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Exposure to metal mixture and growth indicators at 4–5 years. A study in the INMA-Asturias cohort

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ABSTRACT

Background: Exposure to toxic and non-toxic metals impacts childhood growth and development, but limited data exists on exposure to metal mixtures. Here, we investigated the effects of exposure to individual metals and a mixture of barium, cadmium, cobalt, lead, molybdenum, zinc, and arsenic on growth indicators in children 4–5 years of age.

Methods: We used urine metal concentrations as biomarkers of exposure in 328 children enrolled in the Spanish INMA-Asturias cohort. Anthropometric measurements (arm, head, and waist circumferences, standing height, and body mass index) and parental sociodemographic variables were collected through face-to-face interviews by trained study staff. Linear regressions were used to estimate the independent effects and were adjusted for each metal in the mixture. We applied Bayesian kernel machine regression to examine non-linear associations and potential interactions.

Results: In linear regression, urinary levels of cadmium were associated with reduced arm circumference ($\beta_{adjusted} = -0.44$, 95% confidence interval [CI]: −0.73, −0.15), waist circumference ($\beta_{adjusted} = -1.29$, 95% CI: −2.10, −0.48), and standing height ($\beta_{adjusted} = -1.09$, 95% CI: −1.82, −0.35). Lead and cobalt concentrations were associated with reduced standing height ($\beta_{adjusted} = -0.64$, 95% CI: −1.20, −0.07) and smaller head circumference ($\beta_{adjusted} = -0.29$, 95% CI: −0.49, −0.09), respectively. However, molybdenum was positively associated with head circumference ($\beta_{adjusted} = 0.22$, 95% CI: 0.01, 0.43). BKMR analyses showed strong linear negative associations of cadmium with arm and head circumference and standing height. BKMR analyses also found lead and cobalt in the metal mixture were related to reduce standing height and head circumference, and consistently found molybdenum was related to increased head circumference.

Conclusion: Our findings suggest that exposure to metal mixtures impacts growth indicators in children.

1. Introduction

Increased exposure to metals and metalloids (referred to as "metals") have been associated with adverse birth outcomes (e.g., pre-term births and increased risk of fetal and infant mortality and reduced fetal growth) (Milton et al., 2005; Rahman et al., 2007; Howe et al., 2020;

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Signes-Pastor et al., 2019a)) and may also affect growth throughout childhood (Landrigan et al., 2004; Martin et al., 2003; Tchounwou et al., 2012). However, the impact of exposure to metal mixtures on child growth is less understood. This is an important concern as growth restriction during the first years of life increases the risks of type 2 diabetes mellitus, cardiovascular diseases, obesity, and certain cancers (Collins, 2005). Food and water intake, inhalation, and dermal absorption are the primary routes of metal exposure (Buckley et al., 2020).

To our knowledge, only three studies have evaluated the relationships between exposure to metal mixtures and child growth indicators. One study from Bangladesh reported an inverse association between child weight and height at 5 years and concurrent exposure to Cd and As (Gardner et al., 2013) using mixed-effects linear regression. Low blood Pb concentrations were found to be inversely associated with body mass index (BMI) in a Canadian study of preschool-aged children (Ashley-Martin et al., 2019) using a series of linear regression models. Based on data from the US National Health and Nutrition Examination Survey (NHANES), blood Pb and blood manganese (Mn) concentrations were respectively found to be inversely and positively associated with various growth indicators (BMI, standing height, waist circumference, and upper arm length) (Signes-Pastor et al., 2020) using Bayesian Kernel Machine Regression, a more recent statistical approach to estimate the effects of exposure to metal mixtures.

To better understand the effects of nutrient metals and toxic metals, we investigated the associations between exposure to a metal mixture (e.g., urinary Ba, Cd, Co, Pb, Mo, Zn, and As) and growth indicators in 4–5-year-old children in Spain.

2. Methods

2.1. Study design and population

Women who visited the San Agustin Hospital in Aviles during their pregnancy for the first prenatal care visit were enrolled in the *Infancia y Medio Ambiente* (INMA) (Environment and Childhood) Asturias birth cohort study (Fernández-Somoano et al., 2011; Fernández-Somoano and Tardon, 2014; Riaño-Galán et al., 2017; Rodríguez-Dehli et al., 2017; E Vizcaino et al., 2014; Esther Vizcaino et al., 2014). Briefly, 494 pregnant women were recruited between May 2004 and June 2007, four of these women had a spontaneous abortion or fetal death, 5 withdrew from the study and 485 delivered a live, singleton infant. The inclusion criteria are described in our previous study (Fernández-Somoano and Tardon, 2014). A total of 453 children were enrolled at birth and were followed up at 4–5 years of age. The participation rate was 93.4%. The follow-up questionnaires gathered information about environmental health, diet, and sociodemographic characteristics. Spot urine samples were collected from 335 children, and the median age was 4 years. Our complete dataset with no missing values in growth indicators or covariates included 328 children (Fig. S1). All parents provided written informed consent prior to inclusion. Subsequently, they signed a second consent to enroll the children in the INMA-Asturias study. The Asturias Regional Clinic Research Ethics Committee approved the research protocol.

2.2. Metals exposure

2.2.1. Measurement of metals exposure

Urine samples were collected during the pediatric follow-up review at 4–5 years. Urine was collected in 100 mL polyethylene containers and stored at −80 °C. One aliquot of the sample from each of the participants (15 mL) was sent to the Institute of Environmental Assessment and Water Research (IDAEA-CSIC) to be analyzed. Six metals including Ba, Cd, Co, Pb, Mo, and Zn were selected based on the identification of these element in urine samples including children in large-scaled population surveys (Padilla et al., 2010; Shao et al., 2017) and base on availability and reliability as biomarkers of exposure. Metals concentrations were analyzed by Inductively coupled plasma mass spectrometry (ICP-MS). Teflon vessels were cleaned after every use by rinsing with 7% HNO_3, filled with 7% HNO_3, leaved in the oven overnight and finally rinsing with abundant MilliQ water. All polypropylene material was cleaned by soaking 7% HNO_3 for 48 h, followed by rinsing with abundant MilliQ water. An aliquoted of 2 mL of each urine sample was introduced in Teflon vessels, together with 1 mL 60% HNO_3 (Merck; Darmstadt, Germany) and 0.5 mL H_20_2 (Merck). Samples were left in an oven at a maximum temperature 90 °C overnight. After cooling, vessels were opened, and samples were dissolved with 16.5 mL of 1% HNO_3 dilution. Finally, samples were placed in plastic tubes and stored in a refrigerator until instrumental analysis. Before analysis, an internal standard indium (10 μg/L) was introduced and depending on sample density, they were diluted with MilliQ water to 30 mL or 60 mL. One MilliQ water blank was processed in each batch of samples for control of possible contamination. Bio-Rad Level 1 urine reference sample was used as validation of the analytical protocol (Lyphochek Urine Metals Control 4770–03; Marnes-la-Coquette, France). Detail methods of this technique are available from a prior study (Junqué et al., 2020). Instrumental limit of detection (LOD) for all metals was 0.2 μg/L. Metal urine concentrations were standardized to creatinine content (μg/g creatinine). Creatinine was determined by the Jaffé method with Beckman Coulter© reactive in AU5400 (IZASA®). There were no observations below the LOD for Zn and Mo. For Pb and Co 5 and 4 observations were below the LOD, respectively. Regarding to Cd 100 observations were below the LOD. Values below the lower LOD were entered as the LOD divided by the square root of two and included in statistical analyses (Lubin et al., 2004).

