal growth or LGA, either for individual metals or for metal mixtures (2). This represents an important gap because LGA is not necessarily a benign outcome. Fetal overgrowth may reflect disturbances in maternal-fetal glucose and insulin homeostasis and persistent alterations in metabolic regulation (7).

In a systematic review and meta-analysis of 42 studies including 841,325 individuals, Zhang et al. (7) found that LGA was associated with higher odds of overweight/obesity, hypertension, and metabolic syndrome, suggesting that LGA may represent an early marker of susceptibility to adverse cardiometabolic outcomes later in life. Thus, considering both SGA and LGA may provide a more comprehensive assessment of the potential relationship between prenatal metal exposure and fetal growth.

Additionally, these three metals are ubiquitous compounds, and most human populations are exposed simultaneously through air pollution, food, water, and behavioral habits such as smoking (8). Such co-exposure is chronic, as these metals persist in environmental media over the life course, continuously generating overlapping and combined exposures (9).

In Brazil, the site of our study, the landscape of environmental metal contamination is characterized by an intrinsic heterogeneity rooted in regional cultural, industrial, and urban development dynamics. However, regional studies have traditionally prioritized mercury (Hg) exposure within extractive contexts among riverine populations (10). In large, densely populated urban centers, such as Rio de Janeiro, co-exposure to As, Pb, and Hg results from intense industrial activity, air pollution, and heavy vehicular traffic (11). Few studies have addressed urban exposure in Brazil.

Previous investigations within the Childhood and Environmental Pollutant Project (PIPA) conducted on a birth cohort demonstrated that prenatal exposure to As, Pb, and Hg is ubiquitous within the study population (12). The observed median concentrations, particularly of Pb, exceed the thresholds reported in several cohorts from developed countries, suggesting a persistent impact from adjacent industrial complexes and the failure of large-scale environmental monitoring mechanisms (13). Such findings reinforce the need to consider the unique characteristics of the Brazilian socio-environmental context when assessing maternal and child health risks.

Therefore, we leverage data from the PIPA birth cohort study, whose aim is to investigating environmental pollutant effects on child development. We applied different analytical approaches to investigate associations between intrauterine exposure to As, Hg and Pb, individually and as a mixture, and birth outcomes.

Methods

Study design and population

Data are from the PIPA birth cohort. The inclusion criteria were that mothers resided in the city of Rio de Janeiro, were 16 years or older, and delivered at the Federal University of Rio de Janeiro Maternity School Hospital. Pregnant women were recruited between the 28th week of gestation and delivery, from June 2021 to July 2022. The cohort initially recruited 914 participants. Of these, 13 were excluded because they lived outside the city of Rio de Janeiro, leaving 901 eligible mothers. Among these women, 59 delivered in other health facilities, and therefore their newborns were not included in the cohort. Of those 844, 721 had cord blood samples and the necessary outcome and covariate data for analyses (Figure 1) (11).

The participation of mothers and babies, as well as sample collection, was carried out only after the mothers read and signed a Free and Informed Consent Form. The project was approved by the Federal University of Rio de Janeiro Maternity Hospital ethics committee (No: 6.494.730).

Umbilical cord blood metals exposure

Umbilical cord blood samples were collected at the time of birth by a trained hospital nursing team and stored in a refrigerator between 2 °C and 7 °C for up to 48 hours for As, Cd, Hg and Pb

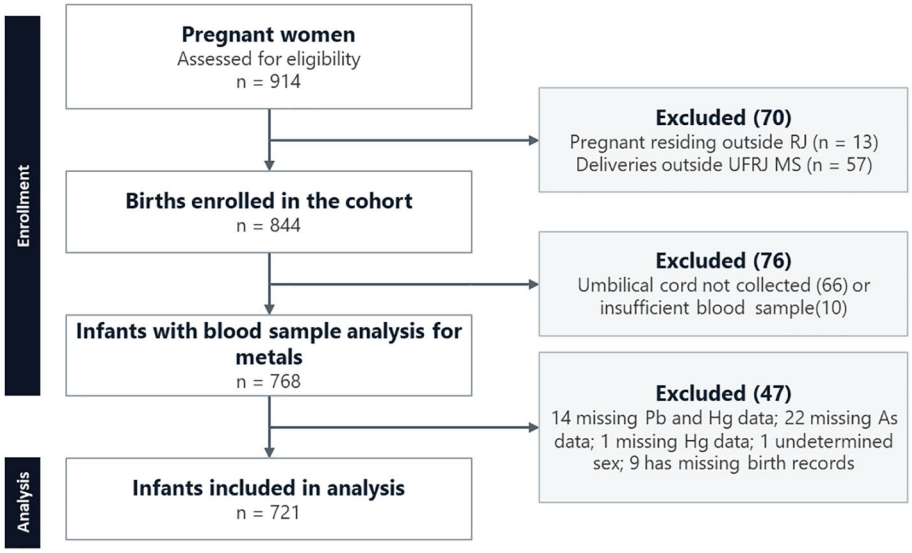


FIGURE 1
Flow diagram of participant selection based on the SRTOBE guidelines (14).

