Environmental Pollution 367 (2025) 125647

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Effects of prenatal exposure to multiple heavy metals on infant neurodevelopment: A multi-statistical approach☆

Xiruo Kou [a,b], Meritxell Pallejà Millán [c,d], Josefa Canals [a,b,e,f], Victoria Rivera Moreno [g,h], Stefano Renzetti [i], Victoria Arija [a,b,f,j,*]

[a] Nutrition and Mental Health (NUTRISAM) research group, Universitat Rovira i Virgili, 43204 Reus, Spain
[b] Institut d'Investigació Sanitaria Pere Virgili (IISPV), 43204 Reus, Spain
[c] Research Support Unit Tarragona, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP JGol), 43202 Reus, Spain
[d] Faculty of Medicine and Health Sciences, University Rovira i Virgili, 43201 Reus, Spain
[e] Centre de Recerca en Avaluació i Mesura de la Conducta (CRAMC), Department of Psychology, Universitat Rovira i Virgili, 43007, Tarragona, Spain
[f] University Research Institute on Sustainability, Climate Change and Energy Transition (IU-RESCAT) Universitat Rovira i Virgili, 43003 Tarragona, Spain
[g] Hospital Universitari de Tarragona Joan XXIII, Tarragona, Spain
[h] Facultativa especialista en Anàlisis clíniques, Laboratori Clínic, ICS Camp de Tarragona, Spain
[i] Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, Università degli Studi di Brescia, Brescia, Italy
[j] Collaborative Research Group on Lifestyles, Nutrition and Smoking (CENIT). Tarragona-Reus Research Support Unit, Jordi Gol Primary Care Research Institute, 43003 Tarragona, Spain

A R T I C L E I N F O

Keywords:
Heavy metal
Multiple pollutants
Metal mixture
Neurodevelopment
Bayesian kernel machine regression
Weighted quantile sum

A B S T R A C T

Prenatal exposure to heavy metals poses risks to fetal brain development, yet the joint effects of these metals remain unclear, with inconsistent findings across statistical models. This study investigates the joint effect of prenatal exposure to cadmium (Cd), nickel (Ni), mercury (Hg), and lead (Pb) on infant neurodevelopment using various statistical approaches. The study included 400 mother-infant pairs. Heavy metal levels were measured in maternal urine samples at the 12th week of gestation, and infant neurodevelopment at 40 days was evaluated by the Bayley Scales of Infant and Toddler Development. Generalized Additive Models (GAM), Multivariable Linear Regression (MLR) with restricted cubic spline (RCS), Bayesian Kernel Machine Regression (BKMR), and Weighted Quantile Sum (WQS) regression were applied to explore the associations between heavy metal exposure and neurodevelopmental outcomes. GAM revealed a significant linear relationship for Cd with cognitive scale ($p = 0.045$) and expressive language ($p = 0.043$). MLR confirmed that Cd was negatively associated with both cognitive scale ($\beta = -1.47$, $p = 0.044$) and expressive language ($\beta = -0.32$, $p = 0.019$) and RCS presented a non-linear association between Pb and language scale ($p = 0.001$). BKMR suggested a negative but non-significant association with most outcomes. WQS indicated a significant adverse effect of metal mixture on expressive language ($\beta = -0.26$, 95% CI $= -0.44$, -0.07), identifying Cd and Ni as the primary contributors. Prenatal exposure to heavy metals have detrimental effects on infant neurodevelopment, especially on language development.

1. Introduction

Fetal brain development is a complex and crucial process, marked by multiple key stages that lay the foundation for proper neurological function later in life (Caito & Aschner, 2017). Any disruptions during early neurodevelopment can lead to long-lasting effects on cognitive function, behavior, and mental health across the lifespan (Syed & Nemeroff, 2017). This period is particularly vulnerable to environmental toxicants such as heavy metals, even at levels considered safe for adults (Fettweis et al., 2023). Despite the protective role of the placenta, it is an imperfect barrier, allowing heavy metals to cross into the developing fetus through passive diffusion (Mathiesen et al., 2021). As industrial activities continue to expand, heavy metals have become prevalent contaminants in food, water, and air, making prenatal

☆ This paper has been recommended for acceptance by Wen Chen.

* Corresponding author. Nutrition and Mental Health (NUTRISAM) research group, Universitat Rovira i Virgili, 43204 Reus, Spain.
E-mail address: victoria.arija@urv.cat (V. Arija).

https://doi.org/10.1016/j.envpol.2025.125647
Received 24 October 2024; Received in revised form 18 December 2024; Accepted 3 January 2025
Available online 4 January 2025

exposure to these toxicants a pressing public health issue (Kou, Bulló, et al., 2023; Kou, Iglesias-Vázquez et al., 2023).

Cadmium (Cd), nickel (Ni), mercury (Hg), and lead (Pb) are identified as heavy metals of major concern due to their toxicity, environmental persistence, and far-reaching ecological impact (Arruebarrena et al., 2023; Dufault et al., 2021; Genchi et al., 2020a). Exposure to these metals during pregnancy can interfere with multiple neurodevelopmental domains in offspring. For example, Cd has been linked to impaired language development, while Hg and Pb have shown associations with deficits in motor skills and cognitive function (Barbone et al., 2019; Kippler et al., 2012; Z. Liu et al., 2019; Shah-Kulkarni et al., 2016). Among these potential environmental contaminants, Ni has been less commonly studied in relation to neurodevelopmental outcomes, despite its emerging significance as a potential neurotoxicant (L. Liu et al., 2018). Maternal exposure to Ni has been shown to trigger inflammatory responses, which may contribute to neurodevelopmental disruptions in offspring (Church et al., 2018; H. Guo et al., 2020; Kwon et al., 2022), while only one recent research identifies that postpartum exposure to Ni is associated with neurological development in infants (C. Liu et al., 2022a). Hence, prenatal exposure to these four heavy metals warrants increased attention due to their potential negative impact on the neurodevelopment of offspring.

In reality, co-exposure to multiple heavy metals is common, yet research exploring the combined effects of these exposures remains limited (Sanders et al., 2015). Recent studies have employed advanced statistical models to investigate metal mixtures, but findings are often inconsistent. For example, it is shown that prenatal toxic metals mixture is not related to developmental disorder like attention deficit disorder or autism, or cognitive development in offspring (Shah-Kulkarni et al., 2020; Skogheim et al., 2021a). Conversely, other research highlights a negative joint effect of prenatal neurotoxic metals on language development and cognitive scores in offspring (C. Liu et al., 2022b; Valeri et al., 2017). These studies primarily utilize either Bayesian Kernel Machine Regression (BKMR) or Weighted Quantile Sum (WQS) regression to assess the joint effect of exposure on outcome, while relying solely on one approach can overlook the complexities inherent in exposure-outcome relationships and may introduce biases due to method-specific assumptions. Recent research using a dual-method approach to assess prenatal metal exposure targets either on the physical development or the neurodevelopment of children aged 3–6 years (Gu et al., 2024; J. Ma et al., 2023). However, early neurodevelopment in infants is particularly critical, as disruptions during this stage can indicate the onset of future developmental challenges (Duncan & Matthews, 2018). Detecting these effects in infancy provides a critical window for early intervention, which plays a vital role in preventing long-term psychological issues (Black et al., 2017). However, research applying multiple advanced statistical models to explore the effect of prenatal heavy metal exposure on infant neurodevelopment remains limited.

Thus, this study aims to explore the effect of prenatal exposure to multiple heavy metals (Cd, Ni, Hg, and Pb) on infant neurodevelopment using multiple complementary statistical methods to provide a comprehensive perspective on the relationship between multiple exposures and neurodevelopmental outcomes.

2. Methods

2.1. Research methodology and participants

The analysis was performed on a subgroup of the ECLIPSES participants, who were part of a community-based study that focused on pregnant women in Spain's Tarragona from 2013 to 2017. Recruitment occurred at primary care facilities during the women's initial prenatal visits with midwives. Comprehensive information on inclusion and exclusion criteria can be found in other reference (Arija et al., 2014). Out of the initial recruitment of 791 women, neurodevelopmental function was evaluated in 40 days infants from 503 cases. Losses to follow-up primarily occurred due to voluntary withdrawal (n = 211), the onset of exclusion criteria during pregnancy (n = 46), miscarriages (n = 13), and unknown reason (n = 18). Additionally, maternal urine sampling and metal determination were not feasible in 103 cases. Consequently, the present analysis included 400 mother-infant pairs for whom both prenatal urine samples and infant neurodevelopment data were available.