2.2.2. Determination of arsenic species

Urine samples from a subset of children ($n = 100$) were analyzed for arsenic speciation (Signes-Pastor et al., 2017a, 2019b, 2017a). We measured arsenobetaine (AsB), dimethylarsinic acid (DMA), MMA, and inorganic arsenic (arsenite and arsenate) using chromatographic detection by ion chromatography (IC) hyphenated to ICP-MS. We included blank and replicate samples of the urine lyophilized material ClinChek® - Control level I (Recipe Chemicals + Instruments GmbH in Munich, Germany) in each analytic batch. Urine dilution was normalized using specific gravity measured with a clinical refractometer. For the arsenic speciation, we calculated from the DMA calibration the LOD and it was 0.011 μg/L (Signes-Pastor et al., 2017a, 2017b, 2017b).

2.3. Anthropometric measurements

Child anthropometry assessment was performed at the 4–5-year clinic visit to measure growth and was carried out by trained field staff. Standing height was measured twice to the nearest 0.1 cm using a wall-mounted stadiometer after the child removed their shoes. A digital scale was used to measure weight to an accuracy of 0.1 kg when the child was wearing only light clothing. Waist, arm, and head circumferences (cm) were measured with an inextensible tape measure. BMI was calculated as the weight (kg) divided by the height squared (m^2).

2.4. Covariates

A trained interviewer used a questionnaire to gather sociodemographic information and other data from the mother at weeks 10–13 and 28–32 weeks of pregnancy. We selected the following covariates as potential confounders: maternal age at enrollment (years, continuous), maternal socioeconomic status (categorized as I–II [highest], III and IV–V [lowest]) (Garí et al., 2019), maternal education (categorized as primary, secondary, or university), smoking during pregnancy (yes *vs.* no, categorical), and passive smoke exposure during pregnancy (yes *vs.* no, categorical). Characteristics and demographic details of the children were gathered at the 4–5 year post-partum visit using questionnaires. The following data were collected for the children: child age (years, continuous), sex (male *vs.* female, categorical), total caloric intake (kcal, continuous), seafood intake (g/day, continuous), shellfish intake (g/day, continuous), rice intake (g/day, continuous), and physical activity (score, continuous). We based our variable selection on prior studies and a direct acyclic graph (Textor et al., 2016).

2.5. Statistical analysis

Summary statistics were calculated for the continuous variables, and the categorical variables are presented as *n* (%). The metal concentrations were natural-log transformed to reduce their skewness, and they were centered and scaled. Spearman's coefficients were calculated for each metal pair and for anthropometric measurements. Arm, waist, and head circumference, BMI, and standing height had a normal distribution.

We performed covariate-adjusted linear regression analysis to quantify the effects of metal exposure on growth indicators. The linear regression models included natural-log transformed urine Ba, Cd, Co, Pb, Mo, and Zn concentrations as independent variables. Subsequently, these metal concentrations were normalized by their interquartile range (IQR). Child growth indicators were used as the dependent variables and were adjusted by maternal age at enrollment, maternal socioeconomic status, maternal education, smoking during pregnancy, passive smoke exposure during pregnancy, child age and sex, and child total caloric intake, seafood intake, shellfish intake, rice intake, and physical activity (Fig. S3). All metal concentrations were consecutively included as independent variables in the models. The Variance Inflation Factor (VIF) was used to study the multicollinearity of the linear regression models (Fox and Weisberg, 2019).

Bayesian Kernel Machine Regression (BKMR) was performed as an exploratory method to investigate non-linear associations, interactions, and joint effects of the metal mixture We used the R package "bkmr" (Bobb et al., 2014) to conduct these analyses. The BKMR models were applied as $Y_i = h(Ba_i, Cd_i, Co_i, Pb_i, Mo_i \text{ and } Zn_i) + \beta^T Z_i + e_i$, where Y is the continuous growth indicator outcome of interest (arm, head, or waist circumference, BMI, or standing height); h () is an exposure-response kernel function that accommodates nonlinearity and interactions among the metals in the mixture; Z is the adjustment variable, and β is the regression coefficient. All modeling was performed using a Gaussian kernel with 5000 as the burn-in and included 50,000 Monte Carlo iterations with Markov chain.

We repeated the described statistical analyses for a subset of children with data on arsenic speciation ($n = 97$). In this case, the models also included the summation of iAs, MMA, and DMA (∑As) as a proxy of iAs exposure. A *p*-value < 0.05 was used to define associations as statistically significant. We performed all statistical analyses and graphing with R version 3.5.2. (R Core Team, 2021).

3. Results

3.1. Study population characteristics

Characteristics of the children are shown in Table 1. Our dataset included both female ($n = 143$) and male ($n = 185$) children. The median child age was 4 years and ranged from 4 to 5 years. The urine concentrations of Ba, Cd, Co, Pb, Mo, and Zn were not correlated or only moderately correlated, with a ρ of −0.07–0.36 (Fig. S2A). The median (IQR) concentrations of Ba, Cd, Co, Pb, Mo, and Zn were 2.6 (1.0–4.4), 0.3 (0.2–0.4), 1.0 (0.7–1.6), 1.9 (1.2–2.8), 109.6 (77.4–156.3), and 588.4 (411.5–796.4) μg/g creatinine, respectively (Table 1). The median (IQR) urinary ∑As concentration was 4.9 (3.1–7.5) μg/L. The descriptive analysis results were similar for the subsample with arsenic speciation (Table 1). Anthropometric measures were correlated to each other (ρ of 0.20–0.83). In particular, BMI was strongly positively correlated with the arm and waist circumferences (ρ > 0.7; $p < 0.0001$). A positive correlation was also observed between arm circumference and waist circumference (ρ = 0.69; $p < 0.0001$) (Fig. S2B). The anthropometric and socioeconomic characteristics of children excluded from the analysis ($n = 81$, Table S1) did not differ from those who were included.

