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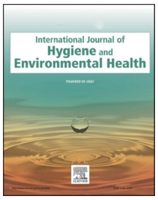

Pro-vegetarian dietary patterns and essential and heavy metal exposure in children of 4-5-years from the INfancia y medio Ambiente cohort (INMA)

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ABSTRACT

Dietary patterns provide a comprehensive assessment of food consumption, including essential nutrients and potential exposure to environmental contaminants. While pro-vegetarian (PVG) dietary patterns have shown health benefits in adults, their effects on children are less well studied. This study aims to explore the association between children's adherence to the most common PVG dietary patterns and their exposure to metals, assessed through urine concentration. In our study, we included a population of 723 children aged 4-5-years from the *INfancia y Medio Ambiente* (INMA) cohort in Spain. We calculated three predefined PVG dietary patterns, namely general (gPVG), healthful (hPVG), and unhealthful (uPVG), using dietary information collected through a validated Food Frequency Questionnaire. Urinary concentrations of various essential and heavy metals (Co, Cu, Zn, Se, Mo, Pb, and Cd) were measured using mass spectrometry. Additionally, urinary arsenic speciation, including arsenobetaine (AsB), dimethylarsinic acid (DMA), monomethylarsonic acid (MMA), and inorganic arsenic (iAs), was measured. The sum of urinary MMA and iAs was used to assess iAs exposure. We estimated primary (PMI) and secondary iAs methylation (SMI) indices. To explore the association between PVG dietary patterns in quintiles and metal exposure, we utilized multiple-adjusted linear regression models and the quantile g-computation approach. Compared with the lowest quintile, participants in the highest quintile of gPVG showed a 22.7% lower urinary Co (95% confidence interval (CI): −38.7; −1.98) and a 12.6% lower Se (95%CI: −22.9; −1.00) concentrations. Second quintile of adherence to hPVG was associated with a 51.7% lower urinary iAs + MMA concentrations (95%CI: −74.3; −8.61). Second quintile of adherence to an uPVG was associated with a 13.6% lower Se levels (95%CI: −22.9; −2.95) while the third quintile to this pattern was associated with 17.5%

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lower Mo concentrations (95%CI: −29.5; −2.95). The fourth quintile of adherence to gPVG was associated with a 68.5% higher PMI and a 53.7% lower SMI. Our study showed that adherence to a gPVG dietary pattern in childhood may modestly reduce the intakes of some essential metals such as Co and Se. Further investigations are warranted to explore any potential health implications.

1. Introduction

Essential trace elements play a crucial role in our bodies as they are necessary for vital functions. However, it is important to bear in mind that humans cannot synthesize them, and imbalances, whether through deficiency or excess, may lead to severe health consequences (Bhattacharya et al., 2016). Food is not only one of the major sources of exposure to these elements, but it is also a complex matrix that includes a mix of vitamins, biocompounds, and even non-essential heavy metals such as arsenic, lead (Pb) and cadmium (Cd) (Miller et al., 2023). Here, both essential and non-essential elements are referred to as essential and heavy metals thereafter.

Essential and heavy metals can interact with each other through agonistic and antagonistic effects (Aguilera, 2019). For instance, fish is recognized as a major source of mercury (Hg), an important toxic element (Rice et al., 2014), but also contains beneficial selenium (Se). Studies have shown that these two elements can interact to form Se–Hg complexes, facilitating Hg detoxification by promoting its excretion (Raymond and Ralston, 2020). Therefore, we encounter a dual scenario: while adequate levels of essential metals are crucial for development and disease prevention (Jomova et al., 2022), chronic exposure to toxic metals such as arsenic, especially inorganic arsenic (iAs), even at moderate/low levels, may raise health concerns, particularly during vulnerable growth and development stages, such as childhood (Signes-Pastor et al., 2019; Tchounwou et al., 2019; Buekers et al., 2023; Vahter, 2008; Parvez et al., 2019; Martinez and Lam, 2021). Certain emerging dietary recommendations have been criticized for not acknowledging this dual role that the diet plays (Ventre et al., 2022).

Although studies exist on metal exposure through the consumption of certain specific foods (Hassan et al., 2017; Signes-Pastor et al., 2020; Taylor et al., 2016), limited knowledge exists regarding the role of the overall diet (Kordas et al., 2016; Burganowski et al., 2019; Li et al., 2019; Notario-Barandiaran et al., 2023a; 2023b). Thus, there is a growing interest in dietary patterns as a comprehensive and more realistic approach to assessing the combined health effects of food consumption (Cespedes and Hu, 2015). In the past decade, plant-based dietary patterns have gained popularity, driven by ethical and environmental considerations (Gibbs and Cappuccio, 2022). In the United States of America (US), the number of people following a vegan diet has increased by 6-fold from 2014 to 2018 (Clem and Barthel, 2021). In Spain, despite limited and low-quality data availability (AECOSAN, 2011), there has been a considerable increase in interest in this type of dietary patterns (Acevedo Cantero et al., 2023). This could lead to an increasing exposure of children to plant-based dietary patterns.

Pro-vegetarian (PVG) dietary patterns offer a novel approach to evaluating health effects by prioritizing plant-based options while still including animal-based foods (Martínez-González et al., 2014; Satija et al., 2016). Studies conducted in adults have shown benefits for cardiometabolic markers and reduced risk of cancer (Gómez-Donoso et al., 2019; Oncina-Cánovas et al., 2022a; Oncina-Cánovas et al., 2022b; Romanos-Nanclares et al., 2020). Greater adherence to PVG patterns is associated with lower mortality risk and improved intake of essential metals and vitamins (Asfura-Carrasco et al., 2022; Martínez-González et al., 2014). Previous studies examining vegetarian diet patterns have investigated their association with isolated metals, including Pb (Taylor et al., 2019) and Cd (Taylor et al., 2020). However, the influence of PVG patterns in children remains uncertain due to scarce research in this vulnerable age group.

In this study, we hypothesize that higher adherence to general (gPVG) and healthful (hPVG) patterns is associated with lower toxic metal exposure, higher essential metal levels, and a better iAs methylation capacity. Conversely, greater adherence to the unhealthful PVG pattern (uPVG) is expected to be associated with higher toxic metal exposure, lower essential element concentrations, and lower iAs methylation capacity, indicative of reduced detoxification capability. We explore the association between childhood level of adherence to the most common PVG diets and exposure to heavy (iAs, Pb, and Cd) and essential (cobalt (Co), copper (Cu), zinc (Zn), Se, molybdenum (Mo)) metals using urine metal concentrations.

