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Assessing metal mixture effects on neuropsychological development: A trade-off between complexity and interpretability

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A R T I C L E I N F O

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A B S T R A C T

Several studies have explored the joint effect of mixtures of metals on health outcomes by using sophisticated statistical techniques such as Bayesian Kernel Machine Regression (BKMR). Although these appealing tools can detect complex relationships between metals, their interpretation is not straightforward. Indeed, BKMR is frequently used jointly with other methods, and final conclusions are simplified in terms of increase/decrease of the risk function at fixed values for individual metals. In this paper, we explore the feasibility and interpretability of such techniques to assess the effect of metal mixture exposures on neuropsychological development in early childhood. This is a cross-sectional study. Initially, we use Principal Components Analysis (PCA) to detect main latent neurodevelopment domains. The scores derived by the BKMR exposure-response function were computed and compared with those provided by traditional linear regression models (LRM). Pearson's correlation coefficients of the estimations obtained by BKMR and LRM accounting for pairwise interactions between metals (lead, molybdenum, and selenium) were 0.95, 0.95 and 0.92, for the three identified latent domains: executive functions, motor functions and visual and verbal functions, respectively. The observed differences between both estimations mainly occurred in participants having low concentrations of lead and low and high values of selenium, which suggest linearity in the associations and not high order interactions between metals. We concluded that, in this case, employing linear regression to model the impact of mixtures on targeted outcomes led to similar results than more complex statistical techniques allowing a better understanding of both individual and interaction effects between metals.

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1. Introduction

Human beings are commonly exposed to multiple pollutants and chemicals in real-life scenarios (Valeri et al., 2017). Exposure can occur, for instance, through natural elements present in air, food, drinking water, and from activities derived from anthropogenic sources such as chemical and pharmaceutical industries, the combustion of fossil fuels, or the waste incineration (Bauer et al., 2020). Although, traditionally, most research on the effects of chemicals on biologic systems was conducted on a single element at a time, it is well accepted the exposure to the mixture of chemicals (Carpenter et al., 2002). Furthermore, the low-dose mixture literature provides evidence supporting relevant mixture effects, even when concentrations of single elements were below their no observable adverse effect level (NOAEL) (Kortenkamp et al., 2007). Metals are a class of chemicals that frequently co-occur in the environment, with growing evidence that the health impact of a metal depends on co-exposure to others (Claus et al., 2014; Hu et al., 2007; Chiu et al., 2023). Therefore, assessing the joint effects as a mixture is crucial to understand the actual impact of metals on health outcomes. The effects should be carefully considered in children, especially in early life and during pregnancy, because of the vulnerability at those life stages of rapid development and growth. Indeed, several studies already reported the effect of exposures to mixtures of metal in childhood and adolescence, for example, on preterm birth, birth weight for gestational age and cognitive function (Kim et al., 2018; Howe et al., 2022; Saxena et al., 2022).

The quantitative characterization of the mixture effects has been tackled with a variety of statistical approaches (Gibson et al., 2019; Hao et al., 2024). Traditional Linear Regression models (LRMs), considering an additive effect of each single component (in this context, 'metal'), are perhaps the easiest methods to build and interpret (Davalos et al., 2017). Besides, they can be combined with other techniques to avoid unstable solutions caused by potential high correlations between independent variables. We highlight backward/forward variable selection and dimensions reduction methods, like Principal Components Analysis (PCA). LRMs allow to explore latent interactions between metals through, for example, adding multiplicative terms, or stratifying the overall analysis of the effect of one metal by the (low, medium, or high) levels of other metals in the mixture. Non-linear effects or higher order interactions could also be included in regression models.

In this context, other statistical methods have been implemented to overcome the LRM limitations. For instance, weighted quantile sum (WQS) regression (Carrico et al., 2015) provides an overall mixture effect estimate while allows to properly handle high multicollinearity. A summary risk score, the so-called WQS index, is estimated as a weighted sum of the single exposure quantiles. The weights give the importance of the association between each metal and the continuous outcome. The effect of the mixture is finally represented as an additive model including the WQS index as a single exposure and covariates, which entails a unique direction (positive or negative) for the mixture effects. A recent update of this technique allows the estimation in both directions (Renzetti et al., 2023). This limitation is also relaxed by the Quantile g-computation (Q-gcomp) (Keil et al., 2020) method that allows to capture positive and negative effects of metals while also provides the overall risk score for the mixture. The weights are interpreted as the partial effect due to a specific metal (Rosato et al., 2022). Both statistical approaches, however, do not permit variable selection making their use not advisable in high-dimensional settings. Notice that, in high-dimensional settings, other procedures, including BKMR and LRM, will have problems depending on the correlation structure and the available sample size. In this context, to use previous knowledge for doing variable selection is frequently the best option.

BKMR has become very popular to assess the simultaneous effects of exposures to multiple metals (mixture) (Valeri et al., 2017; Bauer et al., 2020; Chiu et al., 2023; Saxena et al., 2022; Davalos et al., 2017). This approach models the health outcome as a smooth multivariable function of metals accounting for an additive effect of the potential confounders (Bobb et al., 2015). That is, the expected value of the health outcome, Y, conditioned to the metals, $\boldsymbol{Z}$, and the covariate values, $\boldsymbol{X}$, is assumed to be

$$\mathrm{E}[Y|\boldsymbol{Z},\boldsymbol{X}] = h(\boldsymbol{Z}) + \boldsymbol{\alpha}\cdot\boldsymbol{X}.$$