Table 1
Selected characteristics of the study population.

Characteristics	Total sample ($n = 328$)	Subsample ($n = 97$)
Male/Female (%)	185 (56.4)/143 (43.6)	49 (50.5)/48 (49.5)
Age (years)	4.0 (4.0, 4.0–4.0, 5.0)	4.0 (4.0, 4.0–4.0, 5.0)
Standing height (cm)	106.0 (92.3, 103.0–109.0, 118.2)	106.5 (94.0, 104.3–109.3, 118.2)
Weight (cm)	17.9 (12.8, 16.4–19.9, 30.4)	18.4 (13.5, 17.1–21.9, 27.2)
BMI (kg/m^2)	16.0 (11.5, 15.2–17.3, 24.1)	16.1 (11.5, 15.3–17.5, 23.5)
Waist circumference (cm)	53.0 (40.8, 50.5–56.0, 72.5)	53.5 (45.5, 50.5–57.5, 72.0)
Head circumference (cm)	51.5 (47.5, 50.5–52.5, 55.0)	51.5 (47.5, 50.5–52.5, 54.20)
Arm circumference (cm)	17.5 (14.0, 16.5–18.50, 25.0)	17.5 (14.0, 17.9–19.0, 24.0)
Physical activity (score)	4.0 (1.0, 3.0–4.0, 5.0)	4.0 (1.0, 3.0–4.0, 5.0)
Calories (kcal)	1614 (673, 1405–1873, 2907)	1637 (992, 1447–1889, 2619)
Fish consumption (g/day)	35.4 (0.0 25.9–46.6, 113.2)	33.1 (5.8, 25.9–44.1, 90.0)
Shellfish consumption (g/day)	4.4 (0.0, 1.9–7.8, 48.9)	4.9 (0.0, 2.3–8.6, 40.9)
Rice consumption (g/day)	8.6 (0.0, 8.6–23.6, 60.0)	8.6 (0.0, 8.6–23.6, 23.6)
Maternal age (years)	32.0 (19.0, 29–35.0, 42.0)	32.0 (21.0, 29–35.0, 42.0)
Maternal social class		
I-II (highest)	82 (25.0%)	18 (18.6%)
III	75 (22.9%)	25 (25.7%)
IV-V (lowest)	170 (51.8%)	54 (55.7%)
Maternal education		
Primary	50 (15.2%)	19 (19.6%)
Secondary	142 (43.3%)	38 (39.2%)
University	136 (41.5%)	40 (41.2%)
Smoke during pregnancy		
Yes	81 (24.7%)	25 (25.7%)
No	230 (70.1%)	72 (74.3%)
Maternal passive smoking		
Yes	147 (44.8%)	54 (55.7%)
No	165 (50.3%)	42 (44.3%)
Urine metals (μg/g creatinine)		
Barium	2.6 (0.1, 1.0–4.4, 99.3)	2.3 (0.1, 0.5–3.9, 43.4)
Cadmium	0.3 (0.1, 0.2–0.4, 1.5)	0.3 (0.1, 0.2–0.4, 1.5)
Cobalt	1.0 (0.2, 0.7–1.6, 7.5)	1.1 (0.2, 0.6–1.5, 7.5)
Lead	1.9 (0.1, 1.2–2.8, 22.1)	1.9 (0.1, 1.1–2.6, 15.1)
Molybdenum	109.6 (3.8, 77.4–156.3, 600.4)	101.0 (5.7, 71.2–125.5, 600.4)
Zinc	588.4 (15.6, 411.5–796.4, 2878.0)	588.4 (15.6, 412.5–798.0, 2878.3)
∑As (μg/L)	–	4.9 (0.3, 3.1–7.5, 85.4)
AsB (μg/L)	–	9.3 (0.1, 1.7–26.4, 1036.5)

Categorical variables = *n* (%). Continuous variables = median (min., IQR, max.). BMI = body mass index. ∑As = sum of iAs (i.e. arsenite [As^{III}] and arsenate [As^{IV}]), DMA (dimethylarsinic acid), MMA (monomethylarsonic acid) and AsB (arsenobetaine).

3.2. Linear regression analyses

In the linear regression models, an IQR increase in urine Cd concentration was associated with a −0.37 kg/m^2 decrease in BMI (95% confidence interval (CI): −0.65, −0.09), a −0.44 cm decrease in arm circumference (95% CI: −0.71, −0.18), a −1.25 cm decrease in waist circumference (95% CI: −2.00, −0.50), a −1.31 cm decrease in standing height (95% CI: −2.00, −0.63), and a −0.34 cm decrease in head circumference (95% CI: −0.56, −0.12) (Table 2). For every IQR increase in the urinary Pb concentration, the average child standing height and head circumference decreased by −0.94 cm (95% CI: −1.46, −0.43) and −0.25 cm (95% CI: −0.41, −0.09), respectively. There was a −0.30 cm

Table 2
Difference un children's anthropometric indicators for each IQR increase in population levels of urine metals ($n = 328$).

