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# Association between mediterranean diet and metal(loid) exposure in 4-5-year-old children living in Spain.

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## ABSTRACT

Even relatively low levels of metals exposure may impact health, particularly among vulnerable populations such as infants and young children. However, little is known about the interplay between simultaneous metal exposures, common in real-life scenarios, and their association with specific dietary patterns. In this study, we have evaluated the association between adherence to Mediterranean diet (MD) and urinary metal concentrations individually and as an exposure mixture in 713 children aged 4-5-years from the INMA cohort study. We used a validated food frequency questionnaire to calculate two MD indexes scores: aMED and rMED. These indexes gather information on various food groups within the MD and score differently. To measure urinary concentrations of cobalt, copper, zinc, molybdenum, selenium, lead, and cadmium as exposure biomarkers, we used inductively coupled plasma mass spectrometry (ICP-MS), coupled with an ion chromatography (IC) equipment for arsenic speciation analysis. We applied linear regression and quantile g-computation, adjusted for confounders, to analyse the association between MD adherence and exposure to the metal mixture. High adherence to MD such as the quintile (Q) 5 MD was associated with higher urinary arsenobetaine (AsB) levels than Q1, with β values of 0.55 (confidence interval - CI 95% 0.01; 1.09) for aMED and 0.73 (CI 95% 0.13; 1.33) for rMED. Consumption of fish was associated with increased urinary AsB but reduced inorganic arsenic concentrations. In contrast, the aMED vegetables consumption increased urinary inorganic arsenic content. A moderate level of adherence to MD (Q2 and Q3) was associated with lower copper urinary concentrations than Q1, with β values of −0.42 (CI 95% −0.72; −0.11) for Q2 and -0.33 (CI 95% −0.63; −0.02) for Q3, but only with aMED. Our study, conducted in Spain, revealed that adhering to the MD reduces exposure to certain metals while increasing exposure to others. Specifically, we observed increase in exposure to non-toxic AsB, highlighting the significance

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of consuming fish/seafood. However, it is crucial to emphasize the necessity for additional efforts in reducing early-life exposure to toxic metals, even when adhering to certain food components of the MD.

## Human subjects statement

All participant parents from the Infancia y Medio Ambiente (INMA) project provided informed consent, and the ethical committees of the centres involved in the study approved the protocol (i.e., Hospital La Fe, Valencia; Sabadell Hospital, Sabadell; Central University Hospital of Asturias, Asturias; and Zumarraga Hospital, Gipuzkoa).

## 1. Introduction

Early life environmental exposures to metal(loid) including essential and non-essential elements are of particular concern as they may have long-term health implications (Walker et al., 2009; Zoroddu et al., 2019). Essential elements are fundamental components found in human tissues, playing a vital role in the biological functions of the human body when maintained within an optimal range. However, both an excess and deficiency of essential elements can adversely affect health (Howe et al., 2021; Skogheim et al., 2021; Zhang et al., 2021; Zoroddu et al., 2019). Non-essential elements such as arsenic, cadmium, or lead have no known biological role, yet chronic exposure to even low levels can pose health risks (Fiłon et al., 2020; Signes-Pastor et al., 2019; Soler-Blasco et al., 2022; Zoroddu et al., 2019). Hence, an adequate level of essential elements with limited exposure to non-essential elements is crucial to promote a healthy growth and development of infants and children (Corbo and Lam, 2013; Saghazadeh et al., 2017; Senut et al., 2012).

Humans are simultaneously exposed to a myriad of essential and non-essential elements (hereafter collectively referred to metals or metal mixtures) (Carpenter et al., 2002). The toxicity of individual metals relates to the oxidation state and chemical forms (Kalantzi et al., 2017; Polak-Juszczak and Richert, 2021; Signes-Pastor et al., 2017), but also to interactions with other metals with potential additive, synergistic or antagonistic effects (Henn et al., 2014; Park et al., 2017; Valeri et al., 2017). Assessing the effects of environmental exposure to mixtures of metals is crucial for a better understanding of their impact on children's health.

For populations who do not live in areas with heavy metals-contaminated water, soil, or air, and who are not occupationally exposed, diet is considered as the primary source of metal exposure (Amqam et al., 2020; Buckley et al., 2020; Signes-Pastor et al., 2020). Dietary patterns can help evaluate interactions between food items or nutrients, but current literature on dietary metal exposure often assesses only a limited number of food items or nutrients at a time (Hu, 2002). The Mediterranean diet (MD) is a well-known dietary pattern associated with reduced risk of obesity, diabetes, and cardiovascular disease in children (D'innocenzo et al., 2019; Notario-Barandiaran et al., 2020; Willett et al., 1995). Yet, the association between children's adherence to MD and levels of exposure to metals and metal mixtures is unclear.