2. Material and methods

2.1. Study population, INMA study

Our study focuses on 4-5-year-old children from the *INfancia y Medio Ambiente* cohort study (INMA project), where their diet is regarded as the primary source of metal exposure (Lozano et al., 2022). This is a multicenter prospective birth cohort study that aims to evaluate the effect of different exposures, including diet, on pregnant women and their children (Guxens et al., 2011). For our purposes, we included the available data from four sub-cohorts: Asturias, Gipuzkoa, Sabadell, and Valencia. Of these, we have information for 2,041 participants in the 4–5 years visit. Of these, 819 had information for total urine essential and heavy metals concentrations and 1,191 had information for arsenic speciation (arsenobetaine (AsB), dimethylarsinic acid (DMA), monomethylarsonic acid (MMA) and iAs). Within this subgroup, 765 participants had data available for both variables. Among these, 42 lacked dietary information for the 17 required food groups (12 for the gPVG + 5 in the hPVG and uPVG versions) essential to create the PVG dietary patterns of interest. Therefore, the final sample size for this study comprised 723 participants with complete data for urine essential and heavy metals concentrations, as well as dietary intake (Fig. S1). Before inclusion, all parents provided informed consent, and the protocol received approval from the ethical committees of each participating center (Hospital Universitario Central de Asturias, Asturias; Hospital de Zumarraga, Gipuzkoa; Hospital Parc Taulí, Sabadell; and Hospital la Fe, Valencia).

2.2. Pro-vegetarian dietary patterns

We selected three common PVG dietary patterns to comprehensively examine metal exposure in plant-based foods, distinguishing between healthier and less healthy choices. To create these distinct PVG dietary patterns, we used food intake information derived from a previously validated Food Frequency Questionnaire (FFQ) (Vioque et al., 2016). This FFQ was adapted from a validated questionnaire designed for pregnant women (Vioque et al., 2013) and adjusted to include food items and portion sizes suitable for 4-5-years-old children. During the 4-5-years interview, trained personnel asked to the parents about the child's usual dietary intake in the last year. Responses were recorded on a scale with nine possible frequencies ranging from "never or less than 1 time per month" to "6 or more times per day". The 17 food groups included in the three PVG dietary patterns, along with the scoring criteria for each, are detailed in Table S1.

To create the PVG dietary patterns, we followed established procedures, ensuring consistency with prior methodologies. For the gPVG pattern, we adopted the method outlined by Martínez-González (Martínez-González et al., 2014). For the hPVG and uPVG derivations, we referred to Satija's method (Satija et al., 2016). First, we adjusted the consumption of each food group in grams for energy intake, using the residual method (Willett et al., 1997). Then, the energy-adjusted consumption was categorized into quintiles, assigning values from 1 to 5 based on the consumption quintile (Gómez-Donoso et al., 2019; Kim et al., 2019, 2020, 2021; Chen et al., 2022; Shan et al., 2023). Within the gPVG, seven plant-based food groups received positive scores: vegetables, fruits, legumes, grains (both whole and refined), potatoes (both boiled and fried), nuts, and olive oil. Conversely, five animal-based food groups were scored in reverse, with 5 indicating lower consumption: meat and meat products, animal fats, eggs, fish and other seafood, and dairy products. For the hPVG and uPVG patterns, the grains group was further divided into whole grains and refined grains, and the potatoes group into boiled and fried. Additionally, three food groups (fruit juices, sugar-sweetened beverages, and sweets and desserts) were added. These derivations were constructed using the information available in the scientific literature on the different plant food groups (Malik et al., 2010; Muraki et al., 2015; Ren et al., 2021). If these were associated with positive outcomes (in diabetes and cardiovascular disease), they were considered as healthful (and therefore scored positive on the hPVG and reverse on the uPVG), while if they were associated with negative outcomes, they were considered unhealthful (scoring positive on the uPVG and reverse on the hPVG). The total score for each participant was computed by summing the points across the 12 food groups for the gPVG pattern, and 17 food groups for the hPVG and uPVG versions. In this way, the total scores could remain between 12 points (minimum adherence) to 60 points (maximum adherence) in the case of the gPVG pattern, and between 17 points (minimum adherence) to 85 points (maximum adherence) in the case of hPVG and uPVG patterns. Originally, the hPVG and uPVG patterns included tea and coffee consumption, but we excluded them as relevant food groups in our 4-5-year-old population.

2.3. Laboratory analysis and arsenic methylation indices

In the present study, urinary concentrations of essential and heavy metals serve as biomarkers of metals exposure. These biomarkers are commonly used to assess simultaneous exposures in the scientific literature (Hahn et al., 2021; Pollock et al., 2021; Sanders et al., 2019; Vogel et al., 2021). One advantage of urine essential and heavy metals is its non-invasive nature, facilitating data collection and enabling identification of multiple metabolites (Barbosa et al., 2005; Reid et al., 2020). However, they also have limitations, particularly in relation to nutritional status (Combs, 2015; Cockell, 2015). The determination of urinary metal concentrations was carried out as follows. During the 4-5-year follow-up visit, spot urine samples were obtained and stored at −20 °C in 100 ml polyethylene containers. A single aliquot of urine was taken from each child who participated. The measurement of Co, Cu, Zn, Se, Mo, Pb and Cd in urinary samples was carried out using a Thermo ICAP Q inductively coupled plasma mass spectrometry (ICP-MS) in direct solution acquisition mode using a Cetac ASX-520 Auto Sampler. The limit of detection (LOD) was determined by taking the average of the blank concentrations and adding three times the standard deviation of the blank concentrations, which was then multiplied by the dilution factor. LOD values for each element was 0.10 μg/L for Co, 1.46 μg/L for Cu, 4.71 μg/L for Zn, 1.24 μg/L for Se, 14.36 μg/L for Mo, 0.19 μg/L for Pb and 0.12 μg/L for Cd. We used the $\frac{LOD}{\sqrt{2}}$ value when concentrations were below the LOD. The essential and heavy metals analyzed and the % imputation of the LOD for each one can be found in Table S2. To ensure quality control, blank and replicate samples of freeze-dried Clinchek urine samples were included in each analytical batch. The mean concentration (range) of the reference values in the freeze-dried Clinchek urine samples in μg/L are as follows: Co 2.05 (1.64–2.46), Cu 58.2 (46.6–69.9), Zn 195 (156–234), Se 29.0 (21.8–36.3), Mo 20.2 (16.2–24.3), Pb 26.4 (21.1–31.6), and Cd 2.56 (2.05–3.06). The mean recovery based on 18 Clinchek urine samples was 88.9% (Co), 84.2% (Cu), 84.2% (Zn), 75.0% (Se), 114.0% (Mo), 78.5% (Pb), and 88.2% (Cd).