The so-called exposure-response function, $h(\cdot)$, is approximated by using Gaussian kernels, which allows to identify a wide variety of underlying functional forms. This flexible characterization of $h(\cdot)$ enables to capture non-linear associations between the mixture and the health outcomes, and also detecting complex interactions between metals. In addition, BKMR carries out variable selection which is especially useful in high-dimensional scenarios, where those metals with greater impact on the outcome can be identified. Despite these obvious advantages, the interpretation of the exposure-response relationship as a multidimensional function is far from being easy. In order to understand the nature of the association of the mixture with the outcome, results are reported for fixed concentrations of metals, generally quantiles, without questioning if they are actually achievable in real-world exposures (for example, when metals have a positive high correlation, it is not realistic to consider results for high concentrations of one of them and low concentrations for the others). Furthermore, BKMR is not usually employed alone, but in combination with other statistical methods that also support and help to understand the stated results. In a traditional LRM with interactions, we make a strong assumption on the shape of the exposure-response function, and consider

$$h(\boldsymbol{Z}) = \beta_0 + \beta_1\cdot z_1 + \ldots + \beta_M\cdot z_M + \sum_{k\neq l}\beta_{kl}\cdot(z_k\cdot z_l).$$

We explore, in this paper, the nature of the estimates of the exposure-response function provided by BKMR by comparing them with those obtained using two traditional LRM approaches: *i)* without accounting for interactions between metals (assuming $\beta_{kl} = 0$), and *ii)* including pairwise interactions as multiplicative terms. With this goal, we particularly studied the effects of a mixture of metals on neuropsychological outcomes in four years old children from the INMA cohort (Spain) (Guxens et al., 2012). We hypothesized that linear regression, with pairwise interaction terms for modeling the effect of the mixture, can get similar results to those provided by more complex models, such as BKMR, while offering the advantage of greater simplicity and interpretability.

2. Methods

2.1. Study population

The INMA –*INfancia y Medio Ambiente*- (Environment and Childhood) project is a prospective population-based cohort study conducted in several regions of Spain whose main objectives are to describe the degree of early environmental exposure to pollutants and the internal presence of these chemicals during pregnancy, birth and childhood, and to evaluate both the effect of these exposures and the impact of interactions between pollutants, nutrients and genetic variants, on the growth and development of the children. The project includes mothers aged at least 16 years and their offspring who, among other criteria, reside in the study areas, had a singleton pregnancy, and have not followed an assisted reproduction program. We included in this study participants enrolled in the sub-cohorts of Asturias, Gipuzkoa, Valencia and Sabadell. Recruitment took place during the first prenatal visit (10–13 weeks of gestation) in the main public health center of each area, between years 2003 and 2008. Follow-up surveys were performed in all sub-cohorts at pregnancy, birth and 4–5 years. Of the 2644 participants recruited, we excluded 138 who did not give birth to a live child and 448 who did not complete the 4–5-year follow-up. An additional 998 were excluded due to incomplete or missing neurophysiological assessments. We further excluded 92 participants with missing urinary metal concentrations and 16 with unavailable covariates. The final analytic sample consisted of 962 participants. A flow chart is provided in Fig. S1, and Table S1 compares included (n = 962) and excluded (n = 1682) participants. A sensitivity analysis using multiple imputation on the 1060 participants on which, at least, we have complete information for the neurophysiological assessment is included as supplementary material (Table S6–S9 and Fig. S12–S22). All participants provided informed consent and the ethical committees of the involved health centers (Comité de Ética de la Investigación Médica del Principado de Asturias (CEIM) Zumarraga Hospital, Gipuzkoa; La Fe Hospital, Valencia and Parc Tauli Hospital, Sabadell) approved the protocol.

2.2. Metals(oid) assessment

During the 4–5-year follow-up pediatric interview, spot urine samples were collected and stored in 100 mL polyethylene containers at or below −20 °C until analysis. Urine metal concentrations of cobalt (Co), copper (Cu), selenium (Se), molybdenum (Mo), lead (Pb), and zinc (Zn) were analyzed by inductively coupled plasma mass spectrometry (ICP-MS) in direct solution acquisition mode using a Cetax ASX-520 Auto Sampler. Cadmium (Cd) was initially excluded because the high percentage of missing values (245/962). A Thermo Scientific IC5000 ion chromatography system, with a Thermo AS7, 2 × 250 mm column and a Thermo AG7, 2 × 50 mm guard column interfaced with a Thermo ICAP Q ICP-MS was used to analyze arsenic (As) speciation including the species arsenobetaine (AsB), dimethylarsinic acid (DMA), monomethylarsonic acid (MMA) and inorganic arsenic (iAs).

Each analytic batch included blank and replicate samples of Clinchek® lyophilized urine samples for quality control of Co, Cu, Pb, Se, Mo, and Zn, as well as blank and replicate samples of the National Institute of Standards and Technology (NIST) human urine standard reference material 2669 or ClinChek® Control Level I for quality control of As species. The average recovery was 88.9 % (Co), 84.2 % (Cu), 75.0 % (Se), 114.0 % (Mo), 78.5 % (Pb), 84.2 % (Zn), and 96.8 % including AsB, DMA, MMA and iAs. The limit of detection (LOD) was calculated as the mean of the blank concentrations plus 3 times their standard deviation multiplied by the dilution factor. The LOD for the measured elements ranged from 0.008 μg/L for DMA, to 14.36 μg/L for Mo (Table S2). No values below the LOD were observed for urinary Se, Mo, and Zn concentrations. However, a percentage of values below LOD were observed for Co (2 %), Cu (17 %), Pb (38 %), AsB (4 %), DMA (12 %), MMA (27 %) and iAs (9 %) concentrations. Values below the LOD were imputed by the LOD divided by the square root of two. As sensitivity analysis, we used multiple imputation chain equation (MICE) for imputing values below the LOD (Table S6).