analyses. The samples were then transported to the Diagnosis of Brazil laboratory, where they were kept in a freezer at -4 °C until the time of analysis. Pb and Hg were quantified in whole blood, whereas As was measured in serum. The analyses were performed by inductively coupled plasma source mass spectrometry (ICP-MS). The limits of detection (LOD) were 0.1 µg/L for all three metals. For the data analysis, Pb values were converted to µg/dL. Only metals with detection rates over 60% were maintained in the mixture analysis, namely As, Hg and Pb (15). Cd was only detected in 15% of samples and was excluded from further analyses. For measurements below LOD, values were substituted with $LOD/\sqrt{2}$ (15).

Birth outcomes

The primary outcomes were birth weight and adequacy for gestational age. Birth weight was analyzed as a continuous variable using z-scores calculated according to the Intergrowth-21st standards. Additionally, newborns were categorized into three groups based on gestational age adequacy: small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA).

Covariates

To characterize the study population, data were collected on both maternal and infant profiles. Maternal sociodemographic and lifestyle information was obtained via questionnaire at enrollment, including per capita family income, years of schooling, and age (all analyzed as continuous variables). Maternal anthropometric status was evaluated through pre-pregnancy body mass Index (BMI, kg/m^2) whose data was collected through prenatal pre-records as a continuous variable. Standard World Health Organization (WHO) cut-offs (Underweight:<18.5, Normal weight: 18.5-24.9, Overweight: 25.0 - 29.9, and Obesity: > 30.0 kg/m^2) were used for descriptive categorization.

Maternal-reported clinical history (diabetes mellitus and hypertension) and lifestyle factors (tobacco, drug, and alcohol use during pregnancy) were recorded as dichotomous variables (Yes/No). For diabetes mellitus, a positive report included either pregestational or gestational diabetes, as both conditions may influence fetal growth through alterations in maternal glucose and insulin homeostasis. Similarly, hypertension included both pre-existing and gestational hypertension, as hypertensive disorders may affect fetal growth through alterations *in utero*placental perfusion and placental function. Maternal anthropometric status was evaluated through pre-pregnancy Body Mass Index (BMI, kg/m^2), extracted from maternal prenatal care records.

These conditions were considered potential confounders in the association between prenatal metal exposure and birth weight. At delivery, newborn data, including sex, gestational age (weeks), and preterm status, were documented. Maternal age, education, smoking, alcohol consumption, diabetes, hypertension, BMI pre gestational (kg/m^2 continuous), infant sex, and gestational age were considered potential confounders in the multivariable models.

Statistical analysis

The population was characterized based on socioeconomic and demographic data analyses and maternal clinical condition and behavior during pregnancy. Relative measures, measures of central tendency and variability were described. To describe the population's exposure patterns, the detection rate of each metal (% > Limit of Detection - LOD) and concentration distributions were calculated employing median percentiles, geometric mean, and maximum detected value. Skewness and kurtosis measures showed a right-skewed distributions with positive kurtosis. Exposure was assessed through metal concentrations measured in umbilical cord blood. Concentrations were categorized into higher and lower levels based on the median cutoff for each metal (Pb: 0.8 µg/dL; Hg: 0.8 µg/L; As: 0.13 µg/L). For analyses involving continuous variables, values were natural log-transformed to stabilize variance, reduce skewness, and minimize the influence of extreme observations.

Statistical associations were evaluated using two main approaches: multiple linear regression was applied to assess the relationship between continuous exposure variables and birth weight z-scores (BWZ), while multinomial logistic regression was employed to examine the association between categorized exposure levels and birth weight status, using appropriate for gestational age (AGA) as the reference group compared to small for gestational age (SGA) and large for gestational age (LGA). To account for the potential increase in Type I error due to multiple hypothesis testing, p-values from the individual regression models were adjusted using the Benjamini-Hochberg False Discovery Rate (FDR) correction.

To measure the combined effects, the following approaches were used: First, logistic regression with interaction terms between metals was applied according to exposure categories, with AGA as the reference outcome, comparing the occurrence of SGA and LGA. A set of confounding variables was selected *a priori* based on theoretical relevance and previous literature. A forced entry method was used, in which all potential confounders, including maternal age, education, smoking, alcohol consumption, diabetes, hypertension, and infant sex, were kept in the final models regardless of their statistical significance. Second, PCA was used to identify metal exposure patterns and determine exposure groups. This approach allows the establishment of factors that capture interdependence among variables (16), reducing dimensionality (17). Two components were generated (Supplementary Material), which were used as exposure indices (16) in linear regression for continuous outcomes and logistic regression for categorical outcomes. PCA analyses were conducted using SPSS v.21.