	BMI (kg/m^2)	Arm circumference (cm)	Waist circumference (cm)	Standing height (cm)	Head circumference (cm)
Individual elements β (95% CI) [a]					
Barium	0.07 (−0.16, 0.30)	0.02 (−0.20, 0.24)	0.07 (−0.54, 0.68)	−0.40 (−0.96, 0.17)	−0.13 (−0.31, 0.05)
Cadmium	**−0.37 (-0.65, -0.09)**	**−0.44 (-0.71, -0.18)**	**−1.25 (-2.00, -0.50)**	**−1.31 (-2.00, -0.63)**	**−0.34 (-0.56, -0.12)**
Cobalt	0.12 (−0.14, 0.37)	0.15 (−0.09, 0.39)	0.37 (−0.31, 1.05)	−0.39 (−1.02, 0.24)	**−0.30 (-0.50, -0.10)**
Lead	0.00 (−0.21, 0.21)	−0.12 (−0.32, 0.08)	−0.27 (−0.83, 0.29)	**−0.94 (-1.46, -0.43)**	**−0.25 (-0.41, -0.09)**
Molybdenum	−0.01 (−0.26, 0.24)	−0.03 (−0.26, 0.21)	0.13 (−0.53, 0.79)	−0.14 (−0.75, 0.47)	0.09 (−0.10, 0.29)
Zinc	−0.01 (−0.24, 0.22)	−0.03 (−0.25, 0.20)	0.12 (−0.50, 0.74)	−0.14 (−0.71, 0.44)	0.09 (−0.10, 0.27)
Multiple elements β (95% CI) [b]					
Barium	0.07 (−0.17, 0.31)	0.06 (−0.17, 0.29)	0.15 (−0.49, 0.79)	−0.04 (−0.63, 0.54)	−0.01 (−0.19, 0.18)
Cadmium	**−0.41 (-0.72, -0.11)**	**−0.44 (-0.73, -0.15)**	**−1.29 (-2.10, -0.48)**	**−1.09 (-1.82, -0.35)**	**−0.35 (-0.58, -0.12)**
Cobalt	0.07 (−0.19, 0.34)	0.13 (−0.12, 0.38)	0.35 (−0.35, 1.05)	−0.24 (−0.88, 0.39)	**−0.29 (-0.49, -0.09)**
Lead	0.05 (−0.18, 0.29)	−0.07 (−0.29, 0.16)	−0.08 (−0.70, 0.55)	**−0.64 (-1.20, -0.07)**	−0.15 (−0.33, 0.02)
Molybdenum	0.07 (−0.20, 0.34)	0.06 (−0.19, 0.32)	0.54 (−0.17, 1.25)	0.36 (−0.29, 1.01)	**0.22 (0.01, 0.43)**
Zinc	−0.01 (−0.23, 0.22)	0.01 (−0.21, 0.22)	−0.35 (−0.95, 0.25)	−0.35 (−0.89, 0.19)	−0.02 (−0.20, 0.15)

[a] Based on linear models adjusted for maternal age (years, continuous), maternal social class (I-II, III or IV-V; categorical), smoking during pregnancy (yes vs. no, categorical), passive smoking (yes vs. no, categorical), age (years, continuous), sex (males vs. females), total calorie intake (kcal, continuous), seafood consumption (g/day, continuous), shellfish consumption (g/day, continuous), rice consumption (g/day, continuous), physical activity (score, continuous).

[b] The models include all six metals (Co, Zn, Mo, Cd, Ba and Pb).

(95% CI: −0.50, −0.10) decrease in head circumference for every IQR increase in urinary Co concentration (Table 2). The results from the multi-metal linear regression models for the association between metal concentrations and child growth indicators were similar to those of the single-metal linear regressions (Table 2). Specifically, Mo was positively associated with an increased head circumference (0.22 cm [95% CI: 0.01, 0.43]). We did not find any other significant associations between the remaining components of the metal mixture and child growth indicators.

Using single linear regression analyses for the subsample, an IQR increase in urinary iAs concentration was associated with a 0.47 cm (95% CI: 0.04, 0.90) and 1.30 cm (95% CI: 0.10, 2.50) increase in arm and waist circumference, respectively (Table 3). In addition, for every IQR increment in urinary Cd concentration, the average waist and head circumferences decreased by −1.63 cm (95% CI: −3.17, 0.10) and −0.44 cm (95% CI: −0.83, −0.05), respectively. Furthermore, there was a −1.90 cm (95% CI: −2.91, −0.89) decrease in standing height for every IQR increment in urinary Pb concentration. The results from the multiple linear regression models suggested that for every IQR increment in urinary Mo concentration there was a 1.01 cm (95% CI: 0.03, 1.98) increase in standing height, and for every IQR increment in Pb concentration, there was a −2.06 cm (95% CI: −3.15, −0.97) decrease in standing height. Table S2 presents a comparative summary of the linear regression and BKMR results.

3.3. *Bayesian kernel machine regression*

In the BKMR analyses, we observed that increased Cd concentrations were associated with reduced standing height and smaller arm and waist circumferences, and the effect estimates were more pronounced when there were high urinary concentrations of the other metals in the mixture. Although the confidence interval barely crossed zero, a suggestive inverse association was observed between the Cd concentration and BMI. Pb and Co were associated with reduced standing height and head circumference, respectively, and associations were stronger at lower percentiles of the other metals in the mixture (Fig. 1B). The associations appeared to follow a linear dose–response function; however, there was high variability at low Pb concentrations (Fig. 1A). Conversely, Mo was positively associated with head circumference, especially at higher percentiles of the other metals in the mixture (Fig. 1B). Furthermore, Mo was positively related to standing height and waist circumference, but the confidence interval crossed zero. We did not find any other statistically significant associations between the remaining components of the mixture and the child growth indicators,

Table 3
Difference in children's anthropometric indicators for each IQR increase of urine metals in a subpopulation including $\sum$As ($n = 97$).