2.2. Maternal baseline data collection

Baseline characteristics of the mothers were collected through questionnaires administered during in-person interviews at the time of enrollment. These interviews gathered information on maternal demographics, body mass index (BMI, kg/m^2), socioeconomic status (SES) (by evaluating participants' educational attainment and occupational background), smoking status (classified as never smoke, ex-smoker, and smoker), and adherence to the Mediterranean diet (MedDiet) (Trichopoulou et al., 2003). Maternal psychological distress was measured in both the first and third trimesters using the State-Trait Anxiety Inventory. The scores from these two assessments were averaged to reflect the overall distress experienced by the participants during their pregnancy (Julian, 2011).

2.3. Urinary sample collection and metal analysis

Urinary samples were obtained from all participating women during the first trimester of pregnancy. After thorough homogenization, these samples were aliquoted and preserved in polypropylene tubes at −20 °C. They were later analyzed for Cd, Ni, Hg, and Pb levels, alongside measurements of urine creatinine levels.

To prepare for analysis, urinary samples were allowed to warm to room temperature and diluted 1:10 using a solution contain 2% nitric acid (suprapur 65%), following the standards for calibration. Internal quality control used Lypochek Urine Metal Control for trace elements Level I and II (Bio-rad), ensuring recovery percentages for analyzed heavy metals ranged from 90.6% to 102.1%, within certified values. Metal concentrations in urine (Cd, Ni, Hg, Pb) were determined using Triple Quadrupole Inductively Coupled Plasma Tandem Mass Spectrometry (ICP-MS/MS) (Agilent 8800 triple quadrupole ICP-MS, Agilent Technologies, Santa Clara, CA, USA); detailed methods are described elsewhere (Anual et al., 2021; Lozano et al., 2022). The analysis blanks were created by diluting 2% nitric acid. The limits of detection (LOD) were 0.04, 0.2, 0.04, and 0.2 μg/L for Cd, Ni, Hg, and Pb, respectively. In our dataset, 0.50%, 0.50%, 2.75%, and 29.00% of the values for Cd, Ni, Hg, and Pb, respectively, were below the LOD. To adjust for urine dilution variations, concentrations of urinary heavy metals were normalized using their corresponding creatinine levels. Urinary creatinine levels were assessed using the Reagents Sistema ADVIA 1800 and Sistema ADVIA 2400 Chemistry systems (Lozano et al., 2022). Urinary metal concentrations were expressed in μg/g of creatinine to standardize for differences in urine dilution (Lozano et al., 2022).

2.4. Infant neurodevelopment data collection

When the infants reached approximately 40 days old, trained psychologists conducted assessments using the Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III) (Bayley, 2006). Recognized as a gold standard by clinicians and researchers, the BSID-III evaluates developmental progress in children from 1 to 42 months, focusing on cognitive, language, and motor domains (Del Rosario et al., 2021; Torras-Mañá et al., 2016). The scaled scores for the five subscales are combined to generate composite scores: the cognitive composite score (derived from the cognitive scaled score), the language composite score (a combination of receptive and expressive communication scaled scores), and the motor composite score (a combination of fine and gross motor scaled scores). Each scale produces raw scores, which are then standardized using normative data. The overall scales are standardized with a mean of 100 and a standard deviation (SD) of 15, while subscales have a mean of 10 and an SD of 3. These scores are then used to assess the infant's developmental level in each domain, with higher scores indicating more advanced development. Each assessment session with an infant lasted between 30 and 50 min (Michalec, 2011).

2.5. Statistical analysis

To characterize the population, nominal measures were presented as counts and percentages, while numerical measures were reported as mean with SD. Given the non-normal distribution of heavy metals, natural log-transformed creatinine-adjusted heavy metal levels were used for all analyses. The confounding variables included in all analyses were maternal age, BMI, SES (low/middle vs. high), smoking status (never smoker vs. ex/smoker), Mediterranean diet score during pregnancy, child gender, and feeding methods (breast vs. mixed/formula).

A Spearman correlation coefficient was used to assess the correlation between the heavy metals (Spearman's rank correlation coefficient, 2018). Generalized Additive Models (GAMs) were used to explore potential relationships between heavy metal exposures and neurodevelopment outcomes, utilizing smooth functions for flexible modeling without assuming a predefined relationship (Gomez-Rubio, 2018). Based on the results from the GAM, Multivariable Linear Regression (MLR) models were used to assess the association between metal exposure and the outcomes. Restricted Cubic Splines (RCS) were applied to variables that showed a significant non-linear relationship with the neurodevelopmental scores, with knots placed at the 10th, 50th, and 90th percentiles of the metal distribution. Then, BKMR was employed to evaluate the joint effects of the heavy metal mixture on the neurodevelopment outcome and potential interaction among metals. BKMR is designed to handle both linear and nonlinear relationships between exposures and outcomes (J. F. Bobb et al., 2015; Valeri et al., 2017). We set the number of iterations to 10,000 to ensure model convergence and result stability. Joint associations were assessed by inspecting plots comparing exposure mixture levels at each percentile against individual component levels at their median values, then univariate exposure-response analysis was performed to examine the relationship between each individual metal exposure and the outcome while holding other exposures constant. The posterior inclusion probability (PIP) was computed to assess the relative contribution of each heavy metal in explaining the neurodevelopmental outcomes. Additionally, interaction analysis was performed to explore potential interactions between the metals. Lastly, WQS regression was conducted to evaluate the effect of mixture exposure on neurodevelopmental outcomes. The analysis separately constrained the mixture's effect to be positive and negative, assuming a linear relationship between the exposures and the dependent variables (Carrico et al., 2015). The exposures were transformed into quartiles and combined into a weighted index, which accounts for both positive and negative effects (S. Renzetti et al., 2023). The model was validated by splitting the data, using 60% for training and the remaining 40% for validation. To ensure robustness, 100 bootstrap samples were used and the training – validation steps were repeated 100 times following a repeated holdout procedure (Tanner et al., 2019). All statistical analyses were conducted with R version 4.4.1, the mgcv package was used to apply GAM (Wood, 2017), the rms package was considered to include RCS in the multivariable linear regression models (Harrell Jr, 2024), the bkmr package was used to fit BKMR (J. Bobb, 2022)while the gWQS package was considered to apply WQS regression (S. C. P. G. C. Renzetti, 2023). The statistical significance level was set at $\alpha = 0.05$ and all statistical tests were two-sided.

3. Results

3.1. Descriptive of pregnant women and infants

A total of 400 mother-infant pairs were enrolled as part of the research. The average age of the women was 30.90 ± 5.08 years, with a BMI of 24.73 ± 4.28. Among them, 79.8% belonged to the low/medium social class, and 20.2% to the high social class. Additionally, 69.5% of the women had never smoked, while 30.5% were current or former smokers. The mean MedDiet score during pregnancy was 9.54 ± 2.55.

As for infants, there were 210 males and 190 females. A total of 298 infants were breastfed, while 102 were mixed-fed or formula-fed. Neurodevelopmental scores of the infants at 40 days, assessed by BSID-III, were as follows: cognitive scale 101.98 ± 8.42, language scale 96.49 ± 7.95 (receptive language 10.69 ± 2.02, expressive language 8.08 ± 1.55), and motor scale 107.91 ± 11.71 (fine motor 11.48 ± 1.95, gross motor 11.16 ± 2.40) (Table 1).

3.2. Description and correlation of heavy metal exposures

The geometric means and interquartile ranges of Cd, Ni, Hg, and Pb were 0.22 (0.19), 1.61 (1.33), 0.47 (0.65), and 0.26 (0.52) μg/g of creatinine, accordingly (Table 2). Meanwhile, Fig. 1 showed the Spearman correlation heatmap for the heavy metals. The correlation coefficients were close to 0, indicating a lack of strong linear relationships between them.

3.3. The association between heavy metals and neurodevelopment

GAMs were employed to capture both linear and non-linear patterns between heavy metal exposures and neurodevelopmental outcomes. In individual metal analyses, Cd showed a significant association with expressive language (estimated degrees of freedom [edf] = 1.17, p = 0.031), while Pb displayed a significant non-linear association with the language scale (edf = 2.60, p = 0.009) (Supplementary Table 1). These relationships were visualized in Supplementary Fig. 1.