All urine metal concentrations were adjusted for urine dilution using $E_{sg} = E_0 \bullet [(SG_{median} - 1)/(SG_0 - 1)]$ where E_{sg} is the specific gravity-standardized exposure biomarker concentration, E_0 the observed exposure biomarker concentration, SG_{median} the median of specific gravity value in the study sample, and SG_0 the observed specific gravity value (Kuiper et al., 2022).

2.3. Neuropsychological assessment

McCarthy Scales of Children Ability (MSCA) adapted to Spanish population (McCarthy, 2009) were used to assess the neuropsychological functions of the children at 4–5 years of age. In addition to the six domains included in the MSCA instrument (verbal, perceptual-performance, quantitative, memory, motor and general cognitive), we also considered the following subarea scores: executive functions, visual and verbal span, working memory, verbal memory, gross and fine motor functions, and cognitive functions of the posterior cortex, as previously described in (Notario-Barandiaran et al., 2023). Testing was conducted in research centers of each area of study by six psychologists using a strict protocol to avoid inter-observer variability. This protocol included inter-observer training and sets of quality control. The inter-observer variability assessed by Pearson correlations was lower than 5 %. The raw scores were standardized for the child's age at test administration and for psychologists. In order to homogenize scales, standardized residuals were then typified by having a mean of 100 and a standard deviation of 15 points. Higher scores were associated with better performance in the corresponding domains.

Children from Asturias, Gipuzkoa and Sabadell were 4.4 [4.0–5.3] years old (median [min. – max]), when MSCA tests were performed and those from Valencia were slightly older: 5.7 [5.6, 6.4] years old.

2.4. Covariates

Socio-demographical characteristics of caregivers and child anthropometry data were collected in the follow-up surveys. The information was gathered by trained INMA personnel from a variety of sources, including *ad-hoc* administered questionnaires, physical examinations and in face-to-face interviews, among others (Guxens et al., 2012). We considered the following covariates as potential confounders based on a priori evidence: maternal social class based on occupation at pregnancy, categorized as managers/technicians, skilled manual and skilled non manual/semi-skilled (International standard classification of occupations); parity (0, 1, >1); maternal education (primary, secondary or university studies); sex of the children at birth, body mass index (BMI) at 4 years follow-up and age of the children at MSCA assessment. These covariates were also selected in (Notario-Barandiaran et al., 2023).

2.5. Statistical analysis

Metal concentrations and covariates were described overall through medians and interquartile range (IQR) or their absolute and relative frequencies, as appropriate. We defined the 'Total Arsenic' variable as the sum of iAs and MMA metabolites to reflect the exposure to iAs. Due to the skewness of the distributions, we applied natural logarithm transformations to all metal concentrations and then standardized these variables for analysis. Single imputation was done to avoid missingness in covariates parity and maternal social class. Missing values were replaced by the predicted scores obtained through LRM, where parity and maternal social class were the response variables and the remainder covariates acted as predictors. Outcome variables (neuropsychological domains) were summarized by their means and standard deviations. Principal Components Analysis on the correlation matrix was performed in order to identify main latent domains. Particularly, we selected the three components associated to the highest eigenvalues, explaining approximately the 80 % of the total variance. First component led to a latent domain which we characterized as '*Executive functions*' and accounted for: general cognition, global quantitative, executive, visual and verbal executive and working memory domains. Second and third principal components allowed us to identify '*Motor function*' and '*Visual and verbal functions*' as additional latent factors. Motor function included global, gross, and fine motor, global perceptive performance and visual and verbal span domains, while visual and verbal functions encompassed the following domains: verbal and global memory, global verbal and cognitive function of posterior cortex (Fig. 1). The matrix of correlation between the neuropsychological domains and the loadings matrix resulting from the PCA analysis are provided as Supplementary material (Fig. S2 and Table S3, respectively).

We initially applied BKMR with component-wise variable selection to estimate the exposure-response function, and assess the effects of the mixture of all metals on the three latent domains derived from the PCA. Correlations between metals were previously computed (matrix provided as Fig. S3). We selected for analysis those whose posterior inclusion probability (Table S4) was greater than 0.5 in at least one of the three models. As sensitivity analysis, we consider the hierarchical variable selection option (Tables S7 and S8). Finally included metals were Pb, Se and Mo. It may be useful to move the threshold from 0.5 to below 0.4 in order to include more metals; in this case, Zn and Co would also be