In this study, our hypothesis is that there is an association between adherence to the MD and decreased exposure to non-essential elements (such as arsenic (As), cadmium (Cd), and lead (Pb)) while ensuring a sufficient intake of essential elements (including cobalt (Co), copper (Cu), zinc (Zn), molybdenum (Mo), and selenium (Se)) in children. To evaluate this association, we used MD adherence indexes, assessing overall adherence and adherence to each food component, and measured urinary concentrations of essential and non-essential elements in 4-5-year-old children residing in Spain. Additionally, we explored the primary contributors within the metal mixture that are associated with MD adherence.

## 2. Methods

### 2.1. Study population

The study population investigated here is from the INMA - *INfancia y Medio Ambiente* - (Environment and Childhood) project, a population-based multicentre prospective birth cohort study (Guxens et al., 2012). Pregnant women were recruited during the first trimester of pregnancy between 2003 and 2008 from the INMA sub-cohorts of Asturias, Gipuzkoa, Sabadell and Valencia. Briefly, at 4–5 years of follow-up assessment, 2139 children completed the follow-up paediatric interview. Of these participants, we had data for urine total metals concentration and As speciation for 819 and 1193 children, respectively, with a total of 754 children with data for both. Dietary data were missing for 41 participants. Finally, we had complete data with no missing values in urine metals concentrations or covariates of interest for 713 children (Fig. S1). All participant parents provided informed consent, and the ethical committees of the centres involved in the study approved the protocol (i.e., Hospital La Fe, Valencia; Sabadell Hospital, Sabadell; Central University Hospital of Asturias, Asturias; and Zumarraga Hospital, Gipuzkoa).

### 2.2. Dietary assessment

The INMA project used a semiquantitative food frequency questionnaire (FFQ) of 105 food items to assess the children's usual dietary intake at 4–5 years of age. This FFQ was previously validated in a subsample of the same population (Vioque et al., 2016). This FFQ was derived from a validated pregnant women's version (Vioque et al., 2013) and adapted to include food items and portion sizes appropriate for 4–5-year-old children. Children's dietary intake in the previous year was gathered by parents or caregivers. The FFQ included 9 possible frequencies of consumption, from "never once, or less than once a month" to "six or more times a day." We used the United States Department of Agriculture food composition tables (USDA, 2011) and other published sources as a cultural reference for Spanish foods and portion sizes (Palma et al., 2008; Vicario et al., 2003) to assess the total energy intake and foods nutrient values. Food intake data from the FFQ was used to calculate two of the most widely used MD indexes in nutritional epidemiology: the relative MD score (rMED) and the alternate MD score (Bekelman et al., 2021; Buckland et al., 2022; Notario-Barandiaran et al., 2020). The rMED is considered one of the main dietary indexes; however, it does not fill all the quality criteria regarding conceptual suitability, applicability, and psychometric properties (Buckland et al., 2010; Zaragoza-Marti et al., 2018). Thus, we have complemented the rMED index data with the aMED (Fung et al., 2005).

The rMED and aMED scores were derived from the original MD score (MDS) (Trichopoulou et al., 2003). Both indexes incorporate 8 key components of the MD: vegetables (excluding potatoes), fruits (including nuts), legumes, fish, cereals, meat, dairy products, and olive oil (Table S1). However, the components of aMED have some variations, fruits and nuts are separated in 2 different components, cereals, and meat, only included whole grains and red/processed meat, respectively. In addition, the dairy products component is not included, and the olive oil component is substituted by the ratio of monounsaturated to saturated fatty acids (Table S1). For rMED, each component was calculated in grams per 1000 kcal/day and divided into tertiles of intake. A score of 0, 1, and 2 points was assigned to the first, second, and third tertiles of intake, respectively. The food groups that do not fit within the MD such as meat and dairy products were scored reversely. For example, a score of 2 points for meat means an intake in the first tertile, a lower consumption. The total rMED score ranged from 0 to 16. On the other hand, for each aMED component, intakes above the median of the study participants received 1 point and below 0 points, except for red/-processed meat where the score is reversed, where higher intakes have a lower score since this is a food group that is presumed not to fit the MD. The total aMED score ranged from 0 to 8.

### 2.3. Metal exposure

Spot urine samples were collected during the 4–5 years follow-up paediatric interview. Urine samples were collected in 100 mL polyethylene containers and stored at or below −20 °C until analysis.

A Thermo ICAP Q inductively coupled plasma mass spectrometry (ICP-MS) in direct solution acquisition mode using a Cetac ASX-520 Auto Sampler was used to measure total urinary concentrations of Co, Cu, Zn, Se, Mo, Pb, and Cd. The limit of detection (LOD) was calculated as the mean of the blank concentrations plus three times the standard deviation of the blank concentrations multiplied by the dilution factor. The LOD across batches for each metal analysed in the study 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. Values below the LOD were imputed by the LOD divided by the square root of two and included in statistical analyses (Table S2) (Lubin et al., 2004). For quality control, blank and replicate samples of Clinchek® lyophilized urine samples were included in each analytic batch. The average 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).