Table 1
General characteristics of mother and offspring: sociodemographic data, lifestyle, diet, and neurodevelopment characteristics (n = 400).

Maternal characteristics	Summary Statistics
Age (years), mean ± SD	30.90 ± 5.08
BMI, mean ± SD	24.73 ± 4.28
Social class, n (%)	
Low/Medium	319 (79.8)
High	81 (20.2)
Smoking status, n (%)	
Never smoker	278 (69.5)
Smoker or ex-smoker	122 (30.5)
MedDiet during pregnancy (score), mean ± SD	9.54 ± 2.55
Infants characteristics	
Gestational age (weeks), mean ± SD	39.72 ± 1.38
Sex, n (%)	
Male	210 (52.5)
Female	190 (47.5)
Type of feeding, n (%)	
Breastfeeding	298 (74.5)
Mixed feeding/infant formula	102 (25.5)
Neurodevelopment of infants	
BSID-III at 40 days, mean ± SD	
Cognitive scale	101.98 ± 8.42
Language scale	96.49 ± 7.95
Receptive language	10.69 ± 2.02
Expressive language	8.08 ± 1.55
Motor scale	107.91 ± 11.71
Fine motor	11.48 ± 1.95
Gross motor	11.16 ± 2.40

Abbreviations: BMI, early pregnancy Body Mass Index; MedDiet, Mediterranean diet; BSID-III, Bayley Scale of Infant Development III.

Table 2
Urinary concentrations of heavy metals in pregnant women.

	Percentile			GM	IQR
	25th	50th	75th		
Adjusted (μg/g of creatinine)					
Ni	1.07	1.59	2.38	1.61	1.31
Cd	0.14	0.23	0.33	0.22	0.19
Hg	0.29	0.57	0.94	0.47	0.65
Pb	0.16	0.36	0.68	0.26	0.52

Abbreviations: Ni, nickel; Cd, cadmium; Hg, mercury; Pb, lead; GM, geometric mean; IQR, interquartile range.

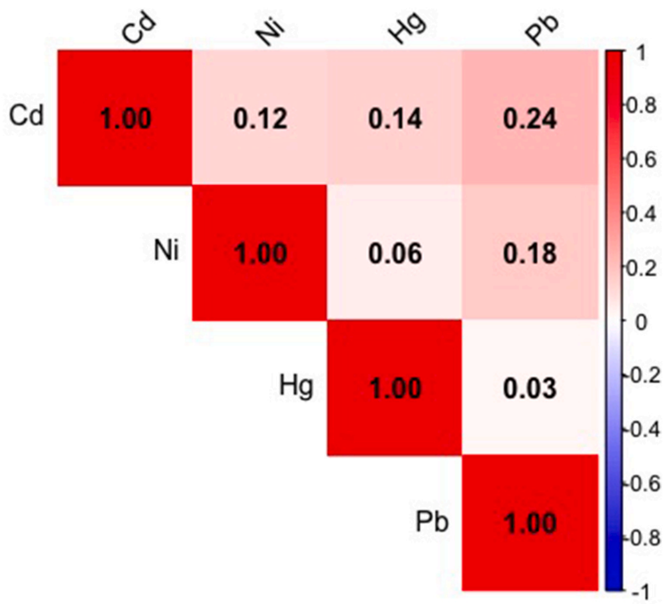

Fig. 1. Spearman correlation heatmap of heavy metals.

When all four metals were included together in the model, Cd was significantly associated with both the cognitive scale (edf = 1, p = 0.045) and expressive language (edf = 1, p = 0.043), with both showing negative linear relationships. Pb maintained a non-linear, inverted U-shaped association with the language scale (edf = 2.54, p = 0.015) (Supplementary Table 2). The above-mentioned GAM results for the relationships between metals and cognitive, language, and motor scales were visualized in Fig. 2, while the relationships with sub-scales were shown in Fig. 3.

The MLR results corroborated that Cd remained negatively associated with the cognitive scale (β = −1.47, p = 0.044) and expressive language (β = −0.32, p = 0.019) while the RCS analysis confirmed a significant non-linear effect of Pb on language development (p = 0.001), with the overall relationship also being significant (p = 0.003) (Table 3), the non-linear relationship of RCS was visualized in Supplementary Fig. 2.

3.4. Joint effect of heavy metal exposure and neurodevelopment

First, BKMR was applied to assess the relationships and potential interactions between heavy metal mixture exposure and neurodevelopmental outcomes. As shown in Fig. 4, the heavy metal mixture exhibited a negative linear association with most outcomes (except for motor-related scales), although these associations were not statistically significant. The conditional PIP for heavy metals and neurodevelopment was illustrated in Supplementary Table 3, indicating that Cd had the highest contribution for expressive language (PIP = 0.76), while Pb had the highest influence for the overall language scale (PIP = 0.79). The univariate exposure-response presented in Supplementary Fig. 3 showed similar trends to those observed in the GAM results. However, no obvious interaction was found among metals (Supplementary Figs. 4 and 5).

Next, WQS regression was applied to investigate the linear relationships between the heavy metal mixture and neurodevelopment, with the analysis performed under both negative and positive constraints. The negative-constrained effect, presented in Table 4, revealed that the heavy metal mixture was associated with adverse effects on expressive language (β = −0.26, 95% CI = −0.44, −0.07), with Cd and Ni identified as the most influential contributors (Fig. 5). In contrast, the positive-constrained effect, detailed in Supplementary Table 4, did not demonstrate any significant associations.

4. Discussion

In this prospective birth cohort, we assessed the association between a mixture of prenatal heavy metals and neurodevelopment in infants. Our results suggest that Cd exposure, both individually and in combination with other heavy metals during this sensitive developmental period, may adversely affect infant neurodevelopment. Specifically, Cd was linearly and negatively associated with both cognitive and expressive language scales. Meanwhile, Pb showed an inverse U-shaped relationship with language development, indicating adverse effects at both low and high prenatal exposure levels. In the joint effect model, BKMR revealed a negative trend between the heavy metal mixture and cognitive and language-related scales, although these associations did not reach statistical significance. Meanwhile, WQS confirmed that the heavy metal mixture was negatively associated with expressive language, with Cd and Ni contributing the most weight. By using both methods to analyze the joint effects of exposure on outcomes, we leveraged their complementary advantages: BKMR enabled us to capture the joint effects of exposures on outcomes, accounting for potential nonlinear relationships, while WQS provided valuable insights into the relative contributions of individual metals in a linear framework. This combined approach may offer a more comprehensive understanding of the complex effects of prenatal heavy metal mixtures on neurodevelopment among infants.

Consistent with our findings on single-metal exposure, other studies have also identified adverse effects of prenatal Cd exposure on neurodevelopment in offspring. For instance, it has been reported that Cd exposure is linked with poorer post-motor development in boys at age of 2 (C. Ma et al., 2021). Additionally, Cd has been shown to adversely affect children's social developmental quotients at 12 months of age (Y. Wang et al., 2016). In the current study, the linear negative association of Cd with cognitive and expressive language scales could be explained by its known ability to disrupt essential metal homeostasis, oxidative stress pathways, and neuronal function (Bhardwaj et al., 2024; Genchi et al., 2020b). Cd could interfere with calcium channels, which are critical for synaptic transmission and plasticity, potentially impairing the development of neural circuits essential for cognitive and language abilities (Shao et al., 2024). Additionally, Cd-induced oxidative stress might contribute to neuronal damage, particularly in brain regions involved in memory, learning, and language processing, such as the hippocampus and frontal cortex (Y. Ma et al., 2022). These mechanisms may explain the consistent negative impact of Cd exposure on the neurodevelopmental outcomes observed. Research suggests that certain neurotoxicants can exhibit non-linear dose-response relationships on neurodevelopment due to varying physiological and biochemical mechanisms at different exposure levels (Skogheim et al., 2021a). In our study, Pb exhibited an inverse U-shaped relationship with language scales, indicating that both low and high levels of exposure may be associated with adverse outcomes. Notably, the decline in language scores became steeper at higher Pb exposure levels, suggesting that the detrimental effects of Pb are more pronounced when exposure is elevated. This non-linear relationship aligns with findings from a