Finally, a supervised Bayesian Weighted Quantile Sum (BWQS) regression (18) was applied to evaluate the associations between the natural log-transformed metal mixture (As, Hg, and Pb) and birth outcomes (BWZ, LGA, and SGA). This approach estimates the overall effect of the mixture and the individual weights of each component, reflecting their relative importance in the detected associations. Unlike traditional WQS regression, BWQS does not require the pre-specification of association directionality (18). For

the continuous outcome (BWZ), a Gaussian link function was used, while for the categorical outcomes (LGA and SGA), the models were implemented with a binomial link function (logistic BWQS), using infants with adequate weight for gestational age (AGA) as the reference group. All BWQS models were adjusted for maternal age, maternal education, smoking, alcohol consumption, Mother's BMI pre-gestational (kg/m^2), pre-existing or gestational diabetes and hypertension, infant sex, and gestational age at delivery. Gestational age at delivery was retained as a continuous covariate across all adjusted models to control for residual intra-week growth variation and potential imprecision in gestational age dating, as well as to reduce unexplained variance in birth outcomes.

All models applied an uninformative normal prior with 20,000 iterations, 5,000 warm-ups, and a thinning of 10. Convergence was confirmed by a potential scale-reduction statistic ($\hat{R}$) approximately equal to 1, indicating optimal Hamiltonian chain stability. Statistical significance was assessed using 95% credible intervals (CrI) (19). All analyses were performed in RStudio version 4.3.3, using the *BWQS* package.

Results

Study population characteristics

Maternal age ranged from 16 to 46 years, with a mean age of 29.2 years (SD 6.9), and 73% self-identified as non-white. The median per capita monthly income observed in the population was US$144.2 (IQI 86.9–232.5). Among the studied families, 22% received monthly government assistance, and 54.2% lived in areas of greater social vulnerability (slums). 5.6% of households were not covered by the water supply network, 3% lacked sewage treatment services, and 9% did not have regular garbage collection. Most mothers (75%) had a maximum of 12 years of study (secondary education), 25% attended higher education (equal or more than 13 years of study). Regarding maternal habits, 7.9% reported smoking during pregnancy. Additionally, 39.9% of the mothers reported having consumed alcohol during pregnancy.

The birth profile indicated that the babies were approximately equal with males at 51.7%, 5.6% were SGA, and 14.4% were premature, with head circumference ranging from 25 to 39 cm, with 2.8% classified under below normal (Table 1).

Population metal exposure

A detection rate (%>LOD) of 98.9% was observed Pb, 94.5% for Hg and 60.5% for As. The investigated metals presented an asymmetric distribution with a right deviation (asymmetry>1). The largest deviations were observed for As (asymmetry 9.0 - kurtosis 104.1) and Pb (asymmetry 6.3 - kurtosis 60.9) (Table 2). A positive correlation was observed between Pb and Hg (p=0.000) and between Hg and As (p=0.000) concentrations (Figure 2).

Outcome distribution

Among the analyzed babies, 5.6% were SGA and 8.5%, LGA. prevalence of LGA babies indicated a significant difference among mothers with reported pre or gestational diabetes. Exposure to tobacco, prematurity and sex were associated with the AGA condition (Table 1).

Individual metal associations

A significant difference in Pb levels was observed among the groups (p=0.003), with the highest median in the LGA group (1.1 µg/dL) compared to AGA (0.8 µg/dL) and SGA (0.7 µg/dL). For Hg, although the difference was of marginal statistical significance (p=0.053), a clear increasing gradient was identified: median concentrations rose progressively from the SGA (0.5 µg/L) to the AGA (0.7 µg/L) and LGA (0.9 µg/L) categories. No significant differences or trends were observed for As (p=0.894) (Table 1).

A weak positive linear correlation was noted between log-transformed Pb and Hg concentration and birth weight Z scores (Pb adjusted B = 0.154 p = 0.005; Hg adjusted B = 0.072 p = 0.001), while no linear relationship was noted for As (Table 3). The AGA analysis indicated a positive relationship between Pb and LGA (ORa = 2.48; IC 95% 1.53 – 4.02). Hg was positively associated with LGA (ORa = 1.30; IC 95% 0.97 – 1.75) (Table 4). While the group with Hg above the median pointed to a protective effect on SGA (OR 0.27; 95% CI 0.11 – 0.67).

Combined metal associations

The regression analysis showed that the interaction between the highest exposure categories of Pb and Hg was positively associated with LGA (ORa = 2.15; 95% CI: 1.16–3.99), while the association with SGA was inverse but not statistically significant (ORa = 0.61; 95% CI: 0.23–1.60). When As was added to the Pb–Hg interaction, the association with LGA was attenuated and lost statistical significance (ORa = 2.15; 95% CI: 0.93–4.99), suggesting that arsenic modifies the effect but does not produce a robust association. Combined exposure to Hg and As was inversely associated with SGA, indicating a significant reduction in occurrence (ORa = 0.23; 95% CI: 0.07–0.72), and positively associated with AGA (ORa = 1.45; 95% CI: 0.64–3.45). When Pb was included in this interaction, the association with LGA became stronger but remained non-significant (ORa = 2.15; 95% CI: 0.93–4.99) (Table 4).