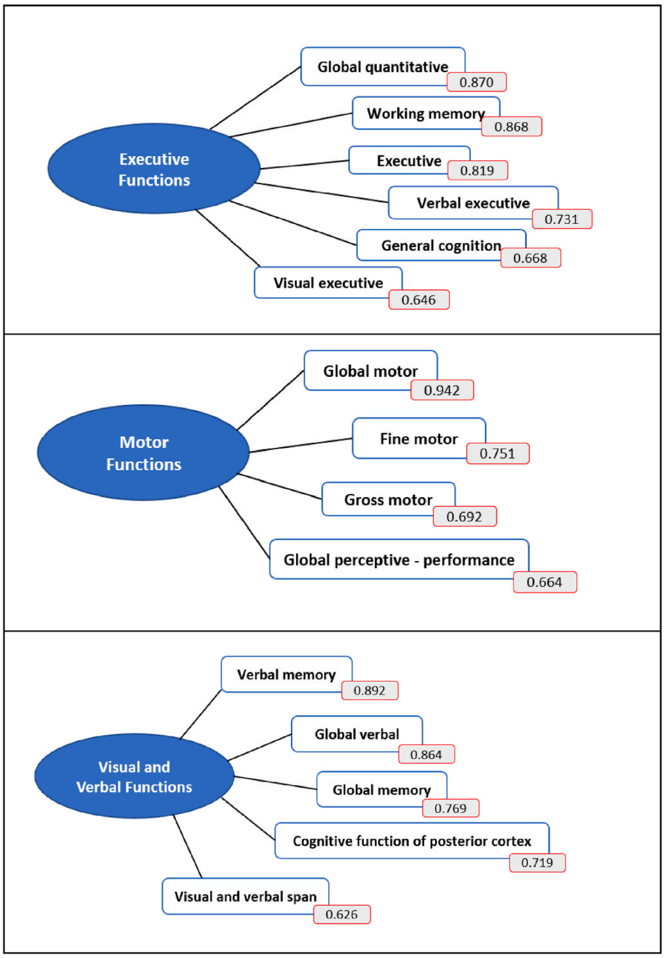

Fig. 1. Latent domains resulting from Principal Components Analysis (PCA) and the domains that comprise them, with their loads to the corresponding component.
The cumulative explained variances from Executive Function (first principal component) to Motor and Visual and Verbal Functions (second and third principal components) are 32.5 %, 52.2 % and 78.8 %, respectively.

included in the analysis. BKMR models were further fitted to explore the effect of the mixture of the three selected metals on each of the three outcomes. Specifically, the exposure-response function, denoted here as *'h-bkmr'*, was approximated by using a Gaussian kernel with 50,000 iterations by the Markov Chain Monte Carlo algorithm, and all models were adjusted for the described covariates. The usual cross-sections summaries (Bobb et al., 2018) were obtained: *i)* univariate relationship between each metal and outcome while maintaining other exposures fixed at the median; *ii)* bivariate exposure-response function for one metal while fixing at its quartiles and median the second and third metals, respectively and *iii)* the comparison of the overall effect of three metals fixed at a range of quantiles with the value when fixed to the median.

As an alternative approach, we fitted generalized LRM adjusted by the aforementioned covariates. First, the exposure-response functions of the metals were modeled additively, *'h-lni'* (linear no-interactions), and then, all pairwise interaction terms were added to these models, *'h-lwi'* (linear with interactions). In both cases, we computed the same cross-sections summaries (described in *i, ii* and *iii*) as for the BKMR fit. Obviously, in this case, the resulting functions will be linear. Since our main goal was to have a deeper understanding of the relationship between the estimation of the exposure-response function, provided by the BKMR and LRM models, for each outcome and each participant, we computed the approximations of $h(\cdot)$ provided by *'h-bkmr'*, *'h-lni'*, and *'h-lwi'*. The Pearson correlation coefficient was used for studying the correlations between the three procedures. Then, we graphically represented the corresponding scatter plots, differentiating the points outside a pre-established band within a distance of 0.1 of the main diagonals (perfect match). We also plot the density functions of the metals discriminating by those points. All analyses were performed with the software R (www.r-project.org), version 4.3.2.

3. Results

From the 962 participants in the study, approximately, 39 % belonged to the Sabadell cohort, 28 % to Gipuzkoa and 23 % and 10 % to the Asturias and Valencia cohorts, respectively. Around 60 % of the mothers were nulliparous and almost half were employed during pregnancy as managers/technicians, 82 % having completed secondary school. Regarding the children, 52 % were male and performed the McCarthy tests at a median (IQR) age of 4.5 (0.2) years. Half of them had a BMI less than 16 kg/m^2 (Table 1).

The univariate exposure-response functions derived from the BKMR model indicated that increasing Pb was associated with a decrease in the scores of all latent domains while increasing Mo showed an increase in these scores. Additionally, increasing Se was negatively associated with executive functions and showed positive associations with *motor*, and *visual and verbal* functions (Figs. S5, S6, S7, Left). Regarding the cumulative effect of the mixture of metals, we observed a decrease in the scores of visual and verbal and executive functions associated with increasing quantiles of the mixture. This decrease was mitigated for higher quantiles in the case of executive functions. On the other hand, there was an increase of the scores of motor functions (Fig. S4, Left). We observed evidence of interaction between Pb and Se for executive functions: the negative effect of Pb was mitigated by high values of Se (Figure S8b, Left). In addition, highest values of Mo also diminished the negative effect of Pb for motor, and visual and verbal functions (Figures S9a and S10a Left). Finally, the positive effect of Mo showed to

Table 1
Descriptive statistics of maternal and children characteristics and urinary concentrations.

Characteristics [a]	N = 962
Maternal	
Number of previous live births	
0	521 (56.8 %)
1	347 (37.8 %)
> 1	50 (5.45 %)
Maternal social class based on occupation at pregnancy	
Managers/technicians	241 (26.2 %)
Skilled manual	263 (28.6 %)
Skilled non-manual/semi-skilled	415 (45.2 %)
Maternal education	
Primary	175 (18.2 %)
Secondary	391 (40.6 %)
University	396 (41.2 %)
Children	
BMI–kg/m2	16.0 [15.0-0.03]
Age MSCA–years	4.45 [4.37; 4.58]
Urine concentrations–μg/L	
Arsenobetaine (AsB)	12.3 [3.19; 42.3]
Inorganic arsenic (iAs)	1.09 [0.39; 2.15]
Monomethylarsonic acid (MMA)	0.41 [0.01; 0.81]
Dimethylarsinic acid (DMA)	3.21 [0.38; 6.56]
Cobalt (Co)	0.77 [0.47; 1.30]
Lead (Pb)	0.49 [0.21; 1.08]
Selenium (Se)	24.90 [18.1; 35.8]
Zinc (Zn)	379 [252; 578]
Molybdenum (Mo)	83.7 [50.4; 124]
Copper (Cu)	8.97 [4.64; 13.2]

[a] Categorical variables are presented as n (%) and continuous variables are presented as median [Q1, Q3]. Values below the LOD are imputed using LOD/$\sqrt{2}$. Urine concentrations are adjusted for specific gravity following the method described by Kuiper et al. (2022)

be higher for the lowest concentrations of Se in the case of motor functions (Figure S9a).