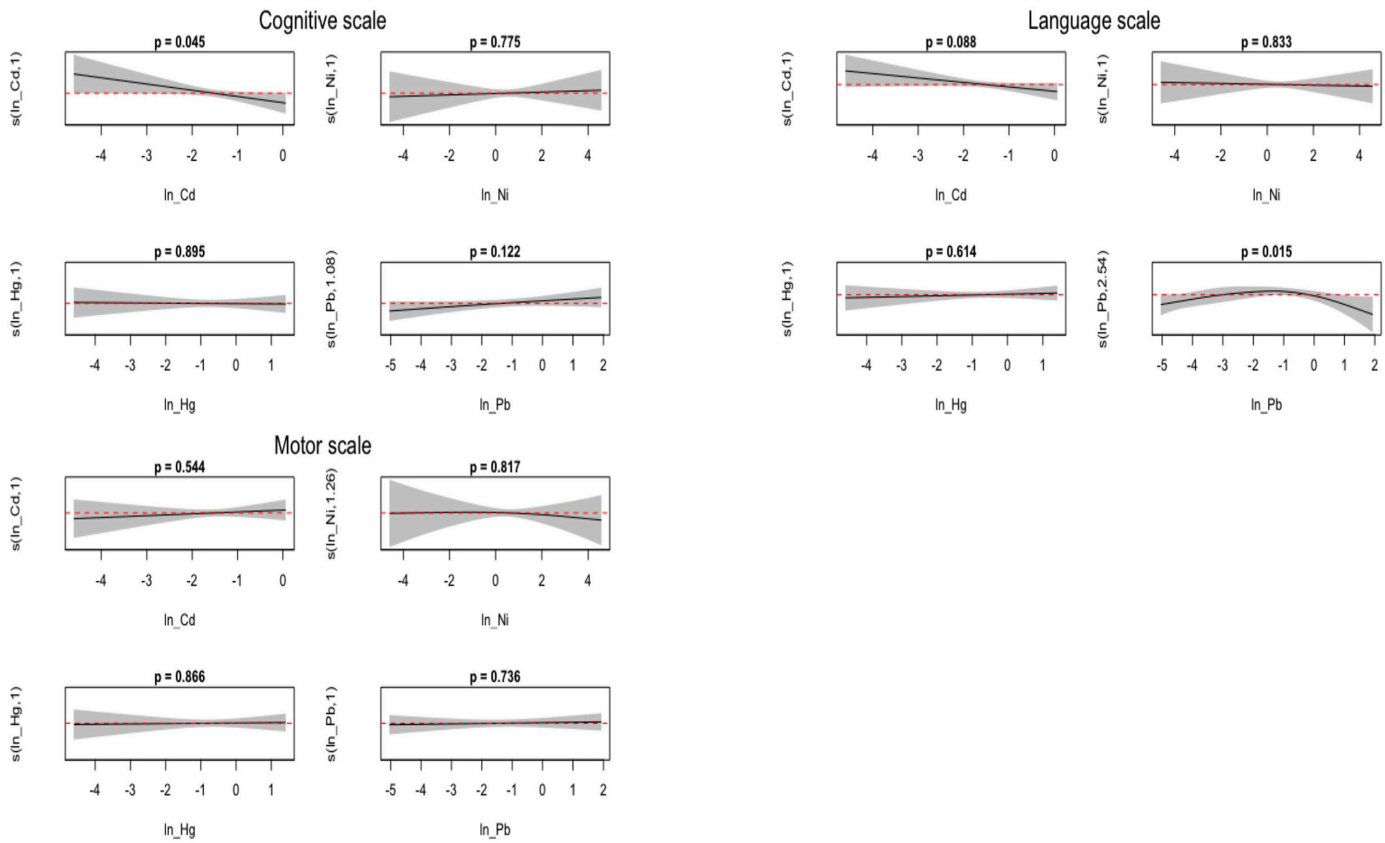

Fig. 2. Visual representation of the Generalized Additive Model results for the associations between heavy metals and cognitive, language, and motor scales, with adjustments for all four metals with other covariates in the model.

prospective study, which reported that both low and high prenatal Pb exposure were associated with an increased risk of autism spectrum disorder (Skogheim et al., 2021b). Additionally, several studies have observed similar non-linear dose–response relationships between childhood Pb exposure and neurodevelopmental outcomes, such as intelligence (Vrijheid et al., 2016). Although the specific mechanisms underlying the non-linear relationship between Pb and neurodevelopment remain unclear, one possible explanation is that low Pb exposure may not sufficiently activate protective mechanisms, while high exposure overwhelms these processes, leading to widespread neurotoxic effects. The steep decline observed at higher Pb levels suggests that neuroprotective responses are unable to compensate, resulting in more severe damage. In contrast, moderate exposure may allow for some compensatory neuroprotective mechanisms, potentially mitigating adverse effects (Lanphear et al., 2018; Y. Liu et al., 2019). At moderate exposure levels, however, some compensatory responses may still be functional, potentially reducing overall damage to neurodevelopment, though this remains speculative and requires further investigation (Calabrese, 2015).

Although BKMR results did not reach statistical significance, we observed a general negative trend between the heavy metal mixture and neurodevelopmental outcomes, particularly cognitive and language-related scales. This suggests that while individual associations may be subtle, the cumulative effects of heavy metals could potentially lead to long-term neurodevelopmental deficits (J. Guo et al., 2020). Conversely, WQS demonstrated a statistically significant association between the heavy metal mixture and expressive language development, with Cd and Ni identified as the dominant contributor. This finding aligned with other studies linking prenatal Cd exposure to language development (Jeong et al., 2015; Z. Liu et al., 2019; C. Ma et al., 2021). While the literature reporting negative effects of prenatal Ni exposure on neurodevelopment is limited, only one recent study indicates that postpartum exposure to Ni is associated with neurological development in infants (C. Liu et al., 2022b). This underscores the need for further research into Ni's potential impact on neurodevelopment, particularly during critical developmental windows. Given this critical role, strategies to reduce heavy exposure could be particularly beneficial. These strategies may include monitoring and regulating dietary sources of heavy metals, such as seafood, and maintaining a safe distance from industrial sites (Kou, Bulló, et al., 2023; Kou, Iglesias-Vázquez et al., 2023). Public awareness campaigns targeting dietary choices, especially among pregnant individuals, can further mitigate exposure to heavy metals. By enhancing knowledge and promoting healthier choices, we can better protect maternal and child health from the adverse effects of heavy metal exposure.

The strength of this study included: (1) the use of multiple statistical methods allowed us to systematically explore the relationship between prenatal heavy metal exposure and neurodevelopment outcomes. GAM, MLR with RCS facilitated the examination of both linear and nonlinear effects, while BKMR enabled us to assess the joint effects of multiple metals. Additionally, WQS highlighted the relative contributions of individual metals within a linear framework, offering complementary insights into these complex associations. (2) The prospective study design minimized recall bias and allowed for a temporally accurate assessment of prenatal exposure about neurodevelopmental outcomes. Additionally, adjusting for key confounders, such as the MedDiet score and socioeconomic status, further enhanced the robustness of our findings by accounting for factors that may influence both exposure and neurodevelopment (Jiang et al., 2022).

Nevertheless, there also existed some limitations. First, the sample size was relatively modest, which may have reduced the statistical power to identify significant associations, particularly in the case of BKMR results that did not reach statistical significance. Second, while we adjusted for several potential confounders, residual confounding