Principal component analysis

In the PCA analysis, the Kaiser-Meyer-Olkin (KMO) test indicated data adequacy (KMO = 0.508) with a 0.001 significance verified by the Bartlett sphericity test.

Two principal components were extracted, together explaining 76.4% of the total variance. The first component (Eigenvalue = 1.28; 42.7% of variance) best summarized the shared variance among metals, with mercury showing the highest loading (0.81), followed

TABLE 1 Mother and birth characteristics and metal exposure patterns according to gestational age adequacy.

Characteristics	Total (n=721)	SGA (N = 41)	AGA (n=618)	LGA (n=62)	*P*
Mother´s age years Mean (SD)	29.2 (6.9)	27.3 (6.8)	29.3 (6.8)	29.9 (7.0)	0.154[a]
BMI (pre gestational)					
<18.5	31	5 (16,1%)	26 (83.9%)	0	**0.010**[b]
18.5– 24.9	264	23 (8.7%)	227 (86.0%)	14 (5.3%)	
25 – 29.9	204	6 (2.9%)	175 (85.8.0%)	23 (11.3%)	
>30	222	7 (3.2%)	190 (85.6%)	25 (11.3%)	
Schooling (%)					
≤12 years	538	29 (5.4%)	461 (85.7%)	48 (8.9%)	0.914[b]
>12 years	180	11 (6.1%)	154 (85.6%)	15 (8.3%)	
Tobacco USE (%)					
Yes	56	**9 (16.1%)**	43 (76.8%)	4 (7.1%)	**0.017**[b]
No	665	**32 (4.8%)**	574 (86.5)	59 (8.7%)	
Alcohol Use (%)					
YES	287	**24 (8.4%)**	246 (85.7%)	**17 (5.9%)**	**0.004**[b]
No	431	**16 (3.7%)**	369 (85.6%)	**46 (10.7%)**	
Diabetes (%)					
Yes	40	0	30 (75.0%)	**10 (25.0%)**	**0.000**[b]
No	681	41 (6.0%)	588 (86.3%)	**53 (7.7%)**	
Hypertension (%)					
Yes	92	5 (5.4%)	81 (88.0%)	6 (6.5%)	0.715[b]
No	629	36 (5.7%)	537 (85.4%)	57 (9.0%)	
Premature (%)					
Yes	104	**14 (13.5%)**	83 (79.8%)	7 (6.7%)	**0.001**[b]
No	617	**27 (4.3%)**	535 (86.7%)	56 (9.1%)	
Sex (%)					
Female	373	**28 (7.5%)**	320 (85.7%)	**25 (6.7%)**	**0.017**[b]
male	348	**13 (3.7%)**	298 (85.6%)	**38 (10.6%)**	
Metals – Median (IQR)					
As µg/L	0.13 (<LOD – 0.29)	0.11 (<LOD – 0.25)	0.13 (<LOD – 0.29)	0.14 (<LOD – 0.35)	0.894[c]
Pb µg/dL	0.8 (0.6 – 1.2)	0.7 (0.5 – 1.1)	0.8 (0.6 – 1.2)	1.1 (0.7 – 1.75)	**0.003**[c]
Hg µg/L	0.8 (0.4 – 1.5)	0.5 (0.3 - 0.95)	0.7 (0.4 – 1.5)	0.9 (0.4 – 2.2)	**0.053**[c]

IQR, Interquartile Range.
LOD, Limit of Detection.
[a]One way ANOVA test.
[b]Chi square Test.
[c]Kruskal Wallis.
Values in bold are statistically significant at $p < 0.05$.

by arsenic (0.63) and lead (0.48). The second component (Eigenvalue = 1.01; 33.7% variance) represented the contrast between lead (0.79) and arsenic (-0.62), indicating distinct exposure patterns.

Linear regression analyses demonstrated that the global index (PCA1) was positively associated with birth weight Z-scores. In the crude model, the association was significant (B = 0.111; 95% CI: 0.036–0.180; p = 0.003) and remained significant after adjustment (B = 0.090; 95% CI: 0.020–0.158; p = 0.011) (Table 5). Each unit increase in the log-transformed PCA exposure index is associated with an average increase of 0.09 points in the birth weight Z-score (BWZ). This effect reflects the combined influence of proportional increases in metal exposure (Hg, As, Pb). The second index (PCA2) also showed a weaker but significant association in the adjusted model (B = 0.073; 95% CI: 0.005–0.141; p = 0.030) (Table 5). In practical terms, it indicates that higher relative exposure to the metal mixture is linked to a modest but measurable upward shift in BWZ, consistent with the observed higher odds of LGA.

Logistic regression analyses highlighted distinct effects on birth weight adequacy. For the PCA1, no significant association was observed with SGA (ORa = 0.83; 95% CI: 0.57–1.20; p = 0.31), but a positive association was found with LGA (ORa = 1.44; 95% CI:

TABLE 2 Metal concentration detection and distribution.