For urinary arsenic speciation analysis, we used the Thermo Scientific IC5000 ion chromatography system, coupled with a Thermo AS7, 2 × 250 mm column, a Thermo AG7, 2 × 50 mm guard column, and interfaced with a Thermo ICAP Q ICP-MS utilizing Helium gas in collision cell mode. This system was employed to determine the following chemical forms: AsB, DMA, MMA, and iAs (arsenite + arsenate). To ensure quality control, we included blank and replicate samples of the National Institute of Standards and Technology (NIST) human urine standard reference material 2669 – level I or ClinChek® Control level I in each analytical batch. The average recovery, based on 28 SRM 2669 and 33 ClinChek® Control level I samples, was 96.8% including AsB, DMA, MMA, and iAs. The LOD was determined using DMA and the mean value across batches was 0.008 μg/L.

We calculated the iAs methylation indices, which serve as a proxy for assessing iAs detoxification capacity, using a previously described methodology (Signes-Pastor et al., 2021; Wei et al., 2017). The Primary Methylation Index (PMI) was obtained by dividing the urinary MMA concentrations by the iAs concentrations ($\frac{MMA}{iAs}$). The Secondary Methylation Index (SMI) was obtained by dividing the urinary DMA concentrations by the MMA concentrations ($\frac{DMA}{MMA}$). A higher PMI and a lower SMI were interpreted as a reduced iAs metabolism capacity.

2.4. Covariates

Other information about sociodemographic characteristics and lifestyles was also collected in the 4–5-year interviews using questionnaires. To identify other variables of interest for include in the multivariable models, we did a Directed Acyclic Graph (DAG) based in our prior knowledge in the scientific literature (Fig. S2) (Textor et al., 2016). Finally, we included the following variables as the minimum sufficient set to establish associations between our PVG dietary patterns and the metal exposures: child's sex (male or female), child's Body Mass Index (BMI) (kg/m^2), child's television hours (hours/day) (Boynton-Jarrett et al., 2003; Ghobadi et al., 2018; Lutz et al., 2023), sub-cohort (Asturias, Gipuzkoa, Sabadell or Valencia) and child's energy intake (kcals/day). In the case of BMI, was obtained using the weight (kg) and the heigh (m) that were measured by trained personal using standard protocols (Viet and Verschuren, 2008). Energy intake was estimated using the information from the FFQ.

2.5. Statistical analysis

We described our population characteristics using median and lower-higher quartiles (Q1 - Q3) when the variable was continuous and *n* (percentage) when was categorical. The urine metal concentrations were standardized using urine specific gravity (SG) for the descriptive analyses. To do so, we multiplied each metal, including arsenic species concentration (E_0), by $E_0 x \frac{SG_{median}-1}{SG_0-1}$ (Kuiper et al., 2022). Prior to the main statistical analysis, we logarithmically transformed urine metal concentrations to address right skewness and then computed Pearson's correlation between essential and heavy metal pairs.

First, we explored the association between the PVG dietary patterns and metal exposure using multiple linear regression models, with the PVG dietary patterns as independent variables represented by quintile scores as described previously (Martínez-González et al., 2014; Oncina-Cánovas et al., 2022a; Oncina-Cánovas et al., 2022b). The adherence categories were defined using quintiles numbers (Q1 to Q5). Quintiles indicate increasing levels of adherence, ranging from the lowest in Q1 to the highest in Q5. This order allows us to assess exposure to essential and heavy metals on a gradient. Although there are no established cut-off points for these patterns, in order to interpret our findings in the context of our population, we specifically categorized each level (each quintile) of adherence as very low, low, moderate, high, and very high, respectively. Urine metal concentrations were the dependent variable in the statistical models, adjusted for child sex (male or female), sub-cohort (Asturias, Gipuzkoa, Sabadell, or Valencia), child BMI (kg/m^2), child television hours (hours/day), energy intake (kcals/day), and SG. The percentage change (PC) from the results of the linear regression analysis was determined by employing the following formula: $100\times\ [\exp(\beta)-1]$ (Notario-Barandiaran et al., 2023b). The sum of urinary iAs and MMA concentrations, excluding AsB and DMA, was used as a proxy for iAs exposure in the main analysis. To ensure precise risk assessment, we adopt this approach, as urinary DMA levels, particularly in fish consumers, may be influenced by exposure to less toxic arsenic forms like specific arsenolipids or arsenosugars (Aylward et al., 2014). However, sensitivity analysis was also conducted, including the sum of urinary iAs + MMA + DMA concentrations. The iAs methylation indices, especially the SMI (DMA and MMA ratio), may also be affected by urinary DMA from sources other than iAs metabolism, which needs to be considered in the interpretation of the results. Statistical analyses were sex-stratified to investigate sex differences in food consumption patterns (Arganini et al., 2012; Enalia, 2016; Keller et al., 2019) and iAs methylation capacity (Lindberg et al., 2007; Llop et al., 2013; Signes-Pastor et al., 2019). We also calculated trend tests using models that included the categorical variable (the PVG patterns in quintiles) as a continuous variable adjusting for all possible confounders described above.

Furthermore, we identified key essential and heavy metals in the mixture according to the level of adherence to the PVG dietary patterns evaluated using the quantile g-computation approach using the R package "qgcomp." The quantile g-computation method estimates the joint effect of the metal mixture on the PVG dietary patterns when increasing all metals by a single quantile, allowing for the individual contributions of each component to the overall estimate, regardless of their effect direction (Keil et al., 2020). We used the "qgcomp.noboot" function for exposure weight effects estimation. Similar to linear regressions, gcomp weights were expressed as percentages.

All statistical analyses and graphics were performed using R version 4.1.2 (R Core Team, 2020). A significance threshold of $\alpha = 0.05$ was applied.

3. Results

Sociodemographic characteristics and lifestyles among mothers and their children in our population are describe in Table 1. In the case of the mothers, 40.7% had university studies and most of them (43.8%) belonged to the lowest category of social class (IV–V). On the other side, 51.9% of the children were males and 48.1% females, with a median (Q1 - Q3) age of 4.4 (4.4–4.5) years. The children also had a median (Q1 - Q3) BMI of 15.9 (15.2–16.9) kg/m^2, with a total energy intake of 1,551 (1,336–1,779) kcal/day and 1.3 (0.8–1.7) television hours/day. Analysis of sociodemographic characteristics among included and excluded study participants (Table S2) reveals similarities in educational level and social class of mothers. Children in both groups also exhibit similar age and BMI. However, Sabadell stands out in sub-cohort participant numbers.