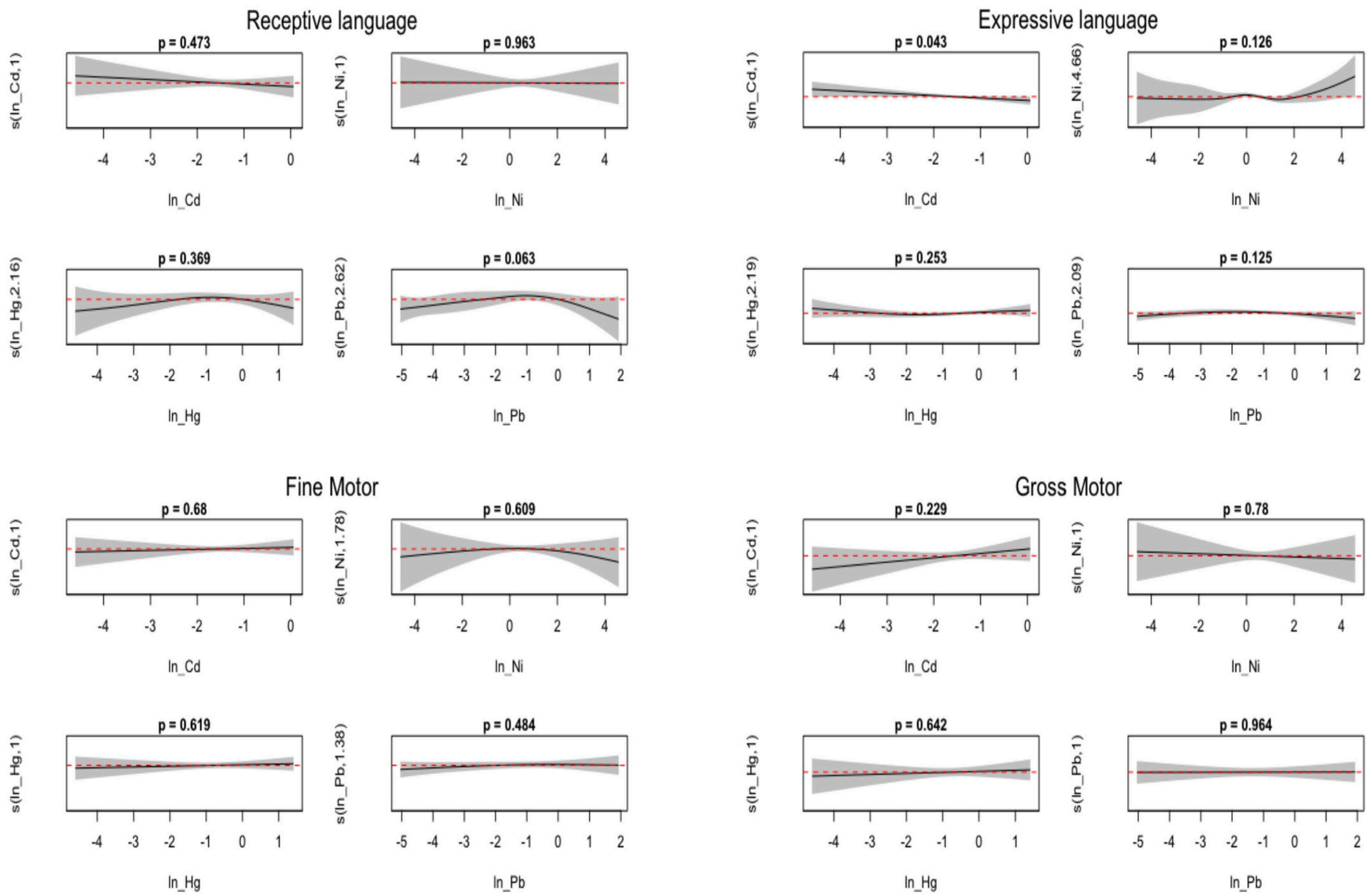

Fig. 3. Visual representation of the Generalized Additive Model results for the associations between heavy metals and sub-scales, with adjustments for all four metals with other covariates in the model.

Table 3
Association between heavy metals and neurodevelopment of infants.

	Cognitive scale[a]	Language scale[b]	Receptive language[a]	Expressive language[a]	Motor scale[a]	Fine motor[a]	Gross motor[a]
	b (95% CI) p	b (95% CI) p	b (95% CI) p	b (95% CI) p	b (95% CI) p	b (95% CI) p	b (95% CI) p
Cd	**−1.47 (-2.90, -0.04)** **0.044**	−1.15 (−2.50, 0.20) 0.097	−0.20 (−0.54, 0.15) 0.271	**−0.32 (-0.59, -0.05)** **0.019**	0.64 (−1.37, 2.65) 0.532	0.07 (−0.26, 0.41) 0.669	0.25 (−0.16, 0.66) 0.229
Ni	0.16 (−0.97, 1.30) 0.779	−0.07 (−1.14, 0.99) 0.890	−0.02 (−0.29, 0.26) 0.905	−0.05 (−0.26, 0.17) 0.676	−0.30 (−1.90, 1.30) 0.716	−0.05 (−0.32, 0.22) 0.710	−0.05 (−0.37, 0.28) 0.780
Hg	−0.06 (−0.94, 0.82) 0.897	0.20 (−0.63, 1.03) 0.635	0.05 (−0.17, 0.26) 0.673	0.05 (−0.11, 0.22) 0.540	0.12 (−1.12, 1.36) 0.846	0.06 (−0.14, 0.27) 0.554	0.06 (−0.19, 0.31) 0.642
Pb	0.47 (−0.09, 1.03) 0.102	**NA** **0.001**[c] **0.003**[d]	0.07 (−0.07, 0.21) 0.309	0.01 (−0.10, 0.11) 0.864	0.14 (−0.65, 0.94) 0.719	0.07 (−0.06, 0.20) 0.312	0.00 (−0.16, 0.17) 0.964

Results in bold are statistically significant.
Model was adjusted by four heavy metals, age, BMI, social class (low/middle vs. high), smoking status (never smoker vs. ex/smoker), MedDiet during pregnancy (score), gestational age (weeks), child sex, type of feeding (breast vs. mix/formula).
[a] , conducted by multivariate linear regression.
[b] , conducted by Restricted Cubic Splines.
[c] , non-linear effect.
[d] , p value of overall effect; Abbreviations: CI, confidence interval; Cd, cadmium; Ni, nickel; Hg, mercury; Pb, lead. NA, not available, since the relationship is not linear.

from unmeasured factors such as other environmental contaminants cannot be completely ruled out (Yi et al., 2022). Third, exposure misclassification is a potential concern, as prenatal metal levels were measured using urine samples, which reflect short-term exposure (Galarneau et al., 2022). Future studies could benefit from repeated exposure assessments throughout pregnancy to capture more accurate exposure windows and potential critical periods of susceptibility. Fourth, further research should expand the scope to include a broader range of metals, providing a more comprehensive assessment of prenatal mixed metal exposure effects on neurodevelopment of offspring.