Arsenic speciation including arsenobetaine (AsB), dimethylarsinic acid (DMA), monomethylarsonic acid (MMA), and inorganic arsenic (iAs = arsenite + arsenate) was measured using a Thermo Scientific IC5000 ion chromatography system, with a Thermo AS7, 2 × 250 mm column and a Thermo AG7, 2 × 50 mm guard column interfaced with a Thermo ICAP Q ICP-MS using He gas in collision cell mode. A gradient mobile phase including A: 20 mM ammonium carbonate and B: 200 mM ammonium carbonate, starting at 100% A, changing to 100% B, in a linear gradient over 15 min was used. The ICP-MS monitored m/z+ 75 using He gas in collision cell mode (Table S2). For quality control, blank and replicate samples of the human urine standard reference materials 2669 – level I from the National Institute of Standards and Technology (NIST) or ClinChek® Control level I were included in each analytic batch. Based on 28 SRM 2669 and 33 ClinChek® Control level I samples, we obtained a median recovery of 93.8% for the combined As species. Moreover, the median recovery of each As specie was 90.9% for AsB, 80.4% for DMA, 93.0% for MMA and 117.0% for iAs. We determined the LOD using DMA. The calculated LOD had a mean value of 0.008 μg/L across batches.

### 2.4. Covariates

Information on sociodemographic and lifestyle factors for children and their mothers were collected by trained interviewers using a structured questionnaire. We included covariates in our statistical models based on prior studies and a directed acyclic graph (DAG) (Fig. S2) (Textor et al., 2016). We selected the following covariates as potential maternal confounders: maternal education (categorized as primary, secondary, or university) and maternal social class (categorized as I-II (highest), III, or IV-V (lowest) (International Labor Office, 2012), the first category (I-II) included managers or professionals, the second category (III) included technicians and associate professionals, clerical support workers, skilled agricultural, forestry and fishery workers and, the third category (IV–V) included craft and related trades workers, plant and machine operators and assemblers. For children, we collected the following covariates: age (years, continuous), sex (male or female, categorical), body mass index (BMI) (kg/m$^2$, continuous), and energy intake (kcal/day, continuous). For BMI, weight (kg) and height (m) were measured by trained personnel using standard protocols (Viet and Verschuren, 2008), and energy intake was estimated from the data collected by the FFQ.

### 2.5. Statistical analysis

Descriptive analyses of participants' characteristics were calculated. Urine metal concentrations were natural logarithm transformed to address their right skewness before statistical analyses. In descriptive analysis, we standardized urinary metal concentrations by specific gravity following a methodology detailed previously (Kuiper et al., 2022). Urinary iAs, MMA, and DMA are the major metabolites from iAs exposure; however, DMA is susceptible to exposure misclassification due to direct exposure or metabolism of complex organosenical compounds (Aylward et al., 2014; Hata et al., 2012). Thus, we calculated the sum of urinary iAs and MMA concentrations excluding AsB and DMA as a conservative biomarker of internal iAs exposure from all sources ($\sum$iAs) (Aylward et al., 2014). Nevertheless, in the sensitivity analysis, we included the urinary concentrations of DMA along with the concentrations of iAs and MMA to evaluate iAs exposure. Ingested AsB is excreted in the urine unchanged and relates to fish/seafood consumption (Kalantzi et al., 2017; Signes-Pastor et al., 2017; Taylor et al., 2017). We performed a stratified sensitivity analysis, including participants with urinary AsB concentrations within the first tertile, to evaluate the potential confounding effect of fish/seafood consumption. We calculated Spearman's rank correlation coefficients to examine the correlations between each metal pair. Before performing the regression analyses, we checked graphically the linearity of the associations with splines and slight evidence of non-linearity was observed. To assess the association between adherence to MD through the rMED and aMED scores and urine metals concentrations we categorized the MD indexes total scores in quintiles (Q) and used multiple linear regression analysis. We also analysed the association between the components of rMED (scored from 0 to 2 according to tertiles of intake) and aMED (scored from 0 to 1 according to the median of intake) and urine metal concentrations. Dietary indexes total score and their components were included in the model as independent variables. Urine metal concentrations were used as the dependent variables and were adjusted by child age (years) and sex (male or female), child BMI (kg/m$^2$), child energy intake (kcal/day), maternal education (primary, secondary, or university), maternal social class (I-II, III, or IV-V), urine specific gravity, and sub-cohort (Asturias, Gipuzkoa, Sabadell, or Valencia).

We also explored the main contributors within the metal mixtures and the MD adherence, overall and for each food component, using the quantile g-computation approach with the R package "qgcomp." This method estimates the joint effect of the mixture on the MD when increasing all metals by a single quantile. It indicates the weighted contribution of each individual metal of the mixture to the global estimation and does not require the same effect direction of exposures in the mixture. In addition, the quantile g-computation approach yields unbiased estimates of overall mixture effects in small sample sizes with acceptable confidence interval (CI) coverage (Keil et al., 2020).