Linear regression models without interactions between metals revealed statistically significant negative associations between Pb and the three latent domains, with effect sizes [95 % CI] ranging from −0.11 [−0.19, −0.03] ($p = 0.009$), to −0.08 [−0.17, 0.00] ($p = 0.046$), for visual and verbal functions and motor functions, respectively. Mo, on the other hand, showed significant positive associations with motor functions (0.11 [0.04, 0.018], $p = 0.001$), and executive functions (0.08 [0.02, 0.15], $p = 0.015$). When interactions terms were included in models, the effect of Pb on executive functions (−0.11 [−0.19, −0.03], $p = 0.010$) was further modified by a significant interaction with Se in the opposite direction: 0.08 [0.01, 0.16], $p = 0.020$. No other interaction terms were statistically significant (Table S5).

The overall mixture effects from linear regression on the three latent domains showed the same trend as the reported by BKMR models (Fig. S4, Middle and Right). We observed differences with BKMR in cross-sectional summaries representing the univariate effect of Se on executive functions (Fig. S5, Middle and Right) and the effect of Pb in both, motor and visual and verbal functions (Fig. S6 and S7 Middle and Right). In these cases, the negative slope represented by linear models did not show the smooth mitigation of the effect for the highest values of Se and Pb, respectively, detected by BKMR. Bivariate effects summaries for LRM clearly showed the reported interaction between Pb and Se for executive functions (Figure S8b, Right), and those between Pb and Mo and Se and Mo for motor functions (Figures S9a and S9b, Right, respectively). In the case of visual and verbal functions, both Mo and Pb showed to modify the effect of Se (Figure S10b, Right), which was not observed in BKMR summaries (we recall that these interactions, however, were not statistically significant).