	BMI (kg/m^2)	Arm circumference (cm)	Waist circumference (cm)	Standing height (cm)	Head circumference (cm)
Individual elements β (95% CI) [a]					
Inorganic Arsenic	0.36 (−0.08, 0.80)	**0.47 (0.04, 0.90)**	**1.30 (0.10, 2.50)**	0.43 (−0.54, 1.41)	0.14 (−0.17, 0.46)
Barium	0.00 (−0.69, 0.69)	−0.24 (−0.93, 0.44)	0.27 (−1.65, 2.19)	−1.12 (−2.63, 0.39)	−0.25 (−0.73, 0.24)
Cadmium	−0.43 (−0.99, 0.13)	−0.53 (−1.08, 0.02)	**−1.63 (-3.17, -0.10)**	−0.36 (−1.62, 0.89)	**−0.44 (-0.83, -0.05)**
Cobalt	−0.10 (−0.68, 0.49)	−0.08 (−0.66, 0.50)	0.25 (−1.38, 1.87)	−1.12 (−2.39, 0.15)	−0.37 (−0.78, 0.03)
Lead	−0.12 (−0.61, 0.38)	−0.22 (−0.71, 0.27)	−0.73 (−2.10, 0.63)	**−1.90 (-2.91, -0.89)**	−0.30 (−0.65, 0.04)
Molybdenum	0.11 (−0.32, 0.54)	0.16 (−0.27, 0.59)	0.36 (−0.84, 1.56)	0.66 (−0.29, 1.60)	0.02 (−0.29, 0.33)
Zinc	0.06 (−0.31, 0.44)	0.04 (−0.33, 0.42)	−0.08 (−1.13, 0.97)	−0.17 (−1.01, 0.66)	−0.08 (−0.35, 0.18)
Multiple elements β (95% CI) [b]					
Inorganic Arsenic	0.28 (−0.36, 0.91)	0.41 (−0.21, 1.03)	1.08 (−0.64, 2.80)	0.78 (−0.48, 2.03)	0.03 (−0.40, 0.46)
Barium	0.13 (−0.61, 0.87)	−0.07 (−0.80, 0.65)	0.80 (−1.20, 2.80)	−0.18 (−1.64, 1.28)	−0.05 (−0.55, 0.46)
Cadmium	−0.23 (−0.98, 0.51)	−0.20 (−0.94, 0.53)	−0.76 (−2.79, 1.28)	0.56 (−0.92, 2.04)	−0.39 (−0.90, 0.12)
Cobalt	−0.19 (−0.83, 0.45)	−0.14 (−0.77, 0.49)	0.13 (−1.61, 1.88)	−0.79 (−2.06, 0.47)	−0.33 (−0.77, 0.11)
Lead	−0.12 (−0.67, 0.43)	−0.21 (−0.76, 0.65)	−0.96 (−2.46, 0.54)	**−2.06 (-3.15, -0.97)**	−0.20 (−0.56, 0.18)
Molybdenum	0.06 (−0.43, 0.56)	0.11 (−0.38, 0.59)	0.32 (−1.02, 1.66)	**1.01 (0.03, 1.98)**	0.11 (−0.23, 0.44)
Zinc	0.02 (−0.41, 0.45)	−0.04 (−0.46, 0.38)	−0.37 (−1.54, 0.79)	−0.41 (−1.26, 0.44)	−0.04 (−0.33, 0.26)

[a] Based on linear models adjusted for maternal age (years, continuous), maternal social class (I-II, III or IV-V; categorical) smoke during pregnancy (yes vs. no, categorical), passive smoking (yes vs. no, categorical), age (years, continuous), sex (males vs. females), total calorie intake (kcal, continuous), seafood consumption (g/day, continuous), shellfish consumption (g/day, continuous), rice consumption (g/day, continuous), physical activity (score, continuous).

[b] The models include all seven metals (Co, Zn, Mo, Cd, Ba, As and Pb).

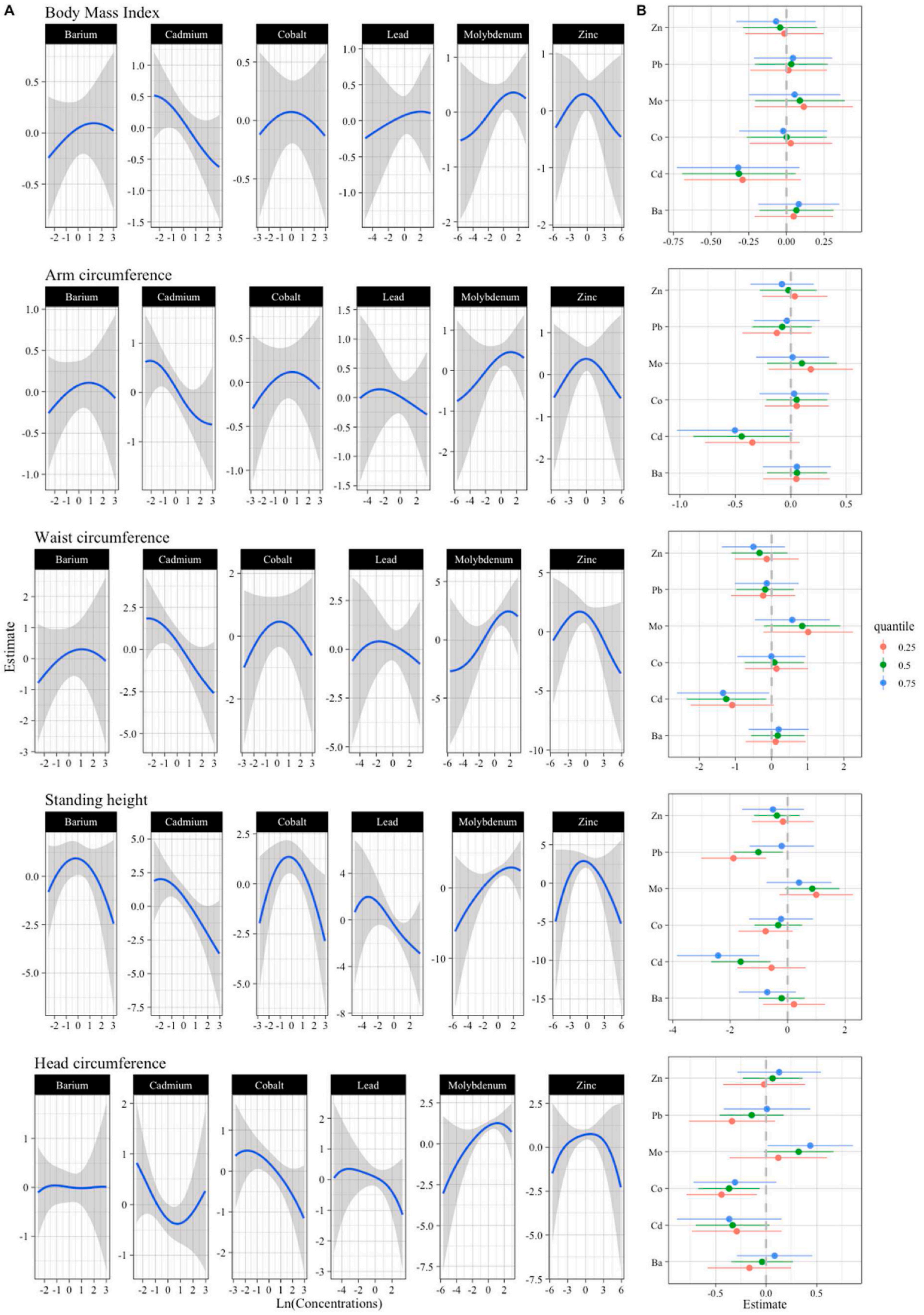

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Fig. 1. Metal exposure and anthropometric indicators in 4-5-year-old children. BKMR dose-response function and interaction within the metal mixture ($n = 328$). Models adjusted for maternal age (years, continuous), maternal social class (I-II, III or IV-V; categorical) smoke during pregnancy (yes vs. no, categorical), passive smoking (yes vs. no, categorical), age (years, continuous), sex (males vs. females), total calorie intake (kcal, continuous), seafood consumption (g/day, continuous), shellfish consumption (g/day, continuous), rice consumption (g/day, continuous), physical activity (score, continuous). **A**, Univariate exposure-response functions and 95% confidence bands for each metal with the other pollutants fixed at the median. **B**, Single pollutant association (estimates and 95% credible intervals, gray dashed line at the null). This plot compares children' size when a single pollutant is at 75th versus 25th percentile, when all the other exposures are fixed at either the 25th, 50th, or 75th percentile. Notice that the scale of the x- and y-axis vary in order to facilitate the visualization of the estimates in each plot.

although the trends for the toxic metals reflected an inverse relationship with growth, while the trends for the essential metals were positive.