Our sensitivity analysis includes Weighted Quantile Sum (WQS) regression models to assess the effect of the metal mixtures and to identify the driving mixture components, applying the "gwqs" function from the R package "gWQS" (Carrico et al., 2015; Czarnota et al., 2015), with the dataset divided into 40% for training and 60% for validation, and 100 bootstrap samples for parameter estimation.

A threshold of $\boldsymbol{\alpha} = 0.05$ was used to define associations as statistically significant. All statistical analyses and graphics were performed with R version 4.1.2 (R Core Team, 2020).

## 3. Results

Of the total study population, 52.0% were male and 48.0% were female. The child participants had a median (interquartile range - IQR) age of 4.4 (0.2) years and a BMI of 15.9 (1.7) kg/m$^2$. The median total child energy intake was 1547.6 (448.8) kcal/day. Regarding maternal characteristics, they predominately had university education (40.9%) and were of lowest social class (40.1%). The median (IQR) score of rMED and aMED were 8 (4) and 4 (2), respectively (Table 1). The median (IQR) of standardized urinary concentrations of Co, Cu, Zn, Se, Mo, AsB, $\sum$iAs, Pb, and Cd were 0.8 (0.9), 8.2 (10.0), 386.4 (357.7), 23.5 (18.3), 93.7 (83.1), 10.4 (38.6), 1.7 (2.0), 0.3 (0.7) and 0.1 (0.1) μg/L, respectively. Spearman's correlation showed the strongest associations between Se and Zn ($\rho = 0.70$, $p$-value $<0.001$), Cd and Mo ($\rho = 0.55$, $p$-value $<0.001$) and Pb and Cu ($\rho = 0.54$, $p$-value $<0.001$) (Fig. S3). With regard to the consumption of the food groups that make up the rMED and aMED indexes, our population obtained a consumption (g/day) mean (standard deviation - sd) of 71.9 (37.3) for vegetables, 157.4 (112.9) for fruits, 3.5 (4.8) for nuts, 120.6 (41.7) for cereals, 19.1 (10.0) for legumes, 36.9 (16.9) for fish, 537.5 (224.8) for dairy products, 82.2 (27.7) for meat and 8.8 (7.9) for olive oil (Table S3).

In the multiple linear regression analyses an inverse association was identified between Q2 and Q3 MD - aMED adherence and urinary Cu compared to Q1 such as $\beta = -0.42$ (CI 95% $-0.72$; $-0.11$) and $\beta = -0.33$ (CI 95% $-0.63$; $-0.02$), respectively. The inverse association was also maintained for Q4 and Q5 but did not reach statistical significance. For the two MD indexes evaluated, the Q5 MD adherence was increased with urinary AsB compared to Q1 such as $\beta = 0.55$ (CI 95% 0.01; 1.09) for rMED and $\beta = 0.73$ (CI 95% 0.13; 1.33) for aMED (Table 2). The Q4 MD - rMED adherence was also associated with an increased urinary AsB with a $\beta = 0.68$ (CI 95% 0.05; 1.30). The MD components that showed the strongest association in both indexes with the urinary metal concentrations were vegetables, fruits, cereals, legumes, meat/meat products and fish/seafood (Fig. 1, Fig. 2, Table S4, and Table S5).

**Table 1**
Sociodemographic characteristics of the mothers and their children.

| Variables | Overall sample ($n = 713$) |
|---|---|
| **Maternal characteristics** | |
| **Education** | |
| Primary | 132 (18.4)[b] |
| Secondary | 290 (40.7) |
| University | 292 (40.9) |
| **Social class** | |
| I-II (highest) | 176 (24.7) |
| III | 196 (27.5) |
| IV-V (lowest) | 286 (40.1) |
| Missing values | 55 (7.7) |
| **Children characteristics** | |
| **Age (years)** | 4.4 (0.2)[a] |
| **Sex** | |
| Male | 371 (52.0) |
| Female | 342 (48.0) |
| **BMI**[c] | |
| Underweight | 25 (3.5) |
| Normoweight | 555 (77.8) |
| Overweight | 103 (14.5) |
| Obesity | 30 (4.2) |
| **Energy intake (kcals/day)** | 1547.6 (448.8) |
| **rMED score** | 8 (4) |
| **aMED score** | 4 (2) |
| **Urine metals (μg/L)**[d] | |
| Cobalt | 0.8 (0.9) |
| Copper | 8.2 (10.0) |
| Zinc | 386.4 (357.7) |
| Selenium | 23.5 (18.3) |
| Molybdenum | 93.7 (83.1) |
| Lead | 0.3 (0.7) |
| Cadmium | 0.1 (0.1) |
| Arsenobetaine | 10.4 (38.6) |
| $\sum$iAs | 1.7 (2.0) |

[a] Continuous variables = median (IQR).