The median (Q1 - Q3) urinary concentrations standardized for urine dilution of each metal for our population (Table S3) were Co: 0.8 (0.5–1.4); Cu: 8.1 (2.8–12.7); Zn: 382.5 (243.5–597.4); Se: 23.1 (16.9–34.4); Mo: 94.9 (61.5–142.9); Pb: 0.3 (0.2–0.8); and Cd: 0.1 (0.1–0.2) μg/L. Regarding arsenic speciation, the median (Q1 - Q3) for each of the measured forms (AsB, DMA, MMA, iAs, iAs + MMA, and iAs + MMA + DMA) in our population (Table S3) was 10.6 (3.0–41.4); 3.4 (0.6–6.6); 0.4 (0.0–0.8); 1.2 (0.4–2.2); 1.7 (0.9–2.9) and 5.3 (2.7–9.3) μg/L, respectively.

Noticeable correlations were observed among essential and heavy metals in the Pearson's correlation matrix, particularly between Cd and Mo ($\rho = 0.55$, *p*-value <0.001), Pb and Cu ($\rho = 0.54$, *p*-value <0.001), and Se and Zn ($\rho = 0.69$, *p*-value <0.001) (Fig. S3).

Table 1
Sociodemographic characteristics and lifestyle among mothers and their 4-5-years children of the INMA cohort study.

Variables	Total sample (*n* = 723)
Mother	
Educational level, *n* (%)	
Primary	133 (18.7)
Secondary	288 (40.6)
University	289 (40.7)
Social class[a], *n* (%)	
I + II (highest)	178 (26.7)
III	197 (29.5)
IV + V (lowest)	292 (43.8)
Children	
Age (years)	4.4 (4.4–4.5)[b]
Sex, *n* (%)	
Male	375 (51.9)
Female	348 (48.1)
Cohort, *n* (%)	
Asturias	61 (8.4)
Gipuzkoa	202 (27.9)
Sabadell	365 (50.5)
Valencia	95 (13.1)
Television (hours/day)	1.3 (0.8–1.7)
Energy intake (kcal/day)	1551.1 (1336.4–1779.8)
BMI, (kg/m^2)	15.9 (15.2–16.9)
gPVG[c]	36 (33–39)
hPVG[c]	51 (47–55)
uPVG[c]	51 (46–56)

BMI, body mass index; gPVG, general pro–vegetarian dietary pattern; hPVG, healthful pro–vegetarian dietary pattern; uPVG, unhealthful pro–vegetarian dietary pattern.

[a] Social Class = I-II (managers, professionals), III (technicians and associate professionals, clerical support workers, skilled agricultural, forestry and fishery workers), IV-V (craft and related trades workers, plant and machine operators and assemblers).

[b] Median (Q1-Q3) (all such values).

[c] Points of adherence to each pattern.

With regard to PVG dietary patterns adherence in our population, the median (Q1 - Q3) child's score for each PVG dietary pattern was, 36 (33–39) for the gPVG, 51 (47–55) for the hPVG and 51 (46–56) for the uPVG (Table 1). When we divided the adherence in quintiles, the number of participants and the range scores obtained for each quintile in each pattern, was: in the case of the gPVG, quintile 1: <33 (*n* = 173), quintile 2: 33–35 (*n* = 157), quintile 3: 36–37 (*n* = 116), quintile 4: 38–40 (*n* = 150) and quintile 5: >40 (*n* = 127); in the case of hPVG, quintile 1: <47 (*n* = 168), quintile 2: 47–49 (*n* = 129), quintile 3: 50–53 (*n* = 172), quintile 4: 54–56 (*n* = 121) and quintile 5: >56 (*n* = 133); and, in the case of uPVG, quintile 1: <46 (*n* = 167), quintile 2: 46–49 (*n* = 130), quintile 3: 50–53 (*n* = 154), quintile 4: 54–57 (*n* = 151) and quintile 5: >57 (*n* = 121). Regarding the consumption of different food groups in the PVG dietary patterns, the mean (standard deviation - SD) for each food group in our population in g/day can be seen in Table S4. Regarding sex differences, boys consume more cereals [108.3 (42.1) *vs* 100.4 (36.2) g/day; *p*-value <0.05], especially refined cereals [101.7 (42.0) *vs* 95.9 (36.0) g/day; *p*-value <0.05], and sugar-sweetened beverages [18.2 (51.3) *vs* 12.0 (29.7) g/day; *p*-value <0.05] (Table S4). Table S5, Table S6, and Table S7 present the daily consumption in grams of each food group across the adherence quintiles of each PVG dietary pattern. Urine metal concentrations for the different PVG dietary patterns (in quintiles) are shown in Table S8, along with their corresponding medians and interquartile ranges (IQR).

The results for multivariable adjusted linear regressions between the adherence to the different PVG dietary patterns and the urinary concentrations of the different essential and heavy metals plus the iAs methylation indices are shown in Table 2, Table 3, and Table 4. The results are shown as PC with 95% confidence intervals (95% CI) and the lowest quintile of adherence was the reference in each pattern. For the gPVG dietary pattern, after adjusting by child sex, sub-cohort, child BMI,

Table 2
Association between general PVG dietary pattern (in quintiles of adherence) and urine essential and heavy metals[1] (*n* = 723).