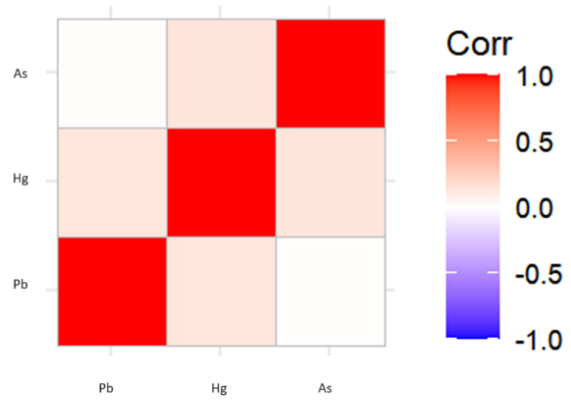
Metals	%>LOD	M value	GM[a]	P25	P50	P 75	P90	P95	Kurtosis	Asymmetry
Pb µg/dL	98.9	13.7	0.87	0.6	0.8	1.2	1.9	2.4	60.9	6.3
Hg µg/L	94.5	11.6	0.82	0.4	0.8	1.5	2.9	4.0	12.1	2.9
As µg/L	60.5	11.3	0.29	<LOD	0.13	0.3	0.7	1.0	104.1	9.0

[a]GM, Geometric Mean calculated only considers results where metal was detected.
LOD, Limit of Detection.

1.07–1.94; p = 0.02). For the second index, no significant association was observed with SGA (ORa = 0.79; 95% CI: 0.55–1.13; p = 0.198), but a robust association was detected with LGA (ORa = 1.65; 95% CI: 1.20–2.28; p = 0.002) (Table 5).

BWQS regression

A similar trend between the investigated metal mixture and outcomes was observed; the BWQS regression models, adjusted for maternal and neonatal covariates, confirmed a consistent association between the metal mixture and BWZ, LGA, and SGA. For the continuous outcome, a significant positive association with BWZ was detected (β= 0.106; 95% CrI: 0.069, 0.141), indicating that an increase in the mixture index is associated with higher BWZ. Analysis of the posterior weights identified Lead (Pb = 0.407) and Arsenic (As = 0.381) as the primary contributors to this positive association, followed by Mercury (Hg = 0.211). This trend was further supported by the categorical models: the mixture was positively associated with the risk of LGA (OR = 1.45; 95% CrI: 1.12, 1.89) and inversely associated with the risk of SGA (OR = 0.80; 95% CrI: 0.65, 0.96). Analysis of the posterior weights revealed that Pb was the primary driver across all models, with the highest contribution to the risk of LGA (62%). While Hg and As showed moderate and varying contributions to the mixture effect, Hg gain increased relevance in the SGA model (34.5%), and As contributed more significantly to the BWZ (38.1%) and LGA (20.8%) associations. These findings indicate that Pb is the dominant driver of the mixture's effect on fetal growth, while Hg and As play secondary, less prominent roles across all evaluated outcomes (Table 6). Among confounders included, maternal smoking (β= -0.372; 95% CrI: -0.625, -0.125) and maternal diabetes (β= 0.538; 95% CrI: 0.228, 0.847), both of which were also significantly associated with BWZ (Supplementary Table S3).



	Pb	Hg	As
Pb	1		
Hg	**0.16 (*0.000*)**	1	
As	-0.024 (*0.51*)	**0.224 (*0.000*)**	1

FIGURE 2
Metal matrix correlation. Bold values indicate statistically significant correlations (p < 0.05).

Discussion

We found that higher metal mixture exposure was associated with higher BWZ in both unsupervised and supervised mixture models in this Brazilian population. In addition, combined exposure to As, Hg, and Pb was associated with higher odds of being born LGA and lower odds of being born SGA. The positive associations observed for BWZ and LGA are somewhat unexpected, given that most previous studies of prenatal exposure to toxic metals have focused on impaired fetal growth and increased risk of SGA. These findings therefore warrant careful interpretation, particularly considering the multiple maternal, metabolic, nutritional, placental, and fetal factors that contribute to fetal growth. Although higher birth weight may initially appear to indicate more favorable fetal growth, the association with LGA should not be interpreted as evidence of a beneficial effect of metal exposure. LGA is a clinically relevant marker of excessive fetal growth and has been associated with increased risks of childhood obesity, hypertension, and metabolic syndrome later in life (7). Therefore, the positive association observed in our study may reflect altered fetal growth and metabolic regulation rather than improved fetal health.

Several studies have investigated associations between exposure to metal mixtures, including As, Hg, and Pb, and birth weight. Some have reported positive associations with SGA, with greater exposure associated with higher frequencies of SGA, whereas others have found no significant associations (2). In contrast, few studies have examined LGA as an outcome. Indeed, only two studies included LGA in a recent systematic review, and the available evidence was inconclusive (2). Although SGA has been extensively investigated in environmental epidemiology, LGA may also have important implications for child health, including increased risks of childhood obesity and metabolic disorders. Our findings therefore support the importance of considering the full spectrum of fetal growth outcomes when investigating the potential effects of prenatal exposure to environmental contaminants.