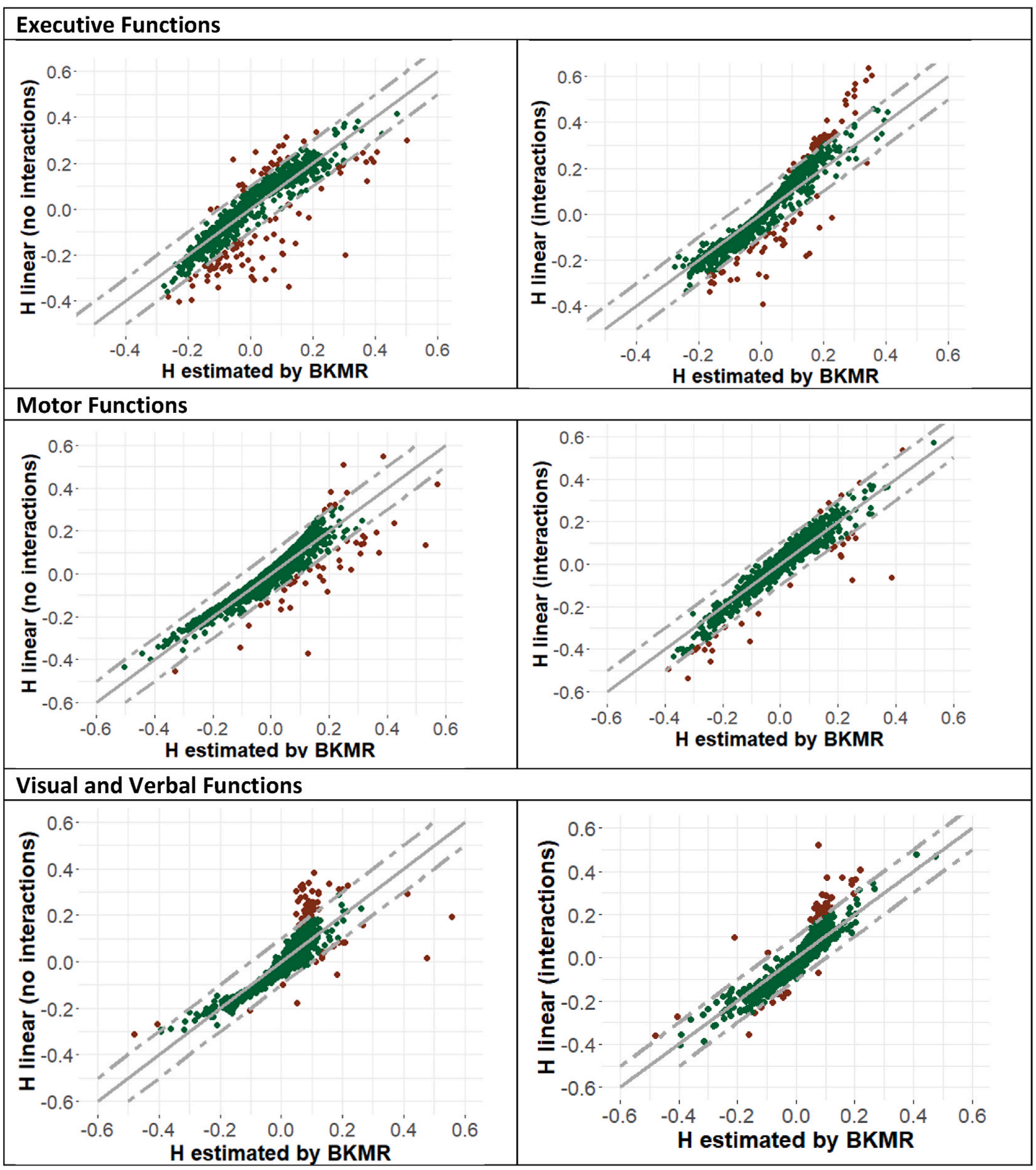

Fig. 2. Predictions from exposure-response functions estimated by BKMR (h-bkmr) vs. predictions estimated by linear regression models (h-linear), not including and including pairwise interactions on **Executive Functions**, **Motor Functions** and **Visual and Verbal Functions**.

Dashed gray lines delimit a band from a 0.1 distance to the mail diagonal (solid gray line). Predictions obtained with exposure response functions from BKMR and linear models that lye inside the preset band are plotted in green and predictions outside the band are plotted in red. Left: linear models not including interaction terms. Right: linear models including interactions terms. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

When exploring the relationship between the h-BKMR and h-linear predictions, we observed that, in the case of executive functions, the Pearson correlation coefficient was 0.89 when pairwise interactions between metals were not considered. Around 10 % (96) of participants did not lie within the 0.1-distance pre-established band. This percentage was reduced to 8.7 % (84) of participants when the regression models included the interactions terms (Fig. 2, Top). In this case, the correlation coefficient increased to 0.95, which suggests high similarities between the effects predicted by both BKMR and the LRM. Exploring the distributions of metals on participants inside and outside the pre-stablished band, we observed that the differences arose for both low and high levels of Pb and Se when no interactions were modeled (Fig. S11, Top) and, although slightly reduced, these differences still remained when linear models included interaction terms (Fig. 3, Top). This suggests that, in addition to the statistically significant interaction modeled in linear regression, BKMR may represent higher order interactions between these metals or capture slightly deviations from linear shape. Only 5.2 % (50) and 3.7 % (36) participants were outside the pre-stablished band when representing *h-linear* (with and without the interaction terms, respectively) versus *h-bkmr* predictions in the case of motor functions (Fig. 2, Middle). Interaction terms were not statistically significant, and correlations were similar (0.92 and 0.95, respectively). Distributions of metals on the 50 differing participants may suggest a slightly different behavior represented by BKMR for low and high levels of the three metals (Fig. S11, Middle). When accounting for pairwise interactions differences were reduced to only 36 participants who also presented high and low levels of the three metals (Fig. 2, Middle), so the linear relationship seemed to be dominant. Regarding visual and verbal functions, a total of 62 (6.4 %) and 53 (5.5 %) participants lied outside the pre-stablished band for *h-linear* predictions not including and including interaction terms, respectively (Fig. 2, bottom). Accounting for these interactions in regression models better approximated *h-linear* and *h-bkmr* predictions, increasing correlations from 0.87 to 0.92. Differences between both predictions seemed to be due to lower levels of Pb