	Q1 (<33)	Q2 (33–35)	Q3 (36–37)	Q4 (38–40)	Q5 (>40)	
Individual metals		PC (95% CI)	PC (95% CI)	PC (95% CI)	PC (95% CI)	*p*-trend[2]
Co	Ref.	−10.2 (−28.1; 11.6)	1.63 (−19.7; 28.4)	−6.91 (−25.2; 16.2)	**−22.7 (-38.7; -1.98)**	**0.039**
Cu	Ref.	0.84 (−31.6; 49.2)	−27.3 (−52.3; 10.5)	11.6 (−24.4; 64.9)	−11.1 (−41.7; 34.9)	0.728
Zn	Ref.	−12.9 (−25.2; 2.02)	2.53 (−13.1; 20.9)	−6.43 (−19.7; 9.42)	−13.9 (−27.4; 2.02)	0.088
Se	Ref.	−6.72 (−16.5; 4.08)	−5.23 (−16.5; 7.25)	−8.18 (−18.1; 3.04)	**−12.6 (-22.9; -1.00)**	**0.009**
Mo	Ref.	−5.21 (−19.7; 11.6)	−3.11 (−18.9; 15.0)	−3.05 (−17.3; 13.9)	−10.2 (−24.4; 7.25)	0.339
Pb	Ref.	−7.12 (−25.9; 17.4)	−20.5 (−38.1; 2.02)	1.10 (−19.7; 27.1)	3.52 (−19.7; 32.3)	0.949
Cd	Ref.	2.07 (−14.8; 22.1)	−13.2 (−28.8; 6.18)	−2.08 (−18.1; 17.3)	−7.06 (−23.7; 13.9)	0.512
AsB	Ref.	20.6 (−34.9; 122.5)	−23.3 (−60.5; 49.2)	−8.51 (−50.3; 69.9)	−4.11 (−50.8; 87.8)	0.961
iAs + MMA	Ref.	**−57.8 (-76.3; -24.4)**	−9.90 (−51.8; 68.2)	−43.0 (−68.0; 1.00)	−27.5 (−61.3; 36.3)	0.335
PMI[3]	Ref.	**84.4 (25.8; 169.1)**	**70.5 (13.9; 155.9)**	**68.5 (16.2; 145.9)**	15.9 (−22.9; 73.3)	0.178
SMI[3]	Ref.	−4.51 (−49.8; 80.4)	−30.8 (−65.3; 37.7)	**−53.7 (-75.6; -12.2)**	−20.4 (−60.1; 58.4)	0.172

PC, percentage change; Co, cobalt; Cu, copper; Zn, zinc; Se, selenium; Mo, molybdenum; Pb, lead; Cd, cadmium; AsB, arsenobetaine; iAs (arsenite + arsenate); MMA, monomethylarsonic acid; PMI, primary methylation index; SMI, secondary methylation index; CI, confidence interval. [1]Multiple linear regression models adjusted by child sex (male or female), sub-cohort (Asturias, Gipuzkoa, Sabadell or Valencia), child body mass index (kg/m^2), child television hours (hours/day), energy intake (kcals/day) and urine specific gravity[2]*p*-value from trend test. [3]Models for primary and secondary methylation indices are also adjusted by the sum of arsenic concentrations (AsB + DMA + MMA + iAs). Bold values are *p-value* < 0.05.

Table 3
Association between healthful PVG dietary pattern (in quintiles of adherence) and urine essential and heavy metals[1] (*n* = 723).

	Q1 (<47)	Q2 (47–49)	Q3 (50–53)	Q4 (54–56)	Q5 (>56)	
Individual metals		PC (95% CI)	PC (95% CI)	PC (95% CI)	PC (95% CI)	*p*-trend[2]
Co	Ref.	−9.08 (−28.1; 15.0)	4.37 (−15.6; 29.7)	−11.3 (−30.2; 12.7)	−3.31 (−23.7; 22.1)	0.238
Cu	Ref.	−4.12 (−37.5; 46.2)	−2.06 (−32.9; 43.3)	−11.4 (−42.3; 34.9)	22.5 (−18.9; 84.0)	0.794
Zn	Ref.	−4.75 (−19.7; 12.7)	−8.66 (−21.4; 6.18)	−7.89 (−22.1; 9.42)	−3.72 (−18.1; 13.9)	0.403
Se	Ref.	−10.1 (−20.5; 2.02)	−8.31 (−18.1; 2.02)	−5.54 (−16.5; 7.25)	−9.94 (−19.7; 1.00)	**0.040**
Mo	Ref.	−1.51 (−17.3; 17.4)	6.69 (−8.61; 24.6)	−0.44 (−16.5; 18.5)	3.72 (−13.1; 23.4)	0.643
Pb	Ref.	−7.22 (−28.1; 19.7)	−0.45 (−20.5; 24.6)	3.19 (−19.7; 32.3)	8.30 (−14.8; 37.7)	0.718
Cd	Ref.	−3.05 (−20.5; 18.5)	3.15 (−13.9; 23.4)	1.49 (−17.3; 24.6)	5.95 (−13.1; 28.4)	0.805
AsB	Ref.	−38.3 (−68.3; 20.9)	−18.4 (−55.1; 47.7)	7.07 (−45.1; 109.6)	49.0 (−22.1; 185.8)	0.361
iAs + MMA	Ref.	**−51.7 (-74.3; -8.61)**	−41.3 (−66.7; 3.05)	−22.7 (−58.9; 46.2)	−12.4 (−52.8; 61.6)	0.547
PMI[3]	Ref.	−5.29 (−37.5; 43.3)	34.7 (−6.76; 95.4)	17.5 (−22.1; 78.6)	12.6 (−24.4; 68.2)	0.500
SMI[3]	Ref.	11.4 (−44.6; 124.7)	−9.55 (−51.3; 68.2)	−21.8 (−61.3; 56.8)	−27.8 (−63.2; 41.9)	0.550

PC, percentage change; Co, cobalt; Cu, copper; Zn, zinc; Se, selenium; Mo, molybdenum; Pb, lead; Cd, cadmium; AsB, arsenobetaine; iAs (arsenite + arsenate); MMA, monomethylarsonic acid; PMI, primary methylation index; SMI, secondary methylation index; CI, confidence interval. [1]Multiple linear regression models adjusted by child sex (male or female), sub-cohort (Asturias, Gipuzkoa, Sabadell or Valencia), child body mass index (kg/m^2), child television hours (hours/day), energy intake (kcals/day) and urine specific gravity. [2]*p*-value from trend test. [3]Models for primary and secondary methylation indices are also adjusted by the sum of arsenic concentrations (AsB + DMA + MMA + iAs). Bold values are *p-value* < 0.05**.**

child television hours, child total energy intake and SG, the highest quintile of adherence was associated with 22.7% and 12.6% lower urinary levels of Co (95% CI: −38.7 to −1.98; *p*-trend: 0.039) and Se (95% CI: −22.9 to −1.00; *p*-trend: 0.009), respectively (Table 2). The fourth quintile of adherence to a gPVG was also associated with a 68.5% higher PMI (95% CI: 16.2 to 145.9; *p*-trend: 0.178) and a 53.7% lower SMI (95% CI: −75.6 to −12.2; *p*-trend: 0.172). The second quintile of adherence was associated with 57.8% lower levels of iAs + MMA urine concentrations (95% CI: −76.3 to −24.4; *p*-trend: 0.335). For the hPVG dietary pattern we only observed an association after adjusting, between

Table 4
Association between unhealthful PVG dietary pattern (in quintiles of adherence) and urine essential and heavy metals[1] (*n* = 723).