TABLE 3 Individual effects on continuous (BWZ) and categorical (AGA) outcome.

Metal	BWZ			
	β adj	*CI 95%*	*p value*	FDR (q value)
Pb (Log^n)[a]	**0.154**	**0.04 – 0.262**	***0.005*** *	**0.015**
Hg (log^n)[a]	**0.072**	**0.014 – 0.137**	***0.030****	**0.045**
As (log^n)[a]	0.008	-0.063 – 0.079	0.831	0.831
Metal	**SGA**			
	OR adj	*CI 95%*	*p value*	FDR (q value)
Pb (Logn)[b]	0.63	0.35 – 1.14	0.127	0.381
Hg (log^n)[b]	0.86	0.61 – 1.21	0.374	0.561
As (log^n)[b]	1.04	0.71 – 1.53	0.833	0.833
Metal	**LGA**			
	OR adj	*CI 95%*	*p value*	FDR (q value)
Pb (Log^n)[b]	**2.48**	**1.53 – 4.02**	**0.000**	**0.000**
Hg (log^n)[b]	1.30	0.97 – 1.75	0.084	0.126
As (log^n)[b]	0.97	0.71 – 1.32	0.828	0.828

[a]Linear regression metal concentration, log natural and BWZ.
[b]Logistic Regression metal concentration log natural and AIG categories (Appropriate for Gestational Age as reference).
Adjusted by maternal age, education, smoking, alcohol consumption, Maternal BMI (K/m^2), diabetes, hypertension, infant sex, and gestational age.
Values in bold are statistically significant at $p < 0.05$.

The positive associations observed for BWZ and LGA should also be interpreted in the context of established determinants of fetal growth. Fetal growth is a complex process influenced by maternal anthropometric, metabolic, nutritional, socioeconomic, placental, and fetal characteristics. Maternal diabetes, in particular, is a well-established determinant of excessive fetal growth and LGA through alterations in maternal-fetal glucose and insulin homeostasis. In our study population, maternal diabetes was associated with LGA, and it was also positively associated with BWZ in the BWQS model. Maternal BMI, hypertension, age, smoking, infant sex, and gestational age were also considered in the adjusted analyses. Nevertheless, residual confounding cannot be excluded, particularly because detailed information on maternal dietary intake, nutritional status, gestational weight gain, and metabolic biomarkers was not available. These factors may influence both maternal-fetal metabolic regulation and fetal growth and could therefore contribute to the associations observed in this study.

The effect of these metals as endocrine disruptors and oxidative stress inducers has been highlighted in several studies (20–22), although their mechanism of action has not been completely elucidated (20). Studies on metabolomics have sought to highlight possible metabolic changes induced by metals and their effects on birth outcomes (20). Additionally, considering studies developed in populations environmentally exposed in urban setting, the biological matrix investigated and the exposure background of each country or region of origin may influence detected effects and trends, especially considering the possibility of non-linear and U-shaped effects, which have been previously pointed out (23, 24).

TABLE 4 Logistic regression for metal individual effects and interactions.

Metal exposure*	SGA		LGA	
	ORc (*CI 95%*)	ORa (*CI 95%*)	ORc (*CI 95%*)	ORa (*CI 95%*)
Pb > 0.8	0.92 (0.46 – 1.86)	0.88 (0.422 – 1.83)	**2.27 (1.25 – 4.15)**	**2.28 (1.23 – 4.26)**
Hg >0.8	**0.33 (0.14 – 0.76)**	**0.27 (0.11 – 0.67)**	1.52 (0.86 – 2.70)	1.58 (0.86 – 2.89)
As >0.13	1.10 (0.54 – 2.21)	1.04 (0.50 – 2.17)	1.11 (0.63 – 1.97)	1.08 (0.60 – 1.95)
Pb*Hg	0.61 (0.23 – 1.60)	0.53 (0.19 – 1.49)	**2.30 (1.28 – 4.14)**	**2.15 (1.16 – 3.99)**
Pb*As	1.30 (0.59 – 2.87)	1.16 (0.41 – 3.24)	1.54 (0.88 – 2.86)	1.62 (0.71 – 3.75)
Hg*As	0.47 (0.18 – 1.25)	**0.23 (0.07 – 0.72)**	1.29 (0.70 – 2.37)	1.45 (0.64 – 3.45)
Pb*Hg*As	0.92 (0.32– 2.70)	0.65 (0.19 – 2.22)	**2.01 (1.01 – 4.00)**	2.15 (0.93 – 4,99)

Logistic regression with interaction test.
Outcome: AGA as reference.
Adjusted by maternal age, education, smoking, alcohol consumption, Maternal BMI (Kg/m^2), diabetes, hypertension, infant sex, and gestational age.
Multiple Comparisons: p-values were adjusted using the Benjamini-Hochberg False Discovery Rate (FDR) procedure (q value).

TABLE 5 Linear regression - PCA exposure index and birth weight Z scores.