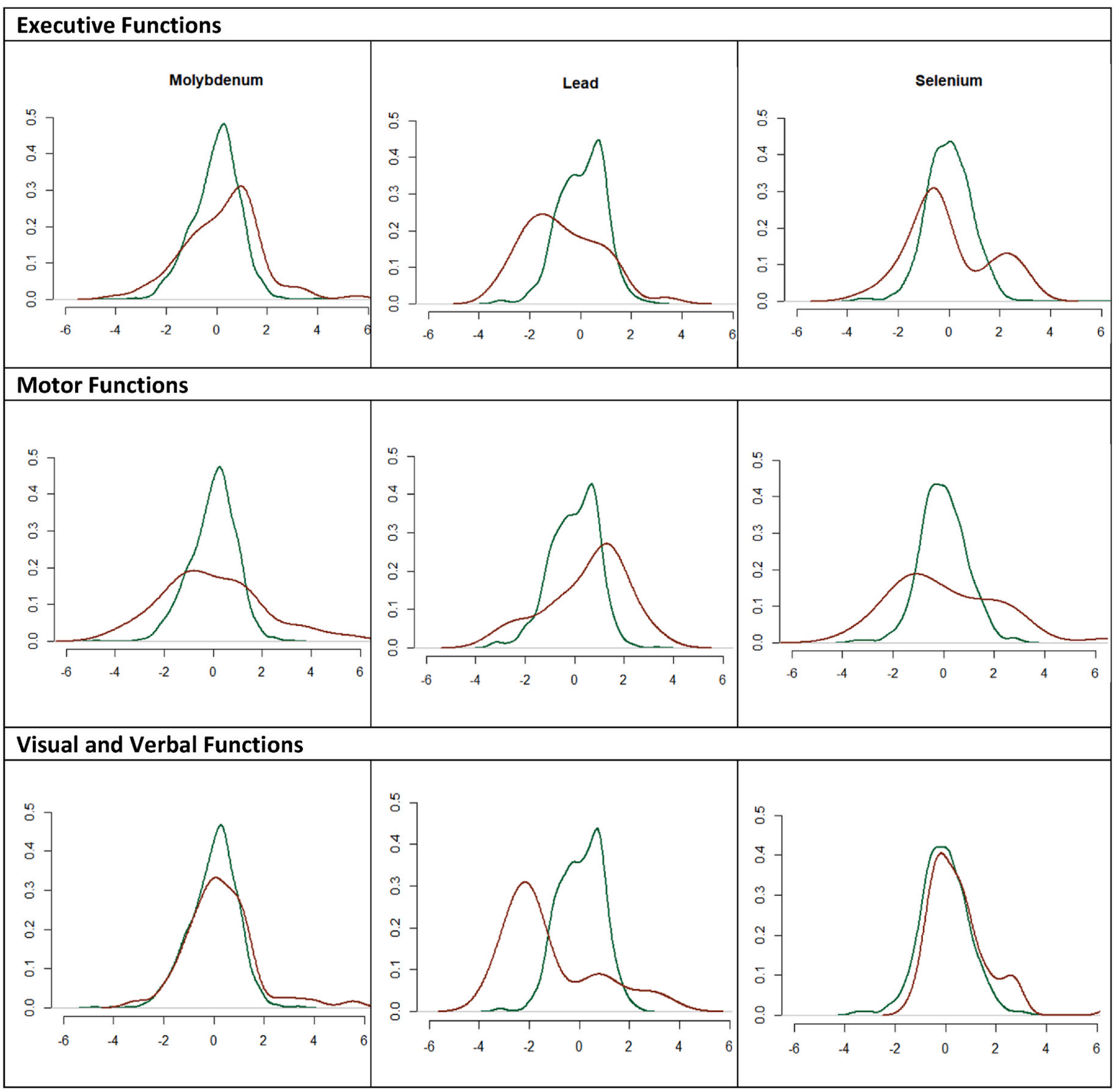

Fig. 3. Distribution of metal concentrations (log-transformed and standardized) on participants **inside** and **outside** the preset bands from linear regression models including interactions terms.
Density distribution functions of **Mo** (left), **Pb** (middle) and **Se** (right) corresponding to participants whose exposure-response functions estimations by BKMR and LRM including interaction terms lied **inside** (green) and **outside** (red) the preset bands from 0.1 distance to the principal diagonal. Exposure-response function estimations for **Executive Functions** (top), **Motor Functions** (middle) and **Visual and Verbal Functions** (bottom). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(Fig. S11, bottom, which were not totally captured including the pairwise interactions in regression models (Fig. 3, bottom). This may induce a non-linear relationship of higher order interactions of this metal with the latent domain, best explained by the BKMR model.

4. Discussion

Modern technologies allow to measure, store, and analyze huge quantities of information. The use of sophisticated statistical procedures allows researchers to address complex scientific questions. High dimensional data or complicated interactions among exposures are just some examples of that. Particularly, environmental epidemiology copes with the problem of how to effectively analyze the real effect of the exposure to mixtures of metals. With this goal, different statistical techniques have been implemented. Frequently, these procedures report complex results not easy to interpret, which used to be simplified in order to get an understandable message. In this paper, we consider the results provided by BKMR in the context of studying the effects of metal mixtures on neuropsychological development in early childhood and compare the obtained punctuations with those provided by LRMs with and without interactions terms. We show how, in this case, traditional LRM provide similar conclusions in simpler manner, and therefore, the advantages provided by BKMR in terms of dealing with non-linearity and/or high order interactions does not really apply on this real-world dataset.

The exposure-response function, $h(\cdot)$, explains the relationship between the mixture exposure and the outcome of interest. In BKMR models, the lack of parameters summarizing the function and its multivariable nature make its interpretation difficult, so results are conventionally presented as cross-sectional functions. Common graphical representations include those defined by the pairs $\left\{Y, h\text{-bkmr}\left(z_1, q_{2,2}, q_{3,2}\right)\right\}$, were z_1 is the metal in the x-axis, and $q_{2,2}$ and $q_{3,2}$ are the medians of the remainder metals considered in the model: z_2 and z_3, in our three-dimensional case. That is, we fix all the metal values but one, and plot the resulting cross-sectional line. Highlight that 1) this situation could be not realistic, and there exists the possibility that no participant fits on the profile determined by these fixed values, and 2) there exist infinite cross-sectional lines and, therefore, making inference based on the observed results is adventured. For having a fully understanding of the function $h(\cdot)$, we should plot the resulting hypersurface, difficult for two metals (three dimensions), and impossible for three or more. In the case of LRM, the exposure-response function is assumed to be

$$h(\mathbf{Z}) = \beta_0 + \beta_1 \cdot z_1 + \ldots + \beta_M \cdot z_M + \sum_{k \neq l} \beta_{kl} \cdot (z_k \cdot z_l).$$

Since the coefficients of the model ('the *betas*') determine the function, no further information is usually reported. However, the above cross-sectional summaries visualized for BKMR can be also obtained for LRM (Fig. S4–S10 **b**). Notice that, in the above model, '*the beta*' associated with the exposure of the i-th metal depends on the values of the rest of the metals through the interaction terms being identified by.

$\beta_i + \sum_{k \neq i} \beta_{k_i} \cdot z_k^*$ where z_k^* stands for the specific values of these metals. Our analysis of the association between metal exposure and child neuropsychological development revealed that exposure to a mixture of Pb, Se, and Mo was negatively associated with all neuropsychological domains, except for the motor functions, where higher scores were observed. Notably, these associations appeared to be primarily driven by Pb. Similar to our results, the New Bedford Cohort study, which included 528 children aged 13–17 years, used BKMR models and found an adverse joint association between a chemical mixture containing Pb and performance on the verbal working memory subtest (Oppenheimer et al., 2022). In line with our findings, a community-based study in Tarragona, Spain, involving 400 mother-infant pairs, applied WQS regression and reported that exposure to a metal mixture—including Cd, nickel, mercury, and Pb—was significantly associated with poorer expressive language outcomes (Kou et al., 2025). Additionally, a study conducted in Italy among adolescents aged 10–14 years found that higher exposure to metal mixtures, including Mb, manganese, chromium, and Cu, was associated with lower intelligence quotient scores (Bauer et al., 2020). Sensitivity analysis does not change these conclusions.