[b] Categorical variables = $n$ (%); BMI = body mass index; Maternal 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). $\sum$iAs = iAs + MMA, MMA (monomethylarsonic) and iAs (inorganic arsenic).

[c] BMI categories were calculated according to the specific cutoffs proposed by the International Obesity Task Force.

[d] Standarized urine metal concentrations by specific gravity.

Higher intake of vegetables from aMED was associated with increased urinary $\sum$iAs with a $\beta = 0.30$ (CI 95% 0.02; 0.57) (Fig. 2 and Table S5). The rMED and aMED fruit consumption was inversely associated with urinary Se such as $\beta = -0.08$ (CI 95% $-0.16$; $-0.01$) and $\beta = -0.07$ (CI 95% $-0.13$; $-0.01$), respectively. An elevated rMED cereals consumption related to lower urinary Co and Cu such as $\beta = -0.24$ (CI 95% $-0.39$; $-0.09$) and $\beta = -0.29$ (CI 95% $-0.54$; $-0.03$), respectively. The cereals consumption was also associated with an increased urinary Mo as shown in Figs. 1 and 2, Table S4, and Table S5. An increased urinary Co related to legumes consumption such as $\beta = 0.17$ (CI 95% 0.02; 0.32) for rMED and $\beta = 0.14$ (CI 95% 0.01; 0.27) for aMED. However, the rMED legumes consumption related to a decreased urinary Cu as depicted in Fig. 1 and Table S4. Fish/seafood consumption was associated with an increased urinary AsB with a $\beta = 1.06$ (CI 95% 0.59; 1.53) for rMED and $\beta = 0.88$ (CI 95% 0.50; 1.25) for aMED. However, the urinary $\sum$iAs decreased with aMED fish/seafood consumption with a $\beta = -0.32$ (CI 95% $-0{,}60$; $-0.04$) (Fig. 2 and Table S5). Higher urinary AsB also related to rMED dairy products consumption and rMED olive oil. An increased urinary Cd related to olive oil consumption with a $\beta = 0.15$ (CI 95% of 0.02; 0.28) for rMED (Fig. 1 and Table S4). A lower consumption of the meat/meat products component was associated with increased urinary Co with a $\beta = 0.26$ (CI 95% 0.11; 0.40) for rMED, and increased urinary $\sum$iAs with a $\beta = 0.61$ (CI 95% 0.27; 0.94) for rMED and a $\beta = 0.36$ (CI 95% 0.06; 0.64) for aMED (Figs. 1 and 2, Table S4, and Table S5). No clear associations were identified between the MD indexes and urine Zn and Pb concentrations.

In the sensitivity analyses, when we included urinary DMA concentrations to estimate iAs exposure, we observed similar trends for the total adherence to the Mediterranean diet (rMED and aMED indexes) compared to our more conservative approach including only the sum of iAs and DMA as biomarker of iAs exposure (Table S6). When we analyse the components of the MD and the concentrations of iAs exposure including DMA, for rMED the associations that were close to statistical significance (fruits and dairy products) are now statistically significant. For aMED, the association between iAs and vegetable consumption disappears, while the rest of the results are similar to those obtained excluding DMA (Table S7 and Table S8). Regarding the analysis including only the population with low concentrations of AsB, urine concentrations $\leq$ tertil 1 (median = 1.06 μg/L), we observed no association between overall adherence to the MD and iAs exposure evaluated as the sum of iAs, MMA and DMA (Table S9). When performing the component analyses, for rMED we observed a negative association between fish consumption and iAs exposure including iAs, MMA, and DMA. For the aMED, we found a positive association between nuts and iAs exposure. The association between iAs exposure and vegetables consumption disappear in comparison with the analysis without DMA (Table S10 and Table S11). Finally, we calculated spearman correlations coefficients between types of seafood intake and urinary DMA concentrations, and we no observed associations (Fig. S5).

The results from the metal mixture approach quantile g-computation support the findings from the multiple linear regression analyses. The weight of each metal represents its contribution to mixture exposure in the adherence to the MD and its components. Urinary AsB was assigned with the highest positive weight for the total score of the MD adherence indexes (i.e., 0.44 for rMED and 0.35 for aMED). The main negative weights were assigned to urinary Co (i.e., $-0.59$ for rMED and $-0.47$ for aMED) and Cu (i.e., $-0.22$ for rMED and $-0.24$ for aMED). The metal mixture approach was also applied for each component of the MD indexes. For fish, the highest positive weight was assigned to urinary AsB (i.e., 0.38 for rMED and 0.42 for aMED) followed by urinary Cd concentrations (i.e., 0.28 for rMED and 0.21 for aMED). For vegetables,

**Table 2**
Multiple linear regression between adherence to Mediterranean Diet and children's urinary metal concentrations.