Metal mixture	BWZ[a] Adj β (CI 95%) p value	SGA ORa (CI 95%) p value	LGA** ORa (CI 95%) p value
PCA index (Global)	**0.090 (0.02 – 0.158) p 0.011**	0.83 (0.57 – 1.20) p 0.31	**1.44 (1.07 – 1.94) p 0.02**
PCA index (pb)	**0.073 (0.005 – 0.141) p 0.03**	0.79 (0.55 – 1.13) p 0.198	**1.65 (1.20 – 2.28) p 0.002**

[a]Linear Regression adjusted.
[b]Logistic Regression adjusted (AIG as reference).
Adjusted by: Mother age, Mother schooling, Tobacco use, alcohol use, Maternal BMI (Kg/m^2), Diabetes and Hypertension, Sex baby, Gestational age in weeks.
Values in bold are statistically significant at $p < 0.05$.

TABLE 6 Metal mixture Bayesian WQS regression.

Outcome	Mixture β or OR (CrI95%)	Metal components	Mixture Weights
BWZ	β = 0.106 (0.069, 0.141)*	Pb	0.407
		As	0.381
		Hg	0.211
LGA	OR = 1.45 (1.12, 1.89)*	Pb	0.619
		As	0.208
		Hg	0.172
SGA	OR = 0.80 (0.654, 0.96)*	Pb	0.403
		As	0.252
		Hg	0.344

Outcome categorical: AGA as reference.
Adjusted by: Mother age, Mother schooling, Tobacco use, alcohol use, Maternal BMI (Kg/m^2), Diabetes and Hypertension, Sex baby, Gestational age in weeks.
Mixture Weights represent the posterior contribution of each metal to the estimated mixture association and should not be interpreted as causal effect estimates.

Non-linear dose-response relationships, including U-shaped effects, have been observed in prenatal metal exposures, where both low and high concentrations may disrupt fetal growth through distinct mechanisms (25).

In our study, conducted in an urban Brazilian population on third trimester of gestation, the lead and mercury median concentrations in cord blood samples were 0.8 µg/dL and 0.8 µg/L, respectively. These values are relatively low when compared to studies from other urban populations. For instance, a study in Hangzhou, China reported median maternal blood lead levels of approximately 2.1 µg/dL (26), while research conducted in Brooklyn, New York found median mercury levels around 1.5 µg/L among pregnant women (27). Such disparities in baseline exposure may contribute to the heterogeneity in birth outcome associations across studies. They also emphasize the importance of contextualizing findings within regional environmental burdens and exposure histories.

In the present study, the population resides in a large metropolis (100% urban area). The metal exposures detected in the umbilical cord blood samples indicate Hg and Pb detected in most of the analyzed samples (98.9% for Pb and 94.5% for Hg), with lower detection rates noted for As (60.5%). Similar detection rates were observed in umbilical cord blood, evidencing fetal exposure and the ability to cross the transplacental barrier in Mexico (28), Brazil (12), and other countries worldwide (13). The LODs differ among studies, making comparisons difficult, but Hg and Pb detections rates are typically above 90%. According to the North American Centers for Disease Control and Prevention (29), although 3.5 µg/dL is currently established as a reference value for Pb in children, no safe values for this compound have been determined to date (29). In the present study, 2.3% of all analyzed babies exhibited concentrations above this value. Regarding Hg, 2.5% of the analyzed babies exhibited values above the reference value of 5 µg/L. For Arsenic, 5% were above the reference value of 1.0 µg/L (30). The determined concentrations varied widely, with maximum values of 13.7µg/dL for Pb, 11.6 µg/L for Hg and 11.3 µg/L for As. The sample characteristics of the investigated population indicate a low and middle-income population, characterized as suffering social and economic vulnerability. The rates of SGA and LGA in our cohort did not differ from those reported for the city of Rio de Janeiro (31), with 4.7% of SGA babies and 7.6% of LGA babies. Prematurity (<37 weeks) was observed in 9.1% of all babies.

Our study has limitations. The cross-sectional design precludes causal inference. Although umbilical cord blood was collected at birth and provides a direct measure of fetal exposure, it represents exposure during late pregnancy and therefore limits our ability to assess the influence of exposure timing on fetal growth. Previous research suggests that the effects of prenatal exposure to toxic metals may vary according to the timing of exposure and critical windows of embryonic and fetal development (32). Nevertheless, cord blood is considered a relevant biomarker of fetal exposure to metals and has been used in previous studies for this purpose (12, 28). The lower detection rate for As compared with Pb and Hg may also have reduced statistical power to detect associations involving As. Although the analyses accounted for several established determinants of fetal growth, including maternal age, BMI, diabetes, hypertension, smoking, infant sex, and gestational age, residual confounding cannot be excluded. In particular, detailed information on maternal dietary intake, nutritional status, gestational weight gain, and metabolic biomarkers was not available. These factors may influence fetal growth and maternal-fetal metabolic regulation and could therefore contribute to the associations observed with BWZ and LGA. Finally, the study was conducted in a single urban cohort in Brazil, which may limit the generalizability of the findings to populations with different socioeconomic, environmental, and exposure profiles.