	Q1 (<46)	Q2 (46–49)	Q3 (50–53)	Q4 (54–57)	Q5 (>57)	
Individual metals		PC (95% CI)	PC (95% CI)	PC (95% CI)	PC (95% CI)	*p*-trend[2]
Co	Ref.	6.94 (−14.8; 34.9)	18.5 (−4.87; 47.7)	10.1 (−12.2; 39.1)	4.34 (−19.7; 34.9)	0.378
Cu	Ref.	5.17 (−30.2; 58.4)	36.5 (−7.69; 101.4)	36.9 (−8.61; 105.4)	14.7 (−28.1; 82.2)	0.304
Zn	Ref.	−4.66 (−18.9; 12.7)	0.28 (−13.9; 17.3)	8.81 (−7.69; 28.4)	−2.81 (−18.9; 17.3)	0.582
Se	Ref.	**−13.6 (-22.9; -2.95)**	−6.75 (−16.5; 4.08)	−0.70 (−11.3; 11.6)	−1.61 (−13.9; 12.7)	0.664
Mo	Ref.	−7.82 (−22.1; 9.42)	**−17.5 (-29.5; -2.95)**	−5.35 (−19.7; 12.7)	−12.2 (−27.4; 6.18)	0.323
Pb	Ref.	−19.9 (−36.9; 2.02)	−9.86 (−28.8; 13.9)	−14.5 (−32.9; 8.33)	5.40 (−19.7; 39.1)	0.849
Cd	Ref.	0.30 (−17.3; 22.1)	−0.51 (−17.3; 19.7)	4.52 (−13.9; 27.1)	−4.77 (−23.7; 18.5)	0.985
AsB	Ref.	−11.4 (−53.2; 68.2)	−20.2 (−56.8; 47.7)	13.6 (−40.5; 115.9)	−50.7 (−76.3; 2.02)	0.114
iAs + MMA	Ref.	39.9 (−23.7; 158.6)	22.1 (−32.3; 120.3)	12.7 (−38.7; 107.5)	27.5 (−36.2; 156.0)	0.740
PMI[3]	Ref.	−10.6 (−39.9; 32.3)	2.79 (−29.5; 50.7)	−11.0 (−40.5; 32.3)	−29.8 (−55.5; 10.5)	0.314
SMI[3]	Ref.	**−52.3 (-75.6; -6.76)**	−22.9 (−59.3; 46.2)	13.9 (−41.7; 122.5)	3.76 (−51.3; 122.5)	0.539

PC, percentage change; Co, cobalt; Cu, copper; Zn, zinc; Se, selenium; Mo, molybdenum; Pb, lead; Cd, cadmium; AsB, arsenobetaine; iAs (arsenite + arsenate); MMA, monomethylarsonic acid; PMI, primary methylation index; SMI, secondary methylation index; CI, confidence interval. [1]Multiple linear regression models adjusted by child sex (male or female), sub-cohort (Asturias, Gipuzkoa, Sabadell or Valencia), child body mass index (kg/m^2), child television hours (hours/day), energy intake (kcals/day) and urine specific gravity. [2]*p*-value from trend test. [3]Models for primary and secondary methylation indices are also adjusted by the sum of arsenic concentrations (AsB + DMA + MMA + iAs). Bold values are *p-value* < 0.05.

the second quintile of adherence and 51.7% lower levels of iAs + MMA (95% CI: −74.3 to −8.61; *p*-trend: 0.547) (Table 3). Conversely, for the uPVG dietary pattern we observed that the third quintile of adherence was associated with 17.5% lower levels of Mo (95% CI: −29.5 to −2.95; *p*-trend: 0.323) and the second quintile of adherence was associated with 13.6% lower levels of Se (95% CI: −22.9 to −2.95; *p*-trend: 0.664) and a 52.3% lower SMI (95% CI: −75.6 to −6.76; *p*-trend: 0.539) (Table 4).

Consistent results were obtained for the metal mixture analysis using the quantile g-computation method compared to those from the multiple linear regression analyses (Fig. 1). The highest positive weights for the different PVG dietary patterns, were assigned to Pb and iAs + MMA (39.2% and 23.2%, respectively) in the case of gPVG, to Mo and AsB (38.2% and 28.4%, respectively) in the case of hPVG, and to Cu and Co (40.3% and 27.3%, respectively) in the case of uPVG. The primary negative weights were assigned to Se and Cd (56.3% and 24.4%, respectively) for the gPVG, to Se and Cd (64.9% and 22.3%, respectively) for the hPVG, and to Mo and AsB (31.5% and 27.9%, respectively) for the uPVG. The sensitivity analysis results on the association between PVG dietary patterns (categorized into quintiles of adherence) and urinary iAs + MMA + DMA are shown in Table S9. We observed a lower exposure in both the second and the fourth quintiles of adherence to a gPVG, with PCs of −50.9% (95% CI: −71.6 to −14.8) and −47.5% (95 %CI: −69.6 to −9.52), respectively.

In the sex-stratified analysis of differences in iAs methylation indices, we observed distinct patterns among boys and girls. In boys, the third quintile of adherence to a gPVG was associated with a higher PMI (PC = 92.7%, 95% CI: 8.33 to 242.1), while the second quintile of adherence to a uPVG was related to a lower SMI (PC = −67.8%, 95%CI: −87.4 to −18.1) (Table S10). Among girls, we found that the second quintile of adherence to a gPVG was related with a higher PMI (PC = 125.3%, 95% CI: 31.0 to 289.6), and the fourth quintile of adherence to a gPVG was also associated with a higher PMI (PC = 72.9%, 95% CI: 1.01 to 194.5) (Table S11).

4. Discussion

In our primary research, we investigated the adherence to PVG patterns in 4-5-year-old children and its association with exposure to essential and heavy metals. Our results showed that very high adherence to gPVG dietary pattern is associated to lower exposure to essential metals Co and Se. Moreover, high adherence to gPVG pattern is associated with a higher PMI and a lower SMI. Lower levels of adherence to hPVG and uPVG patterns also seems to influence exposure to some essential and heavy metals.