| rMED | Q1 | Q2 | | Q3 | | Q4 | | Q5 | |
|---|---|---|---|---|---|---|---|---|---|
| | | β (95% CI)[a] | *p*-value | β (95% CI) | *p*-value | β (95% CI) | *p*-value | β (95% CI) | *p*-value |
| **Co** | Ref. | 0.07 (−0.14; 0.28) | 0.524 | 0.05 (−0.11; 0.20) | 0.545 | −0.04 (−0.24; 0.16) | 0.709 | −0.09 (−0.26; 0.09) | 0.334 |
| **Cu** | Ref. | 0.27 (−0.10; 0.64) | 0.153 | −0.03 (−0.30; 0.24) | 0.827 | −0.20 (−0.55; 0.15) | 0.262 | −0.04 (−0.34; 0.26) | 0.800 |
| **Zn** | Ref. | −0.06 (−0.21; 0.10) | 0.477 | −0.07 (−0.18: 0.04) | 0.236 | −0.08 (−0.23; 0.07) | 0.289 | −0.04 (−0.17; 0.09) | 0.544 |
| **Se** | Ref. | −0.01 (−0.13; 0.10) | 0.794 | 0.01 (−0.07; 0.09) | 0.836 | −0.03 (−0.14; 0.07) | 0.514 | −0.05 (−0.14; 0.04) | 0.241 |
| **Mo** | Ref. | −0.06 (−0.20; 0.09) | 0.450 | −0.02 (−0.13; 0.08) | 0.644 | 0.10 (−0.04; 0.23) | 0.157 | 0.11 (−0.01; 0.22) | 0.074 |
| **Cd** | Ref. | 0.15 (−0.01; 0.31) | 0.068 | −0.02 (−0.14; 0.09) | 0.731 | −0.01 (−0.17; 0.14) | 0.866 | 0.03 (−0.11; 0.16) | 0.706 |
| **Pb** | Ref. | −0.12 (−0.36; 0.11) | 0.310 | −0.04 (−0.21; 0.13) | 0.664 | −0.01 (−0.23; 0.21) | 0.954 | −0.04 (−0.23; 0.15) | 0.694 |
| **AsB** | Ref. | −0.00 (−0.67; 0.67) | 0.994 | 0.18 (−0.30; 0.67) | 0.459 | **0.68 (0.05; 1.30)** | **0.033** | **0.55 (0.01; 1.09)** | **0.047** |
| **∑iAs** | Ref. | 0.16 (−0.33; 0.65) | 0.512 | 0.07 (−0.28; 0.43) | 0.685 | 0.03 (−0.42; 0.49) | 0.888 | −0.03 (−0.43; 0.36) | 0.873 |
| **aMED** | **Q1** | **Q2** | | **Q3** | | **Q4** | | **Q5** | |
| | | **β (95% CI)[b]** | ***p*-value** | **β (95% CI)** | ***p*-value** | **β (95% CI)** | ***p*-value** | **β (95% CI)** | ***p*-value** |
| **Co** | Ref. | −0.06 (−0.24; 0.11) | 0.485 | 0.08 (−0.09; 0.25) | 0.373 | −0.02 (−0.21; 0.16) | 0.826 | −0.07 (−0.27; 0.12) | 0.442 |
| **Cu** | Ref. | **−0.42 (-0.72; -0.11)** | **0.007** | **−0.33 (-0.63; -0.02)** | **0.034** | −0.18 (−0.50; 0.14) | 0.276 | −0.29 (−0.62; 0.05) | 0.092 |
| **Zn** | Ref. | 0.04 (−0.08; 0.17) | 0.506 | −0.10 (−0.23; 0.02) | 0.116 | 0.02 (−0.11; 0.16) | 0.718 | 0.04 (−0.10; 0.18) | 0.596 |
| **Se** | Ref. | 0.00 (−0.09; 0.09) | 0.961 | 0.02 (−0.07; 0.11) | 0.708 | −0.07 (−0.17; 0.03) | 0.146 | −0.06 (−0.16; 0.04) | 0.214 |
| **Mo** | Ref. | 0.06 (−0.06; 0.18) | 0.342 | 0.04 (−0.08; 0.16) | 0.543 | 0.04 (−0.09; 0.16) | 0.566 | 0.08 (−0.05; 0.21) | 0.247 |
| **Cd** | Ref. | 0.01 (−0.12; 0.15) | 0.829 | 0.03 (−0.11; 0.16) | 0.666 | 0.03 (−0.12; 0.17) | 0.711 | 0.07 (−0.08; 0.22) | 0.374 |
| **Pb** | Ref. | 0.03 (−0.17; 0.22) | 0.778 | 0.00 (−0.19; 0.20) | 0.982 | 0.01 (−0.20; 0.22) | 0.925 | 0.06 (−0.15; 0.27) | 0.570 |
| **AsB** | Ref. | 0.32 (−0.24; 0.87) | 0.262 | 0.27 (−0.28; 0.82) | 0.333 | 0.48 (−0.11:1.06) | 0.109 | **0.73 (0.13; 1.33)** | **0.018** |
| **∑iAs** | Ref. | 0.01 (−0.40; 0.41) | 0.972 | 0.01 (−0.39; 0.41) | 0.961 | 0.09 (−0.33; 0.52) | 0.672 | 0.16 (−0.28; 0.60) | 0.487 |

$n = 713$. rMED, relative Mediterranean Diet Score; aMED, alternate Mediterranean Diet Score; ∑iAs = iAs + MMA. Total score for both indexes has been divided into quintiles, where Q1 (reference) and Q5 represent the lowest and highest adherence to MD, respectively.