5. Conclusion

Prenatal Cd exposure is negatively associated with

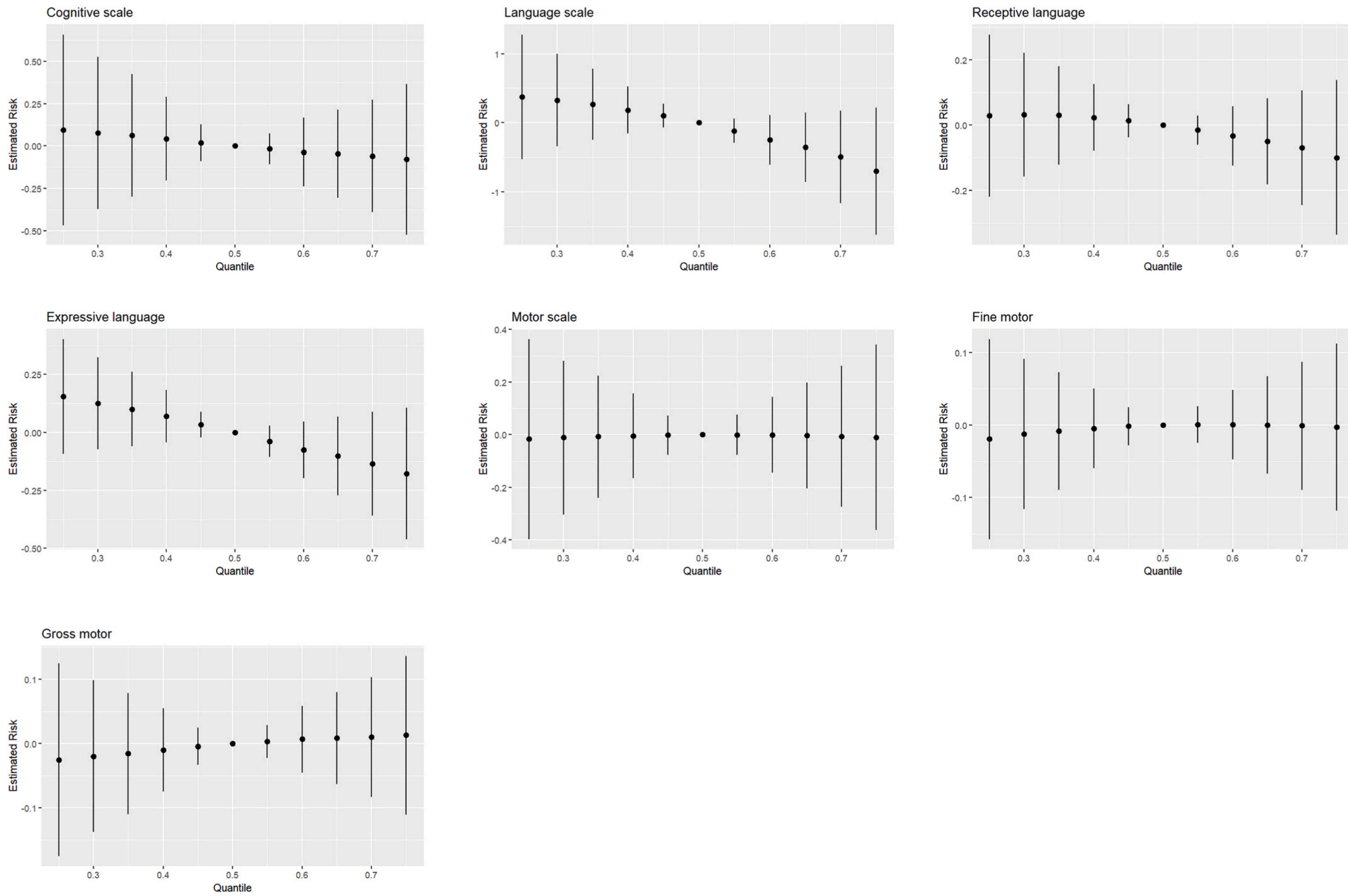

Fig. 4. Cumulative effect of the heavy metal mixture on infant neurodevelopment using Bayesian Kernel Machine Regression.

Table 4
Joint effects of heavy metal exposures on neurodevelopment.

	WQS Index (Cd, Ni, Hg, Pb)	
	Estimate	95%CI
Cognitive scale	−0.60	−1.56, 0.35
Receptive language	0.05	−0.19, 0.28
Expressive language	**−0.26**	**−0.44, -0.07**
Motor scale	0.73	−0.66, 2.13
Fine motor	0.21	−0.03, 0.45
Gross motor	0.16	−0.11, 0.44

Abbreviations: WQS, Weighted Quantile Sum regression. Ni, nickel; Cd, cadmium; Hg, mercury; Pb, lead; CI, Confidence Interval. Results in bold are statistically significant. gWQS model was adjusted by four heavy metals, age, BMI, social class (low/middle vs. high), smoking status (never smoker vs. ex/smoker), MedDiet during pregnancy (score), gestational age (weeks), child sex, type of feeding (breast vs. mix/formula).

neurodevelopment of infants, while exposure to mixtures of heavy metals adversely affects infants' expressive language scale, with Cd and Ni emerging as key contributors to this challenge. Additionally, Pb shows an inverse U-shaped relationship with language development, suggesting that both low and high levels of exposure may be detrimental. Further investigation into the long-term effects of heavy metals on neurodevelopment beyond infancy is crucial for understanding their potential influence on children's developmental trajectories. Additionally, analyzing this cohort will help clarify the predictive accuracy of early screening assessments and provide insight into the lasting consequences of in-utero and early childhood exposure to heavy metals.

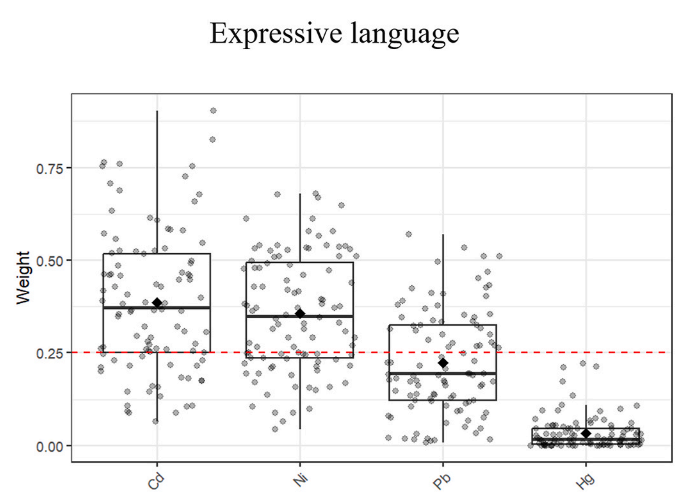

Fig. 5. Weight contribution of each heavy metal on infant expressive language using generalized Weighted Quantile Sum regression.

CRediT authorship contribution statement

Xiruo Kou: Writing – original draft, Visualization, Methodology, Formal analysis. **Meritxell Pallejà Millán:** Writing – review & editing, Visualization, Formal analysis. **Josefa Canals:** Writing – review & editing, Visualization, Methodology. **Victoria Rivera Moreno:** Data curation. **Stefano Renzetti:** Writing – review & editing, Visualization, Methodology. **Victoria Arija:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization.

Funding statement

This research received support from the Instituto de Salud Carlos III, Fondo de Investigacion Sanitaria, Ministerio de Sanidad y Consumo, under Grant Numbers PI12/02777 and PI17/01754. The funding was co-funded by the European Union (ERDF/ESF, "A way to make Europe"/ "Investing in your future"). The authors declare no financial disclosures in relation to this paper.

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.envpol.2025.125647.

Data availability

The data that has been used is confidential.

References

Anual, Z.F., Mohammad Sham, N., Ambak, R., Othman, F., Shaharudin, R., 2021. Urinary concentrations of metals and metalloids in Malaysian adults. Exposure and Health 13 (3), 391–401. https://doi.org/10.1007/s12403-021-00390-z.

Arija, V., Fargas, F., March, G., Abajo, S., Basora, J., Canals, J., Ribot, B., Aparicio, E., Serrat, N., Hernández-Martínez, C., Aranda, N., 2014. Adapting iron dose supplementation in pregnancy for greater effectiveness on mother and child health: protocol of the ECLIPSES randomized clinical trial. BMC Pregnancy Childbirth 14, 33. https://doi.org/10.1186/1471-2393-14-33.

Arruebarrena, M.A., Hawe, C.T., Lee, Y.M., Branco, R.C., 2023. Mechanisms of cadmium neurotoxicity. Int. J. Mol. Sci. 24 (23). https://doi.org/10.3390/ijms242316558.

Barbone, F., Rosolen, V., Mariuz, M., Parpinel, M., Casetta, A., Sammartano, F., Ronfani, L., Vecchi Brumatti, L., Bin, M., Castriotta, L., Valent, F., Little, D.L., Mazej, D., Snoj Tratnik, J., Miklavčič Višnjevec, A., Sofianou, K., Špirić, Z., Krsnik, M., Osredkar, J., et al., 2019. Prenatal mercury exposure and child neurodevelopment outcomes at 18 months: results from the Mediterranean PHIME cohort. Int. J. Hyg Environ. Health 222 (1), 9–21. https://doi.org/10.1016/j.ijheh.2018.07.011.

Bayley, N., 2006. Bayley Scales of Infant and Toddler Development.

Bhardwaj, J.K., Bikal, P., Sachdeva, S.N., 2024. Cadmium as an ovarian toxicant: a review. J. Appl. Toxicol. : JAT 44 (1), 129–147. https://doi.org/10.1002/jat.4526.

Black, M.M., Walker, S.P., Fernald, L.C.H., Andersen, C.T., DiGirolamo, A.M., Lu, C., McCoy, D.C., Fink, G., Shawar, Y.R., Shiffman, J., Devercelli, A.E., Wodon, Q.T., Vargas-Barón, E., Grantham-McGregor, S., 2017. Early childhood development coming of age: science through the life course. Lancet 389 (10064), 77–90. https://doi.org/10.1016/S0140-6736(16)31389-7.

Bobb, J., 2022. Bkmr: Bayesian Kernel Machine Regression, 0.2.2.

Bobb, J.F., Valeri, L., Claus Henn, B., Christiani, D.C., Wright, R.O., Mazumdar, M., Godleski, J.J., Coull, B.A., 2015. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. Biostatistics 16 (3), 493–508. https://doi.org/10.1093/biostatistics/kxu058.

Caito, S., Aschner, M., 2017. Developmental neurotoxicity of lead. Advances in Neurobiology 18, 3–12. https://doi.org/10.1007/978-3-319-60189-2_1.

Calabrese, E.J., 2015. Hormesis : Principles and Applications, pp. 69–82. February.

Carrico, C., Gennings, C., Wheeler, D.C., Factor-Litvak, P., 2015. Characterization of weighted quantile sum regression for highly correlated data in a risk analysis setting. J. Agric. Biol. Environ. Stat. 20 (1), 100–120. https://doi.org/10.1007/s13253-014-0180-3.