When we included urinary $\sum$As in the models, the associations were generally similar to those found in the main analysis. However, Mo was positively associated with standing height (Fig. 2A), and this association was stronger at higher percentiles of other metals in the mixture (Fig. 2B).

4. Discussion

Our study suggests that exposure to a mixture of Ba, Cd, Co, Pb, Mo, and Zn impacts body size and growth in Spanish children with a median age of 4 years. The results indicated that the effects varied according to the exposure concentration of each metal in the mixture. Urine Cd was associated with reduced arm and waist circumferences and standing height when the concentrations of the other metals were high. Pb and Co were associated with reduced standing height and head circumference. In contrast, Mo concentrations were associated with an increased head circumference. In addition, when we included urinary $\sum$As, Mo was positively associated with standing height at higher percentiles of the mixture.

Urine collection is easy and non-invasive, and its metal concentrations reflect kidney excretion. Thus, urine samples are commonly used in environmental studies, including the NHANES and the German Environmental Survey for Children (Esteban and Castaño, 2009; Padilla et al., 2010; Shao et al., 2017). Here, we used urinary metal concentrations as valid biomarkers of metal exposure (Castiello et al., 2020; Esteban and Castaño, 2009; Lewis et al., 2018; Padilla et al., 2010; Shao et al., 2017). The $\sum$As is a short-term biomarker of iAs exposure; yet, it may reflect long-term iAs exposure among individuals who have consistent patterns of exposure. This applies to children, as their diet often varies less than that of adults (Kile et al., 2009; Navas-Acien et al., 2009; Signes-Pastor et al., 2017c).

In real-world scenarios, individuals are exposed to mixtures of metals. However, most of the available evidence has focused on single-metal exposure assessments (Padilla et al., 2010; Scinicariello et al., 2013; Shao et al., 2017). The urinary metal concentrations found in the current study are relevant to the general Spanish population and others with generally low metal exposure (Castiello et al., 2020). This study combined traditional and newer statistical techniques to assess the effect of exposure to metal mixtures on child growth indicators (Bobb et al., 2014; Domingo-Relloso et al., 2019; Howe et al., 2020; Li et al., 2019; Signes-Pastor et al., 2019a, 2020; Valeri et al., 2017). Our literature search for studies focusing on exposure to metal mixtures found very few prior studies on prenatal exposure, and only one was found on childhood exposure (Howe et al., 2020; Kim et al., 2019; Signes-Pastor et al., 2020; Vázquez-Salas et al., 2014).

Cd is a nonessential toxic metal widely distributed in the environment, and its toxicity results in a range of biochemical and physiological dysfunctions in humans (Ercal et al., 2001). Cd accumulates in the human body after absorption and can negatively impact development, reproduction, neurological outcomes, cardiovascular diseases, and metabolic disorders (Diamanti-Kandarakis et al., 2009; Moon, 2014). The main exposure route for Cd is through smoking; however, vegetables and cereals are sources of Cd exposure in the diet. Other exposure sources include emissions from industrial activities, including mining, smelting, and manufacturing of batteries, pigments, stabilizers, and alloys (Tchounwou et al., 2012). The concentrations of urinary Cd reported in the INMA-Granada cohort among male adolescents were similar to those found here (Castiello et al., 2020), but they were 1–2 times lower than those reported in other studies from Europe and the US (Berglund et al., 2015; Madrigal et al., 2018; Roca et al., 2016). In our analyses, we found evidence that the exposure to Cd may adversely affect BMI and waist circumference. The reduced BMI and/or waist circumference related to Cd exposure is possibly linked to its toxic effect on the gastrointestinal tract (Nie et al., 2016; Padilla et al., 2010; Shao et al., 2017). The acute and chronic toxic effects of Cd are well known in adults, but related evidence remains scarce for children (Kido et al., 1990; Molina-Villalba et al., 2015). We found a linear dose–response association between Cd exposure and child standing height. The mechanisms by which Cd might play a role in child growth are still unclear. Studies on Cd exposure and osteoporosis suggest that Cd might be toxic to bone in adults (Engström et al., 2009; Schutte et al., 2008). In 10-year-old children, Cd exposure increased bone resorption and demineralization by 1.72-fold (Sughis et al., 2011). Additionally, urine Cd concentrations were found to be inversely associated with bone-related biomarkers in 9-year-old children (Malin Igra et al., 2019). The deterioration of childhood bone growth may result in a reduction in standing height. Cd may also act as an endocrine-disrupting chemical. It can affect the generation of progesterone and mimic the effect of androgens and estrogens (Iavicoli et al., 2009; Stoica et al., 2000). Our findings also suggest a reduction in children's BMI and arm and waist circumferences with exposure to Cd. This agrees with previous studies in children between 6 and 19 years of age enrolled in NHANES, where urinary Cd was found to be inversely associated with BMI and waist circumference (Padilla et al., 2010; Shao et al., 2017). Given that 30% of our Cd concentrations were less than the level of detection, caution is needed when interpreting the results, and further studies are required to confirm or refute the findings of this study.