[a] Based on multiple linear models adjusted for child sex (male or female), child age (years), maternal education (primary, secondary or university), maternal social class (I-II, III or IV-V), sub-cohort (Asturias, Gipuzkoa, Sabadell or Valencia), child body mass index (kg/m$^2$) and urine specific gravity.

[b] The aMED models include the adjusting variable total calorie intake (kcals/day) in addition to the other covariates.

urinary ∑iAs has one of the highest positive weights (i.e., 0.20 for rMED and 0.43 for aMED), while urinary Co has the negative ones (i.e., −0.46 for rMED and −0.57 for aMED). For cereals, urinary Mo had the greatest positive weight (i.e., 0.53 for rMED and 0.18 for aMED). On the contrary, the highest negative weight was assigned to urinary Co (i.e., −0.47 for rMED and −0.25 for aMED) followed by urinary Cu (i.e., −0.28 for rMED and −0.44 for aMED). Further details regarding the metal mixture analysis of each MD component are shown in Figs. 3 and 4.

The findings from the WQS regression sensitivity analysis are in line with the main results (Fig. S4).

Urinary Pb had almost half of the values below the LOD; however, we kept Pb in our main analyses as it is a major contaminant (Delgado et al., 2018; Swaringen et al., 2022). The sensitivity analysis excluding urinary Pb concentrations did not differ from the main findings (Table S12 and Table S13).

## 4. Discussion

This is among the first studies to explore the association between children's MD adherence indexes and exposure to metal mixtures. Our main results suggest that a higher adherence to the MD related to increased AsB exposure and decreased Cu, consistent with a prior US study regarding dietary patterns and erythrocytes metal concentrations in pregnant women (Lin et al., 2021). The metal mixture analysis showed that AsB had the highest positive weight as a major contributor to MD adherence, while Cu and Co had negative weights. The consumption of fish/seafood, meat/meat products, cereals, legumes, fruits, and vegetables were the major MD components related to metals exposure. The median concentrations of Co, Zn and Se observed in this study were similar to those observed in children aged 8–14 years from Mexico (Lewis et al., 2018). The metal concentrations in this study were lower than in a previous study with 5–11-year-old children in Italy, which could be because children in this study were exposed to tobacco smoke in their domestic environment (Protano et al., 2016).

Our child study population had a fish/seafood intake comparable to the average consumption of 40.6 g/day reported for children of 4–9 years by the AECOSAN - *Agencia Española de Consumo, Seguridad Alimentaria y Nutrición* (AECOSAN, 2017). Fish/seafood intake is considered a major source of dietary As, especially organic forms such as the non-toxic AsB that is excreted in the urine unchanged (Kalantzi et al., 2017; Signes-Pastor et al., 2017; Taylor et al., 2017). In this study a higher consumption of fish/seafood in both MD indexes was associated with increased exposure to AsB. Urine concentrations of AsB in this study (median 10.41 μg/L) was 2 times higher than that reported in two studies carried out in Canada and Italy in children (Bocca et al., 2020; Lew et al., 2010). The way the fish is cooked, in this case frying in olive oil, could explain the positive association found between consumption of olive oil and exposure to AsB (Notario-Barandiaran et al., 2020). The fish/seafood component was not associated with iAs exposure, which could be related to the scarce consumption of marine products susceptible to accumulating high iAs such as algae (Murai et al., 2020; Serrano et al., 2016). We did not find any significant association between fish consumption and urinary concentrations of DMA. However, it is important to note that the possibility of urinary DMA being derived from direct exposure or metabolism of complex organosenical compounds cannot be ruled out (Aylward et al., 2014; Hata et al., 2012). In contrast, the study found that higher consumption of certain vegetables, which have been shown to accumulate iAs from water and soil, was associated with increased iAs exposure (Ma et al., 2017; Signes-Pastor et al., 2008). A prior study with pregnant women also reported a positive association between vegetables consumption and increased urinary As (Osorio-Yáñez et al., 2018). However, urinary As speciation was not performed and thus the findings are susceptible to iAs exposure misclassification (Cullen and Reimer, 1989; Osorio-Yáñez et al., 2018). In this study, we used the sum of urinary iAs and MMA as biomarker of iAs exposure. The sum of urinary iAs and MMA is considered the most adequate approach, especially among populations that consume marine products (Aylward et al., 2014; Hata et al., 2012).