Although high adherence to the gPVG pattern was not associated with most of the essential and heavy metals, it was associated with lower urinary Co and Se. Co is an essential component of vitamin B12, primarily found in animal-based foods such as meat, eggs, and dairy products, but excessive exposure can be toxic (Leyssens et al., 2017). Vitamin B12 is crucial for DNA formation and repair, as well as the function of the nervous system (Azzini et al., 2021). While we did not directly measure this vitamin in our study, Co exposure could affect B12 status (González-Montaña et al., 2020). Therefore, vegetarians are advised to take B12 supplements to meet their requirements (Melina et al., 2016). Similarly, Se, obtained mainly from fish and seafood, is essential for immune modulation, but it is limited in vegetarian diets (Bakaloudi et al., 2020; Kieliszek et al., 2021). Therefore, our results align with existing literature as this plant-based pattern resemble vegetarian diets, potentially leading to lower intake of Co and Se. Some nutrition organizations caution that vegetarian diets in children may result in nutritional deficiencies (Agnoli et al., 2017; Lemale et al., 2019). However, the hPVG pattern did not show an association with lower Co and Se exposure. Therefore, it's essential to consider dietary quality when choosing a PVG pattern for children. Adding small amounts of fish and selected nut-based products to the regular diet, with precautions to prevent choking, may enhance the intake of essential metals, particularly Co and Se.

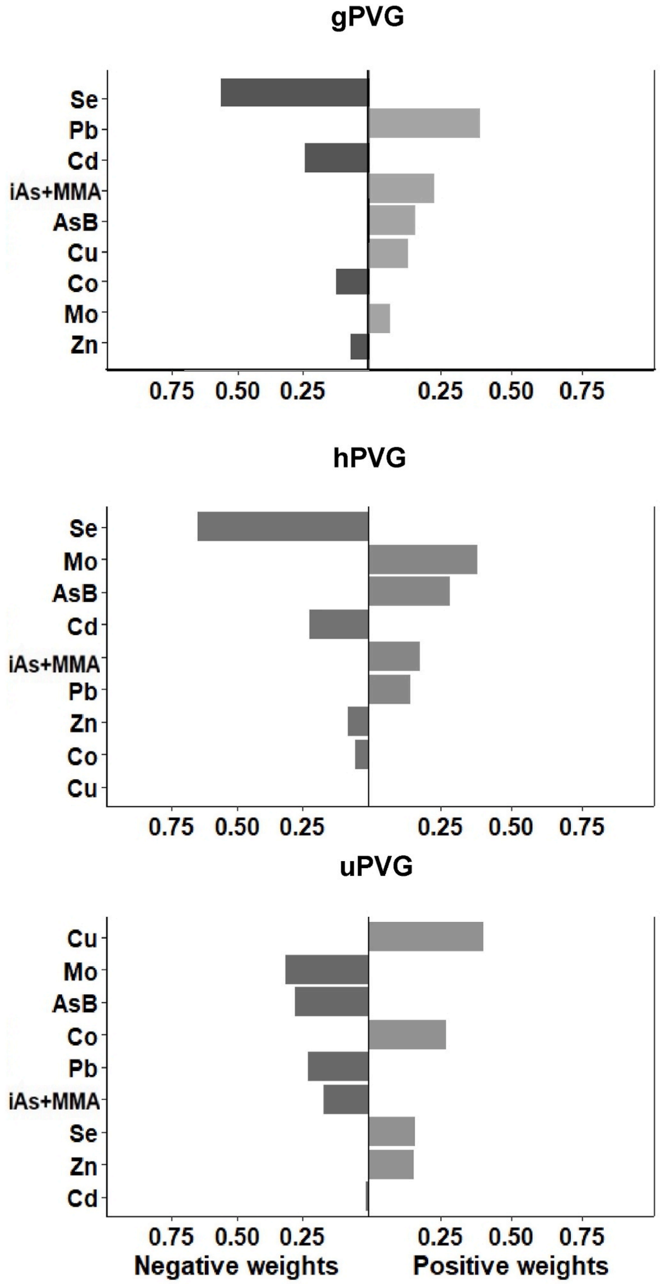

Fig. 1. Quantile g-computation between metal concentrations and PVG dietary patterns (gPVG, hPVG, uPVG) in children of 4–5 years of age.
gPVG negative weights: Se = 56.3%; Cd = 24.4%; Co = 12.2%; Zn = 7.1%. gPVG positive weights: Pb = 39.2%; iAs + MMA = 23.2%; AsB = 16.2%; Cu = 13.8%; Mo = 7.6% (*p*-value: 0.147). hPVG negative weights: Se = 64.9%; Cd = 22.3%; Zn = 7.7%; Co = 5.1%. hPVG positive weights: Mo = 38.2%; AsB = 28.4%; iAs + MMA = 18.3%; Pb = 14.7%; Cu = 0.4% (*p*-value: 0.662). uPVG negative weights: Mo = 31.5%; AsB = 27.9%; Pb = 22.7%; iAs + MMA = 16.9%; Cd = 0.8%. uPVG positive weights: Cu = 40.3%; Co = 27.3%; Se = 16.5%; Zn = 15.9%. (*p*-value: 0.509).

Vitamin B12 and Se play crucial roles in childhood iAs detoxification process. Higher plasma B12 levels are related to improved iAs methylation (Lin et al., 2019), while higher plasma Se concentrations are associated with better iAs methylation and developmental outcomes in preschool children (Su et al., 2019). The impact of Se on iAs methylation is more pronounced in children than adults (Löveborn et al., 2016), potentially supporting iAs excretion through chelation (Zwolak, 2019).

Se and iAs compete in biological functions, displaying an antagonistic relationship (Zeng et al., 2005). Vitamin B12's antioxidant effects and influence on methylation pathways may also affect iAs methylation through homocysteine regulation (Howe et al., 2017). The association between high adherence to the gPVG pattern, a higher PMI, and a lower SMI may be explained by these factors. A lower SMI is concerning due to its association with bladder cancer in adults with cumulative arsenic exposure (Chen et al., 2003), while higher PMI is associated with higher breast cancer risk in women (López-Carrillo et al., 2014). However, studies investigating iAs methylation capacity using these indices in children are still limited (Bocca et al., 2020; Torres-Sánchez et al., 2016).

In this study, we examined differences in iAs methylation capacity based on children's sex. Both girls (low and high adherence) and boys (moderate adherence) adhering to the gPVG pattern showed a higher PMI in our study. However, only boys with low adherence to the uPVG pattern was associated with a lower SMI. It has been suggested that boys may be more susceptible to harmful effects from iAs exposure (Rahman et al., 2006). One explanation is that girls may have greater iAs methylation efficiency (Lindberg et al., 2008). Hormones and other biological factors may also influence methylation pathways, even in childhood, when hormone production is not at its peak (Lindberg et al., 2007). Additionally, differences in exposure levels may play a role. In our study, boys exhibited higher consumption of refined grains, particularly white rice, which is widely recognized as a substantial source of iAs exposure during childhood (Karagas et al., 2016). This finding could account for the observed sex differences in iAs methylation indices in our population.