Our study also has several strengths. First, we used multiple analytical approaches, including supervised Bayesian Weighted Quantile Sum (BWQS) regression and unsupervised Principal Component Analysis (PCA), for a robust comparison of methods. The consistency observed across these approaches strengthens the evidence base and highlights the importance of applying complementary techniques in environmental mixture research (18). The integration of analyses at both the individual and mixture levels

provided a comprehensive view of the effects of As, Hg, and Pb on birth outcomes. While individual associations were modest, the metal mixture revealed consistent positive relationships with BWZ and LGA, underscoring the relevance of mixture models in environmental epidemiology (33, 34). The BWQS analysis also provided information on the relative contribution of each metal to the mixture. Pb showed the highest weight across all three outcomes, with contributions of 0.407 for BWZ, 0.619 for LGA, and 0.403 for SGA. For BWZ and LGA, As had the second-highest weight, whereas Hg ranked second for SGA. However, the relatively small differences between the weights of As and Hg do not necessarily indicate outcome-specific effects and should therefore be interpreted cautiously. Overall, the consistently higher weight of Pb across outcomes suggests a greater contribution of Pb to the observed mixture associations with fetal growth.

Another strength lies in the identification of distinct exposure patterns through PCA, which captured both a global co-exposure profile and a contrasting pattern between Pb and As. This approach highlights heterogeneity in metal mixture association and aligns with recent calls to better characterize complex exposure scenarios (19, 35). Furthermore, the study population represents an urban, socioeconomically vulnerable group in Brazil, a context often underrepresented in environmental health research. This enhances the external validity of the findings for populations facing similar environmental and social challenges (1, 8).

The consistency between continuous (BWZ) and categorical (SGA/LGA) outcomes, with stronger associations observed in categorical analyses, further reinforces the robustness of the results. Importantly, the inclusion of LGA as an outcome, rarely investigated in environmental epidemiology, adds novelty, given its implications for childhood obesity and long-term metabolic risk (2, 6).

Future research should prioritize longitudinal designs during pregnancy and better capture the potential effects of prenatal exposure to toxic metals. Such studies would allow the identification of critical developmental windows and provide insights into whether the observed associations with increased birth weight and LGA persist into childhood and beyond. Moreover, mechanistic investigations are warranted to explore biological pathways, including oxidative stress, endocrine disruption, and placental dysfunction, that may underlie the observed effects. Understanding these mechanisms is essential for clarifying causal relationships and informing preventive strategies to reduce early-life exposure to hazardous metals. Future research should also investigate the socioeconomic, residential, and environmental determinants of metal co-exposure, as previous analyses in this population have identified maternal age, fish consumption, and residential location/social vulnerability as factors associated with individual metal concentrations, whereas no clear associations were observed with per-capita income or maternal schooling (36). A more detailed investigation of the determinants of metal mixtures may help identify relevant exposure pathways and inform targeted public health interventions.

Conclusion

Positive individual relationships between Pb and Hg concentrations and birth weight were detected. The combined analysis of the different methodological approaches indicated a positive relationship between the investigated metal mixture and BWZ scores, with similar effects for both the PCA and BWQS. Asdid not show significant individual associations, but appeared to attenuate associations in metal mixture. PCA revealed distinct metal mixture patterns: a global co-exposure profile of Hg, As, and Pb associated with higher BWZ and LGA, and a contrasting Pb and As pattern, in which Pb emerged as a stronger driver of excessive fetal growth. These heterogeneous profiles suggest that not only overall exposure but also the relative balance among metals may influence fetal growth trajectories. While association sizes were modest, the results highlight the need for caution and encourage further longitudinal studies to explore long-term health implications of these mixture structures.

Although As did not show significant associations when analyzed individually. The inclusion of As in the interaction models attenuated the estimated associations observed for Pb and Hg; however, these findings should be interpreted cautiously. These findings underscore the importance of evaluating complex environmental exposures through metal mixture approaches, which better capture the synergistic and potentially non-linear effects of multiple contaminants.

The relevance of these results is heightened by the socioeconomic vulnerability of the study population, characterized by low income, limited education, and high rates of environmental exposure. Notably, the association between metal mixtures and LGA, a birth outcome less frequently explored in environmental epidemiology, highlights a critical gap in current research. Given that LGA infants are at increased risk for obesity and metabolic disorders later in life, understanding environmental contributors to this outcome is essential.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Maternity School Ethics Committee of the Federal University of Rio de Janeiro approval number: 6.494.730. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

NF: Data curation, Conceptualization, Methodology, Project administration, Investigation, Writing – original draft, Writing – review & editing, Formal Analysis. MR: Conceptualization, Supervision, Writing – review & editing, Methodology, Investigation. RL: Formal Analysis, Methodology, Writing – review & editing, Supervision. CA: Methodology, Conceptualization, Supervision, Funding acquisition, Writing – review & editing, Project administration.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2026.1959669/full#supplementary-material

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