In contrast to our findings, the Wuhan Healthy Baby Cohort study in China, which included 1088 mother-infant pairs, reported that maternal exposure to higher levels of metal mixtures, including Pb, was associated with lower Motor and Psychomotor Development Index scores in two-year-old children, as determined by WQS analysis (Xie et al., 2025). These discrepancies may be explained by differences in the populations studied, as most previous research has focused on prenatal exposures and their effects during infancy, whereas our study assessed exposure during childhood.

In contrast to Pb exposure, higher Se and Mo levels were associated with improved performance in the visual, verbal, and motor domains. However, Se also exhibited a negative association with executive function scores. The role of Mo in neurodevelopment remains unclear, as previous studies have reported conflicting results (Forns et al., 2014; Vázquez-Salas et al., 2014; Nozadi et al., 2021). Furthermore, as an essential metal, Mo has been less frequently studied in relation to neurodevelopment, underscoring the need for further research in this area. Our findings align with a study conducted in China among 703 mother-child pairs, which reported that higher prenatal serum Mo concentrations were associated with better social developmental quotients in children aged 2–3 years (Liu et al., 2022). Similarly, a study from the Croatian Mother and Child Cohort, involving 205 mother-child pairs, found that maternal blood Se levels were positively correlated with children's cognitive abilities (Močenić et al., 2019). Furthermore, previous studies have suggested a potential "protective" role of Se in mitigating the neurotoxic effects of Pb. For instance, a study conducted among 1007 adults from Gulf states demonstrated that Se modulated the association between Pb exposure and peripheral nervous system symptoms. Specifically, individuals with lower Se levels exhibited a stronger association between Pb exposure and the occurrence of symptoms across all quartiles of exposure (Werder et al., 2020).

Regarding the negative association between Se exposure and executive function scores, our results are consistent with findings from the INMA Valencia cohort. In this study of 490 mother-child pairs, an inverted U-shaped relationship was observed between serum Se concentrations and executive function scales, suggesting that both insufficient and extreme Se levels may have adverse effects on executive functioning (Amorós et al., 2018).

In summary, we have shown that with our dataset, results obtained by BKMR are similar to those provided by LRM. This suggests that the nature of the relationships of the mixture exposure and the studied neuropsychological domains can be more easily explained and understood by using LRMs. Besides, our results are aligned with those obtained in a previous paper (Notario-Barandiaran et al., 2023) working with the same dataset and using other statistical approach: principal components analysis was used to identify latent mixture exposures and their impact was assessed on each individual neuropsychological domain. Our findings also agreed with previous epidemiological studies reporting negative associations between metal mixtures—including Pb—and neuropsychological development outcomes, as well as the complex role of essential metals such as Se and Mo in modulating these effects (Oppenheimer et al., 2022; Kou et al., 2025; Bauer et al., 2020; Xie et al., 2025; Liu et al., 2022; Močenić et al., 2019; Werder et al., 2020).

LRMs are techniques straightforward to implement whose reported coefficients are easier to interpret as average effects. Besides, their underlying assumptions seem to reasonably describe many real-world datasets. We recommend their use and reserve the power of BKMR for complex and strongly non-linear associations, where LRMs do not capture the relationships between mixtures and outcomes.

As usual, this study has several limitations. Although the main goal was to understand and compare results from alternative statistical techniques, the INMA dataset was used as a driver, and this dataset has a number of known drawbacks already reported in (Notario-Barandiaran et al., 2023). The use of one-time urine collection as a biomarker for metal exposure could Pb to potential misclassification. The cross-sectional design prevents establishing causality, as it does not determine the direction of the relationship between exposure and outcomes. The small sample size may have limited statistical power, though significant associations were still observed. While various potential confounders were adjusted for, residual confounding cannot be entirely ruled out. The study was conducted in a Spanish child population with relatively low exposure to metals, which may limit the generalizability of the findings. However, the external validity is partially supported by the consistency of observed associations with findings reported in other populations, suggesting that the results may be relevant to similarly exposed cohorts. Additionally, using fixed values for metal concentrations below the LOD could introduce bias. Despite these limitations, the study has notable strengths, including the analysis of As speciation—critical given that As toxicity depends on its chemical form, with iAs being the most harmful.

Finally, we want to remark that the results obtained in this single dataset should not be used for making

General statements about the relationship between LRMs and BKMR procedures. Beyond that, our objective was to draw a parallel between the outcomes reported by both the LRM and the BKMR in order to have a better understanding of what the more complex procedure provides in comparison with the simpler one.

CRediT authorship contribution statement

Susana Diaz-Coto: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Leyre Notario-Barandiaran:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Data curation, Conceptualization. **Pablo Martinez-Camblor:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Methodology, Investigation, Data curation, Conceptualization. **Manuel Lozano:** Writing – review & editing. **Sabrina Llop:** Writing – review & editing. **Adonina Tardón:** Writing – review & editing. **Cristina Rodríguez-Dehli:** Writing – review & editing. **Amaia Irizar:** Writing – review & editing. **Nerea Lertxundi:** Writing – review & editing. **Mónica Guxens:** Writing – review & editing. **Jordi Julvez:** Writing – review & editing. **Antonio J. Signes-Pastor:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2025.114697.

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