Unlike the gPVG, the hPVG and uPVG were not consistently associated with exposure to essential and heavy metals. On one hand, the hPVG pattern was associated with a lower urinary level of iAs + MMA, but only in the low adherence category and without an apparent trend. This lack of associations with the hPVG pattern may be attributed to several reasons. Being a pattern that includes healthier foods (and, therefore, is richer in essential metals) than the gPVG, it may not be linked to lower Co and Se exposure. Our study sample was limited, which may reduce the possibility of finding positive associations. Finally, we cannot dismiss the possibility that this dietary pattern is not associated with exposure to essential and/or heavy metals in our population. On the other hand, moderate adherence to the uPVG pattern was associated with lower levels of Mo, aligning with our hypothesis. Mo, essential for human enzymes (Novotny and Peterson, 2018), is primarily present in legumes, which are inversely weighted in this pattern. Dairy products and animal viscera, also recognized as good sources of Mo (Sardesai, 1993), are inversely scored in all PVG patterns. The uPVG pattern emphasizes plant-based ultra-processed foods like fries, sugary drinks, and sweets (Karnopp et al., 2016; Leal et al., 2015). Literature shows that such diets in adulthood associate with poor cardiometabolic profiles (Huang et al., 2023; Oncina-Cánovas et al., 2022a), increased diabetes risk (Satija et al., 2016), and cancers, including stomach cancer (Oncina-Cánovas et al., 2022b). Hence, it is vital to study associations related to these dietary patterns across age groups. Low adherence to the uPVG pattern was associated with lower Se levels and a lower SMI, supporting previous findings. Plant-based diet followers often have lower Se concentrations (Bakaloudi et al., 2020), potentially affecting iAs detoxification. However, these results should be interpreted with caution, as these associations with the uPVG pattern were only at isolated levels of adherence and lacked a clear trend.

The correlation matrix of urine metal concentrations shows relevant associations among the essential and heavy metals, suggesting shared exposure sources. The strong correlation between Se and Zn, both essential metals primarily obtained from animal foods, may account for lower urinary Se concentrations in individuals with high adherence to a gPVG.

In terms of strengths and limitations, the cross-sectional design of this study constrains the establishment of causality and leaves it susceptible to reverse causation. We conducted numerous comparisons, and apart from Se and Co, a clear trend was not observed in the remaining associations (e.g., the associations for arsenic were observed in isolated quintiles). Therefore, we cannot dismiss the possibility that these associations may be spurious. Self-reported dietary intake through a FFQ introduces the possibility of recall bias, relying on parental reporting and referring to the previous year. In addition, the use of a FFQ introduces an inherent limitation, as it may lead to both exposure and effect misclassification. The FFQ did not consider exposure-relevant factors, such as the intake of specific foods (e.g., fortified foods) and the origin of the food. These factors could contribute to the levels of essential and heavy metals in the food content, thereby influencing the ultimate exposure (Signes-Pastor et al., 2008, 2016). Despite this, the FFQ was validated in a subsample of our population (Vioque et al., 2016) and is considered a reliable method for epidemiological studies (Willett, 2013). We used three PVG dietary patterns, including a general pattern and two derived ones, for more precise conclusions about the impact of plant-based foods on metal exposure. Urine samples, commonly used to assess metal exposure, may introduce estimation bias due to variations in excretion levels. For example, urinary arsenic levels reflect exposure only in the 2–3 days leading up to collection (Meharg et al., 2014), while elements such as Se or Cd may indicate chronic exposure (Phiri et al., 2019; Vacchi-Suzzi et al., 2016). Furthermore, using urine samples to assess essential metals exposure may not be adequate as a biomarker for nutritional status (Combs, 2015; Cockell, 2015). Therefore, our findings should be interpreted with caution. We performed arsenic speciation, crucial to account for variations in toxicity, as inorganic forms are the most toxic (El-Ghiaty and El-Kadi, 2022). Despite Pb having the highest number of urinary concentrations below the LOD, we included it in our analyses due to its significance as a contaminant (Kumar et al., 2020; Gundacker et al., 2021). Despite the limited sample size, we identified noteworthy associations after adjusting for potential confounders in the main and sensitivity analyses such as the sex stratified (Lindberg et al., 2007; Torres-Sánchez et al., 2016) and after including urinary DMA in the iAs exposure assessment analyses (Aylward et al., 2014). Finally, we also identified some notable trends in associations, particularly for Co and Se, thereby adding robustness to our findings.

5. Conclusions

In conclusion, this study addresses a novel question regarding the association between children's adherence to the most common PVG dietary patterns and their exposure to metals, using a comprehensive approach that incorporates both dietary assessment and urinary metal concentration analysis. The two derived patterns, the hPVG and uPVG, do not appear to be consistently associated with exposure to essential or heavy metals, as well as with the ability to iAs methylation. However, adherence to a gPVG dietary pattern during childhood may result in a modest reduction in exposure to certain essential metals, such as Co and Se. Furthermore, this pattern may also affect children's metabolism of toxic compounds like iAs, especially in boys. Thus, our study highlights the complexity of investigating the relationship between simultaneous exposures such as diet and metals, warranting further longitudinal studies to explore any potential health implications.

Authors contribution

AO-C contributed to methodology, formal statistical analysis and writing; AJS-P contributed to conceptualization, methodology, visualization, support in statistical analysis, reviewing of manuscript and obtaining funding; JV, GR-M, RS-B, AI, ZB, AF-S, AT, MV and MG were responsible for the acquisition of data and made a critical revision of the manuscript for intellectual content and approved the final manuscript. AM, MC, CM, KR, and McC performed urinary essential and heavy metals concentrations analysis and made a critical revision of the manuscript for intellectual content and approved the final manuscript.

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CRediT authorship contribution statement

Alejandro Oncina-Cánovas: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Jesús Vioque:** Writing – review & editing. **Gabriel Riutort-Mayol:** Writing – review & editing. **Raquel Soler-Blasco:** Writing – review & editing. **Amaia Irizar:** Writing – review & editing. **Ziortza Barroeta:** Writing – review & editing. **Ana Fernández-Somoano:** Writing – review & editing. **Adonina Tardón:** Writing – review & editing. **Martine Vrijheid:** Writing – review & editing. **Mònica Guxens:** Writing – review & editing. **Manus Carey:** Writing – review & editing. **Caroline Meharg:** Writing – review & editing. **Kathryn Ralphs:** Writing – review & editing. **Coalain McCreanor:** Writing – review & editing. **Andrew Meharg:** Writing – review & editing. **Antonio J. Signes-Pastor:** Writing – review & editing, Visualization, Supervision, Methodology, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Appendix A. Supplementary data

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