Church, J.S., Tijerina, P.B., Emerson, F.J., Coburn, M.A., Blum, J.L., Zelikoff, J.T., Schwartzer, J.J., 2018. Perinatal exposure to concentrated ambient particulates results in autism-like behavioral deficits in adult mice. Neurotoxicology 65, 231–240. https://doi.org/10.1016/j.neuro.2017.10.007.

Del Rosario, C., Slevin, M., Molloy, E.J., Quigley, J., Nixon, E., 2021. How to use the Bayley scales of infant and toddler development. Archives of Disease in Childhood. Education and Practice Edition 106 (2), 108–112. https://doi.org/10.1136/archdischild-2020-319063.

Dufault, R.J., Wolle, M.M., Kingston, H.M.S., Gilbert, S.G., Murray, J.A., 2021. Connecting inorganic mercury and lead measurements in blood to dietary sources of exposure that may impact child development. World J. Methodol. 11 (4), 144–159. https://doi.org/10.5662/wjm.v11.i4.144.

Duncan, A.F., Matthews, M.A., 2018. Neurodevelopmental outcomes in early childhood. Clin. Perinatol. 45 (3), 377–392. https://doi.org/10.1016/j.clp.2018.05.001.

Fettweis, A., Hansul, S., Schamphelaere, K. De, Smolders, E., 2023. Metal mixture toxicity of Ni, Cu, and Zn in freshwater algal communities and the correlation of single-species sensitivities among single metals: a comparative analysis. Environ. Toxicol. Chem. 42 (12), 2666–2683. https://doi.org/10.1002/etc.5735.

Galarneau, J.-M., Beach, J., Cherry, N., 2022. Urinary metals as a marker of exposure in men and women in the welding and electrical trades: a Canadian cohort study. Annals of Work Exposures and Health 66 (9), 1111–1121. https://doi.org/10.1093/annweh/wxac005.

Genchi, G., Carocci, A., Lauria, G., Sinicropi, M.S., Catalano, A., 2020a. Nickel: human health and environmental toxicology. Int. J. Environ. Res. Publ. Health 17 (3). https://doi.org/10.3390/ijerph17030679.

Genchi, G., Sinicropi, M.S., Lauria, G., Carocci, A., Catalano, A., 2020b. The effects of cadmium toxicity. Int. J. Environ. Res. Publ. Health 17 (11). https://doi.org/10.3390/ijerph17113782.

Gomez-Rubio, V., 2018. Generalized additive models: an introduction with R (2nd edition). J. Stat. Software 86 (Book Review 1), 1–5. https://doi.org/10.18637/jss.v086.b01.

Gu, J., Huang, H., Tang, P., Liao, Q., Liang, J., Tang, Y., Long, J., Chen, J., Huang, D., Liu, S., Pan, D., Zeng, X., Qiu, X., 2024. Association between maternal metal exposure during early pregnancy and intelligence in children aged 3–6 years: results from a Chinese birth cohort. Environ. Res. 261, 119685. https://doi.org/10.1016/j.envres.2024.119685.

Guo, H., Liu, H., Jian, Z., Cui, H., Fang, J., Zuo, Z., Deng, J., Li, Y., Wang, X., Zhao, L., He, R., Tang, H., 2020a. Immunotoxicity of nickel: pathological and toxicological effects. Ecotoxicol. Environ. Saf. 203, 111006. https://doi.org/10.1016/j.ecoenv.2020.111006.

Guo, J., Wu, C., Zhang, J., Qi, X., Lv, S., Jiang, S., Zhou, T., Lu, D., Feng, C., Chang, X., Zhang, Y., Cao, Y., Wang, G., Zhou, Z., 2020b. Prenatal exposure to mixture of heavy metals, pesticides and phenols and IQ in children at 7 years of age: the SMBCS study. Environ. Int. 139, 105692. https://doi.org/10.1016/j.envint.2020.105692.

Harrell, Jr F., 2024. Rms: Regression Modeling Strategies, 6.vols. 8–2.

Jeong, K.S., Park, H., Ha, E., Hong, Y.-C., Ha, M., Park, H., Kim, B.-N., Lee, B.-E., Lee, S.-J., Lee, K.Y., Kim, J.H., Kim, Y., 2015. Performance IQ in children is associated with blood cadmium concentration in early pregnancy. J. Trace Elem. Med. Biol. : Organ of the Society for Minerals and Trace Elements (GMS) 30, 107–111. https://doi.org/10.1016/j.jtemb.2014.11.007.

Jiang, C.-B., Kao, C.-S., Chien, L.-C., Chen, Y.-J., Liao, K.-W., 2022. Associations among prenatal and postnatal arsenic, lead, and cadmium exposures and motor development in 3-year-old children: a longitudinal birth cohort study in Taiwan. Environ. Sci. Pollut. Res. Int. 29 (28), 43191–43200. https://doi.org/10.1007/s11356-021-18321-5.

Julian, L.J., 2011. Measures of anxiety: state-trait anxiety inventory (stai), beck anxiety inventory (bai), and hospital anxiety and depression scale-anxiety (HADS-A). Arthritis Care Res. 63 (Suppl. 1), S467–S472. https://doi.org/10.1002/acr.20561, 0 11.

Kippler, M., Tofail, F., Hamadani, J.D., Gardner, R.M., Grantham-McGregor, S.M., Bottai, M., Vahter, M., 2012. Early-life cadmium exposure and child development in 5-year-old girls and boys: a cohort study in rural Bangladesh. Environmental Health Perspectives 120 (10), 1462–1468. https://doi.org/10.1289/ehp.1104431.

Kou, X., Bulló, M., Rovira, J., Díaz-López, A., Arija, V., 2023a. Dietary intake of metals, metalloids, and persistent organic pollutants in Spanish pregnant women. ECLIPSES study. Chemosphere 344, 140319. https://doi.org/10.1016/j.chemosphere.2023.140319.

Kou, X., Iglesias-Vázquez, L., Nadal, M., Basora, J., Arija, V., 2023b. Urinary concentrations of heavy metals in pregnant women living near a petrochemical area according to the industrial activity. Environ. Res. 235, 116677. https://doi.org/10.1016/j.envres.2023.116677.

Kwon, H.-K., Choi, G.B., Huh, J.R., 2022. Maternal inflammation and its ramifications on fetal neurodevelopment. Trends Immunol. 43 (3), 230–244. https://doi.org/10.1016/j.it.2022.01.007.

Lanphear, B.P., Rauch, S., Auinger, P., Allen, R.W., Hornung, R.W., 2018. Low-level lead exposure and mortality in US adults: a population-based cohort study. Lancet Public Health 3 (4), e177–e184. https://doi.org/10.1016/S2468-2667(18)30025-2.

Liu, C., Huang, L., Huang, S., Wei, L., Cao, D., Zan, G., Tan, Y., Wang, S., Yang, M., Tian, L., Tang, W., He, C., Shen, C., Luo, B., Zhu, M., Liang, T., Pang, B., Li, M., Mo, Z., Yang, X., 2022a. Association of both prenatal and early childhood multiple metals exposure with neurodevelopment in infant: a prospective cohort study. Environ. Res. 205, 112450. https://doi.org/10.1016/j.envres.2021.112450.

Liu, C., Huang, L., Huang, S., Wei, L., Cao, D., Zan, G., Tan, Y., Wang, S., Yang, M., Tian, L., Tang, W., He, C., Shen, C., Luo, B., Zhu, M., Liang, T., Pang, B., Li, M., Mo, Z., Yang, X., 2022b. Association of both prenatal and early childhood multiple metals exposure with neurodevelopment in infant: a prospective cohort study. Environ. Res. 205. https://doi.org/10.1016/J.ENVRES.2021.112450.

Liu, L., Urch, B., Szyszkowicz, M., Evans, G., Speck, M., Van Huang, A., Leingartner, K., Shutt, R.H., Pelletier, G., Gold, D.R., Brook, J.R., Godri Pollitt, K., Silverman, F.S., 2018. Metals and oxidative potential in urban particulate matter influence systemic inflammatory and neural biomarkers: a controlled exposure study. Environ. Int. 121, 1331–1340. https://doi.org/10.1016/j.envint.2018.10.055.

Liu, Y., Téllez-Rojo, M.M., Sánchez, B.N., Zhang, Z., Afeiche, M.C., Mercado-García, A., Hu, H., Meeker, J.D., Peterson, K.E., 2019a. Early lead exposure and pubertal development in a Mexico City population. Environ. Int. 125, 445–451. https://doi.org/10.1016/j.envint.2019.02.021.