Pb is a well-known toxic element, and the major exposure sources are inhalation/ingestion of Pb-contaminated dust, water, and food (Abernethy et al., 2010; Llop et al., 2011, 2013). A biomonitoring study carried out in Catalonia analyzed trace elements in hair samples from schoolchildren over a 20 year period and found a significant reduction in Pb concentrations from 1998 to 2018 (Esplugas et al., 2019). We found a negative association between urinary Pb and standing height, especially at lower concentrations of other metals in the mixture, and the linear regression analysis confirmed this finding (0.64 cm decrease for each IQR increase in Pb concentration). The identified association between Pb exposure and child standing height is consistent with many epidemiological studies that have reported an inverse association between standing height measured during childhood and Pb concentrations (Ballew et al., 1999; Burns et al., 2017; Deierlein et al., 2019; Donangelo et al., 2021; Hong et al., 2014; Kafourou et al., 1997; Kerr et al., 2019; Min et al., 2008; Raihan et al., 2018; Yang et al., 2013; Zeng et al., 2019). These studies have included a wide age range of children, from childhood to adolescence. Childhood Pb exposure has also been attributed to adult disorders such as osteoporosis (Nash et al., 2004). The biological mechanisms through which Pb might influence children's physical growth and body composition might be related to Pb interfering with bone cell function and metabolism and bone mineralization. Another proposed mechanism is that Pb affects bone at the cellular level to induce bone loss. Some studies have reported that the effects of Pb may operate through bone turnover by altering the circulating levels of hormones, especially 1,25-dihydroxy vitamin D3, which regulates bone cell function and directly impacts osteoblast and osteoclast function, but

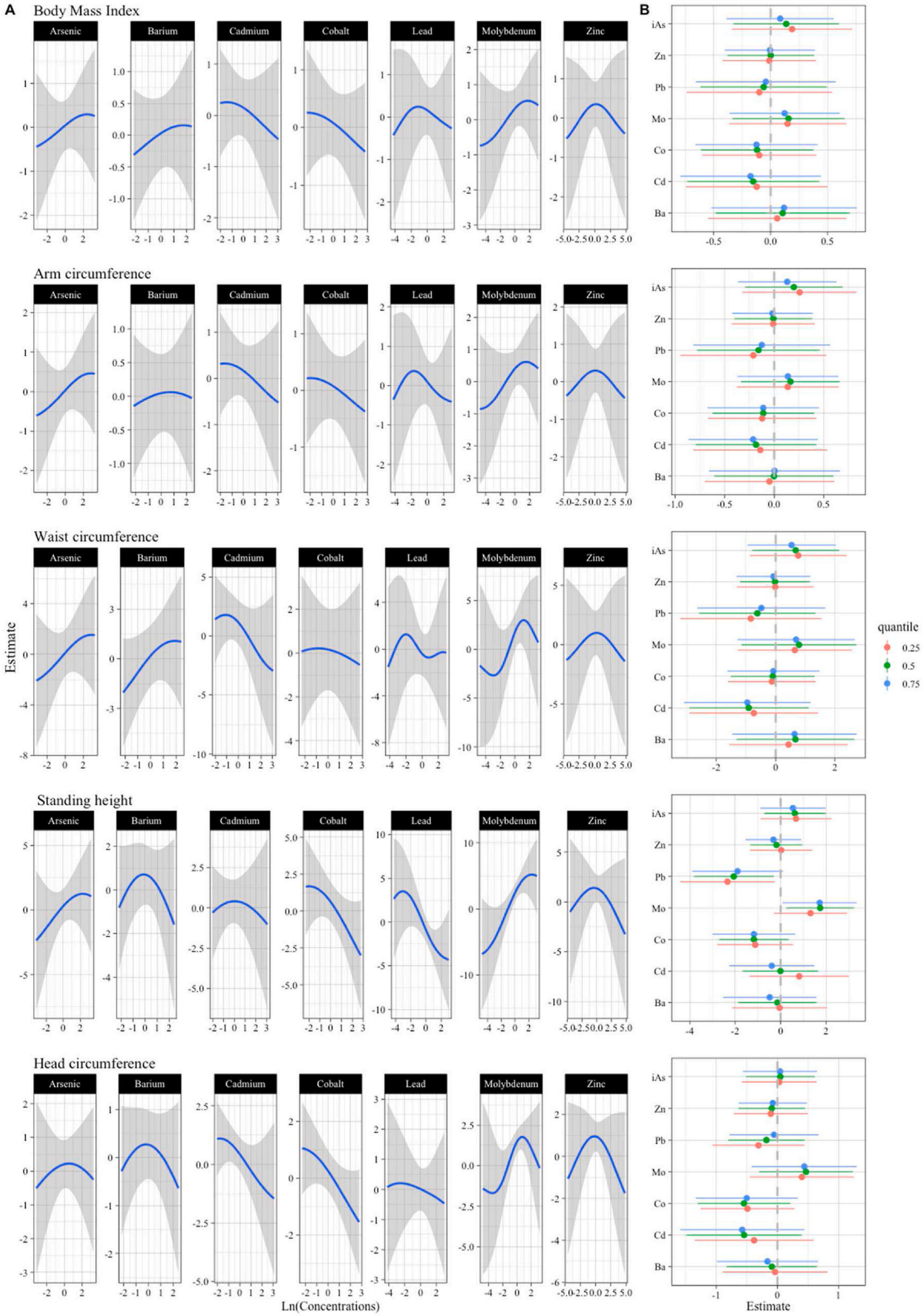

Fig. 2. Metal exposure and anthropometric indicators in 4-5-year-old children. BKMR dose-response function and interaction within the metal mixture and including inorganic arsenic ($n = 97$). Models adjusted for maternal age (years, continuous), maternal social class (I-II, III or IV-V; categorical) smoke during pregnancy (yes vs. no, categorical), passive smoking (yes vs. no, categorical), age (years, continuous), sex (males vs. females), total calorie intake (kcal, continuous), seafood consumption (g/day, continuous), shellfish consumption (g/day, continuous), rice consumption (g/day, continuous), physical activity (score, continuous). **A**, Univariate exposure-response functions and 95% confidence bands for each metal with the other pollutants fixed at the median. **B**, Single pollutant association (estimates and 95% credible intervals, gray dashed line at the null). This plot compares children' size when a single pollutant is at 75th versus 25th percentile, when all the other exposures are fixed at either the 25th, 50th, or 75th percentile. Notice that the scale of the x- and y-axis vary in order to facilitate the visualization of the estimates in each plot.

these mechanisms are not well characterized (Berglund et al., 2000; Ohta et al., 2002; Pounds et al., 1991; Schutte et al., 2008).