Liu, Z., Cai, L., Liu, Y., Chen, W., Wang, Q., 2019b. Association between prenatal cadmium exposure and cognitive development of offspring: a systematic review. Environmental Pollution (Barking, Essex : 1987) 254 (Pt B), 113081. https://doi.org/10.1016/j.envpol.2019.113081.

Lozano, M., Murcia, M., Soler-Blasco, R., Casas, M., Zubero, B., Riutort-Mayol, G., Gil, F., Olmedo, P., Grimalt, J.O., Amorós, R., Lertxundi, A., Vrijheid, M., Ballester, F., Llop, S., 2022. Exposure to metals and metalloids among pregnant women from Spain: levels and associated factors. Chemosphere 286 (Pt 2), 131809. https://doi.org/10.1016/j.chemosphere.2021.131809.

Ma, C., Iwai-Shimada, M., Nakayama, S.F., Isobe, T., Kobayashi, Y., Tatsuta, N., Taniguchi, Y., Sekiyama, M., Michikawa, T., Yamazaki, S., Kamijima, M., 2021. Association of prenatal exposure to cadmium with neurodevelopment in children at 2 years of age: the Japan Environment and Children's Study. Environ. Int. 156, 106762. https://doi.org/10.1016/j.envint.2021.106762.

Ma, J., Geng, S., Sun, Q., Zhang, X., Han, L., Yao, X., Zhang, B., Zhu, L., Wen, J., 2023. Exposure to metal mixtures and young children's growth and development: a biomonitoring-based study in Eastern China. Ecotoxicol. Environ. Saf. 268, 115726. https://doi.org/10.1016/j.ecoenv.2023.115726.

Ma, Y., Su, Q., Yue, C., Zou, H., Zhu, J., Zhao, H., Song, R., Liu, Z., 2022. The effect of oxidative stress-induced autophagy by cadmium exposure in kidney, liver, and bone damage, and neurotoxicity. Int. J. Mol. Sci. 23 (21). https://doi.org/10.3390/ijms232113491.

Mathiesen, L., Buerki-Thurnherr, T., Pastuschek, J., Aengenheister, L., Knudsen, L.E., 2021. Fetal exposure to environmental chemicals; insights from placental perfusion studies. Placenta 106, 58–66. https://doi.org/10.1016/j.placenta.2021.01.025.

Michalec, D., 2011. Bayley scales of infant development: third edition. In: Encyclopedia of Child Behavior and Development. Springer US. https://doi.org/10.1007/978-0-387-79061-9_295, 215–215.

Renzetti, S.C.P.G.C., 2023. gWQS: generalized weighted quantile sum regression, 3 (0.5).

Renzetti, S., Gennings, C., Calza, S., 2023. A weighted quantile sum regression with penalized weights and two indices. Front. Public Health 11, 1151821. https://doi.org/10.3389/fpubh.2023.1151821.

Sanders, A.P., Claus Henn, B., Wright, R.O., 2015. Perinatal and childhood exposure to cadmium, manganese, and metal mixtures and effects on cognition and behavior: a review of recent literature. Current Environmental Health Reports 2 (3), 284–294. https://doi.org/10.1007/s40572-015-0058-8.

Shah-Kulkarni, S., Ha, M., Kim, B.-M., Kim, E., Hong, Y.-C., Park, H., Kim, Y., Kim, B.-N., Chang, N., Oh, S.-Y., Kim, Y.J., Lee, B., Ha, E.-H., 2016. Neurodevelopment in early childhood affected by prenatal lead exposure and iron intake. Medicine 95 (4), e2508. https://doi.org/10.1097/MD.0000000000002508.

Shah-Kulkarni, S., Lee, S., Jeong, K.S., Hong, Y.C., Park, H., Ha, M., Kim, Y., Ha, E.H., 2020. Prenatal exposure to mixtures of heavy metals and neurodevelopment in infants at 6 months. Environ. Res. 182. https://doi.org/10.1016/J.ENVRES.2020.109122.

Shao, Y., Zheng, L., Jiang, Y., 2024. Cadmium toxicity and autophagy: a review. Biometals : An International Journal on the Role of Metal Ions in Biology, Biochemistry, and Medicine 37 (3), 609–629. https://doi.org/10.1007/s10534-023-00581-y.

Skogheim, T.S., Weyde, K.V.F., Engel, S.M., Aase, H., Surén, P., Øie, M.G., Biele, G., Reichborn-Kjennerud, T., Caspersen, I.H., Hornig, M., Haug, L.S., Villanger, G.D., 2021a. Metal and essential element concentrations during pregnancy and associations with autism spectrum disorder and attention-deficit/hyperactivity disorder in children. Environ. Int. 152, 106468. https://doi.org/10.1016/j.envint.2021.106468.

Skogheim, T.S., Weyde, K.V.F., Engel, S.M., Aase, H., Surén, P., Øie, M.G., Biele, G., Reichborn-Kjennerud, T., Caspersen, I.H., Hornig, M., Haug, L.S., Villanger, G.D., 2021b. Metal and essential element concentrations during pregnancy and associations with autism spectrum disorder and attention-deficit/hyperactivity disorder in children. Environ. Int. 152, 106468. https://doi.org/10.1016/j.envint.2021.106468.

Spearman's rank correlation coefficient, 2018. In: BMJ (Clinical Research Ed.), vol. 362, p. k4131. https://doi.org/10.1136/bmj.k4131.

Syed, S.A., Nemeroff, C.B., 2017. Early life stress, mood, and anxiety disorders. Chronic Stress (Thousand Oaks, Calif.) 1. https://doi.org/10.1177/2470547017694461.

Tanner, E.M., Bornehag, C.-G., Gennings, C., 2019. Repeated holdout validation for weighted quantile sum regression. MethodsX 6, 2855–2860. https://doi.org/10.1016/j.mex.2019.11.008.

Torras-Mañá, M., Gómez-Morales, A., González-Gimeno, I., Fornieles-Deu, A., Brun-Gasca, C., 2016. Assessment of cognition and language in the early diagnosis of autism spectrum disorder: usefulness of the Bayley Scales of infant and toddler development. J. Intellect. Disabil. Res. : JIDR (J. Intellect. Disabil. Res.) 60 (5), 502–511. https://doi.org/10.1111/jir.12291 third edition.

Trichopoulou, A., Costacou, T., Bamia, C., Trichopoulos, D., 2003. Adherence to a Mediterranean diet and survival in a Greek population. N. Engl. J. Med. 348 (26), 2599–2608. https://doi.org/10.1056/NEJMoa025039.

Valeri, L., Mazumdar, M.M., Bobb, J.F., Claus Henn, B., Rodrigues, E., Sharif, O.I.A., Kile, M.L., Quamruzzaman, Q., Afroz, S., Golam, M., Amarasiriwardena, C., Bellinger, D.C., Christiani, D.C., Coull, B.A., Wright, R.O., 2017. The joint effect of prenatal exposure to metal mixtures on neurodevelopmental outcomes at 20-40 Months of age: evidence from rural Bangladesh. Environmental Health Perspectives 125 (6), 67015. https://doi.org/10.1289/EHP614.

Vrijheid, M., Casas, M., Gascon, M., Valvi, D., Nieuwenhuijsen, M., 2016. Environmental pollutants and child health—a review of recent concerns. Int. J. Hyg Environ. Health 219 (4–5), 331–342. https://doi.org/10.1016/j.ijheh.2016.05.001.

Wang, Y., Chen, L., Gao, Y., Zhang, Y., Wang, C., Zhou, Y., Hu, Y., Shi, R., Tian, Y., 2016. Effects of prenatal exposure to cadmium on neurodevelopment of infants in Shandong, China. Environmental Pollution (Barking, Essex : 1987) 211, 67–73. https://doi.org/10.1016/j.envpol.2015.12.038.

Wood, S.N., 2017. Generalized Additive Models: an Introduction with R, second ed. Chapman and Hall/CRC, Boca Raton.

Yi, C., Wang, Q., Qu, Y., Niu, J., Oliver, B.G., Chen, H., 2022. In-utero exposure to air pollution and early-life neural development and cognition. Ecotoxicol. Environ. Saf. 238, 113589. https://doi.org/10.1016/j.ecoenv.2022.113589.