Associations with Mo and Co on head circumference were in the opposite directions. The single-pollutant association plot from our BKMR models indicated an inverse association between Co and head circumference, particularly at lower concentrations of the other components in the mixture. In contrast, a positive trend was observed for Mo, especially at higher concentrations of the other metals. Essential metals are often crucial antioxidants, and deficiency has been associated with increases in markers of oxidative damage such as lipid peroxidation and DNA oxidation (Valko et al., 2016). Co is an essential metal present in the diet as part of vitamin B_{12} (Leyssens et al., 2017) and plays an important role in blood pressure regulation patterns (Akinrinde et al., 2016). Despite these clear benefits, the ionic form of Co may be toxic for humans. A study in the US that investigated the effects of Co exposure on the growth of 6–19-year-olds reported a negative association with obesity (Shao et al., 2017). Co can increase plasma HDL-cholesterol and decrease LDL-cholesterol, triglycerides, and free fatty acids (Kawakami et al., 2012). Thus, Co could influence body weight by regulating stored glycogen and suppressing glucagon signaling (Tascilar et al., 2011). Mo is another essential metal with potential toxicity. The major source of exposure to the general population is through the consumption of plant-based foods (e.g., grain products and legumes) and drinking water (WHO, 1996). Studies on Mo exposure have focused on central nervous system development. However, a lack of Mo-focused studies has led to a weak understanding of the potentially toxic effects of Mo in humans (Vázquez-Salas et al., 2014). Our findings do not suggest that Mo adversely affects BMI, either as a single element or when it is part of a metal mixture. However, a study carried out in Mexico in 10-year-old children reported that a one-unit increase in BMI z-score was associated with a 6% decrease in Mo (Lewis et al., 2018).

Zn is an essential nutrient, and children are vulnerable to Zn deficiency (Hess et al., 2009). However, toxic exposure can occur through the gastrointestinal, dermal respiratory, and parenteral routes (Barceloux, 1999). Zn deficiency has been thought to impair growth and contribute to stunting in children. The main mechanism suggested for this is through alterations in growth hormone metabolism (Mozaffari-Khosravi et al., 2008). Suboptimal dietary intake is becoming an increasingly evident worldwide health problem. The consumption of high phytate-containing cereals and a low protein intake may contribute to Zn deficiency because this diet impairs Zn absorption, and this diet is common in non-industrialized populations (Brown et al., 2001).

Ba is an alkaline earth metal that is ubiquitously present at low to moderate concentrations in the natural environment (Kravchenko et al., 2014). We did not find any associations between urinary Ba and growth indicators. However, previous studies have found a positive association between urinary Ba and obesity (Padilla et al., 2010; Shao et al., 2017).

In our BKMR analyses of urinary arsenic as the subsample, Pb and Mo were the elements in the metal mixture with the strongest antagonistic relationships for standing height. In our single linear regression models, urinary $\sum$As was associated with increased arm and waist circumferences. Cd and iAs interfere with the distribution and function of micronutrients and have endocrine-disrupting properties, which may hinder growth in young children. Evidence to date has suggested that Cd disrupts steroidogenesis, mimicking or inhibiting the functions of endogenous estradiol (Henson and Chedrese, 2004). With regard to As, it is an ubiquitous element that can be found in the environment in different oxidation states and in both organic and inorganic form. Similarly to what occurs with Mercury, the total amount of As could lead to distorted conclusions about its health influence due to the fact that, while the organic form is the most frequent, the inorganic one is the most effecting. Therefore, discriminative organic and inorganic analysis must be taken with respect to As form (Batista et al., 1996). iAs may affect insulin signaling and glucose metabolism, and the early disruption of glucose uptake by tissues plausibly leads to impaired growth (Paul et al., 2007). However, further research is required to clarify the mechanisms by which iAs might affect growth in early life (Gardner et al., 2013).

A strength of this study is the anthropometric measurement of children at 4–5 years of age, which is a period of physiological change related to growth and development. Furthermore, in addition to standing height and head circumference, we considered three biomarkers that are indirect estimations of adiposity: BMI, waist circumference, and arm circumference. These three measurements are correlated, but they allowed for a deeper assessment of how metal exposures might influence children's body composition. We also assessed the health effects of multi-pollutant exposures because people are simultaneously exposed to multiple metals in the environment.

Some limitations should also be considered when interpreting our findings. The cross-sectional design of our study did not allow us to draw conclusions regarding the temporal associations between growth indicators and metal exposures. Many other pollutants also exist in the environment and in children's bodies, and these metal exposures might be confounding factors. We performed the analysis of iAs to address this issue. Another limitation was that the information on tobacco use during pregnancy was self-reported and may not be reliable; this might have introduced residual confounding, especially for metals such as Cd, where the main exposure source is from smoking. In addition, our findings from the subsample were based on a modest sample size; thus, the statistical power was reduced. The degree of exposure to the metals studied in our population was lower than in other studies (Gardner et al., 2013; Saha et al., 2012), which limits our ability to identify the smaller impacts that would likely occur at low doses. We only had a one-time measurement of metal concentrations available, and data from a single urine spot per individual may increase the risk of exposure misclassification. The short biological half-lives of urinary metals could be a challenge and may reflect current or recently absorbed doses, as occurs with Pb or iAs. Nonetheless, urinary concentrations can be an informative biomarker of long-term exposure for many metals, such as Cd. In contrast to blood, urine concentrations could represent long-term or chronic exposure owing to their long half-lives and ability to accumulate in the liver and kidneys (Amzal et al., 2009; Bermejo-Barrera et al., 1998). Urinary As is considered a reliable biomarker of short-term As exposure and depends on dietary patterns (Marchiset-Ferlay et al., 2012). We used two adjustment methods for urinary dilution (creatinine and specific gravity), which might have impacted the results.

In conclusion, our findings indicate that exposure to metals at 4–5 years of age influences childhood growth indicator outcomes, such as standing height, and may be related to simultaneous exposures to other metals. Further studies with larger samples should be conducted to confirm our findings.

Author contributions

Miguel García-Villarino: Formal analysis, Investigation, Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Antonio J. Signes-Pastor**: Formal analysis, Conceptualization, Investigation, Methodology, Visualization, Supervision, Writing – review & editing. **Margaret Karagas**: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. **Isolina Riaño-Galán**: data collection, Writing – review & editing. **Cristina Rodríguez-Dheli**: data collection. **Joan O. Grimalt**: Methodology, Resources, Writing – review & editing. **Eva Junqué**: Methodology, Resources. **Ana Fernández-Somoano**: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. **Adonina Tardón**: Supervision, Project administration, Funding acquisition, Writing – review & editing. All authors have read an agreed to the publisher version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.112375.

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