Our population had a 28% lower meat consumption compared to that described by the AECOSAN study in children aged 4–9 years (AECOSAN, 2017). Higher meat/meat products consumption related to reduced exposure to Co and iAs in accordance with a recent study with children aged 3–5 years living in the US (Jain, 2021). In a study carried out with pregnant women in Spain they also observed an inverse association between meat consumption and MMA urine exposure

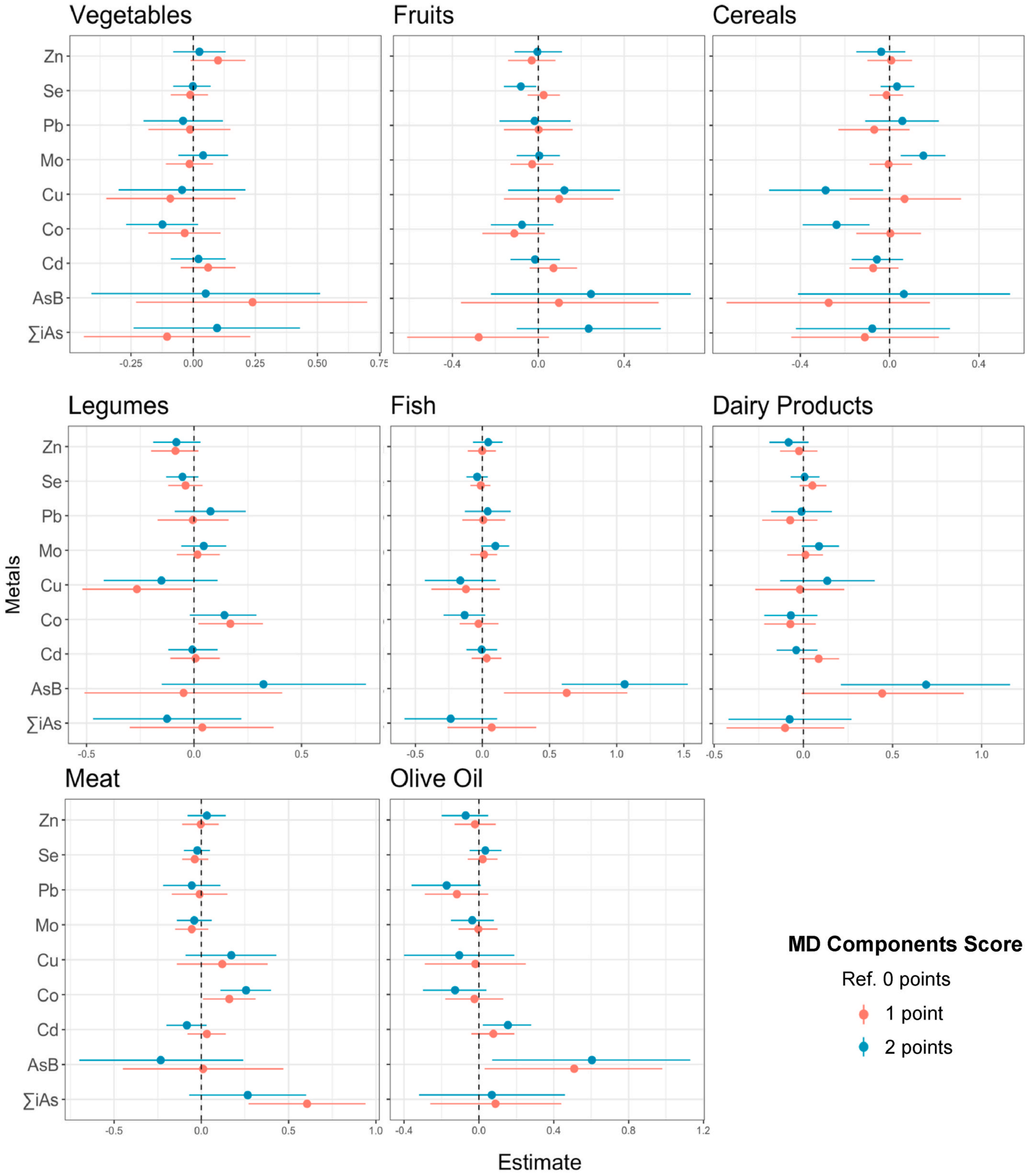

**Fig. 1.** Multiple linear regression estimates (CI) between the rMED index components and urine metals concentrations in children of 4–5 years of age. Models are adjusted for child sex (male or female), child age (years), maternal education (primary, secondary or university), maternal social class (I-II, III or IV-V), sub-cohort (Asturias, Gipuzkoa, Sabadell or Valencia), child body mass index (kg/m$^2$) and urine specific gravity. In rMED index a score of 0, 1, and 2 was assigned to the first, second, and third tertiles of intake, respectively; higher intakes scored positively. Bear in mind that the scoring of the meat and dairy products components was reverted. Notice that the scale of the y-axis varies to facilitate the visualisation of the estimates in each plot.

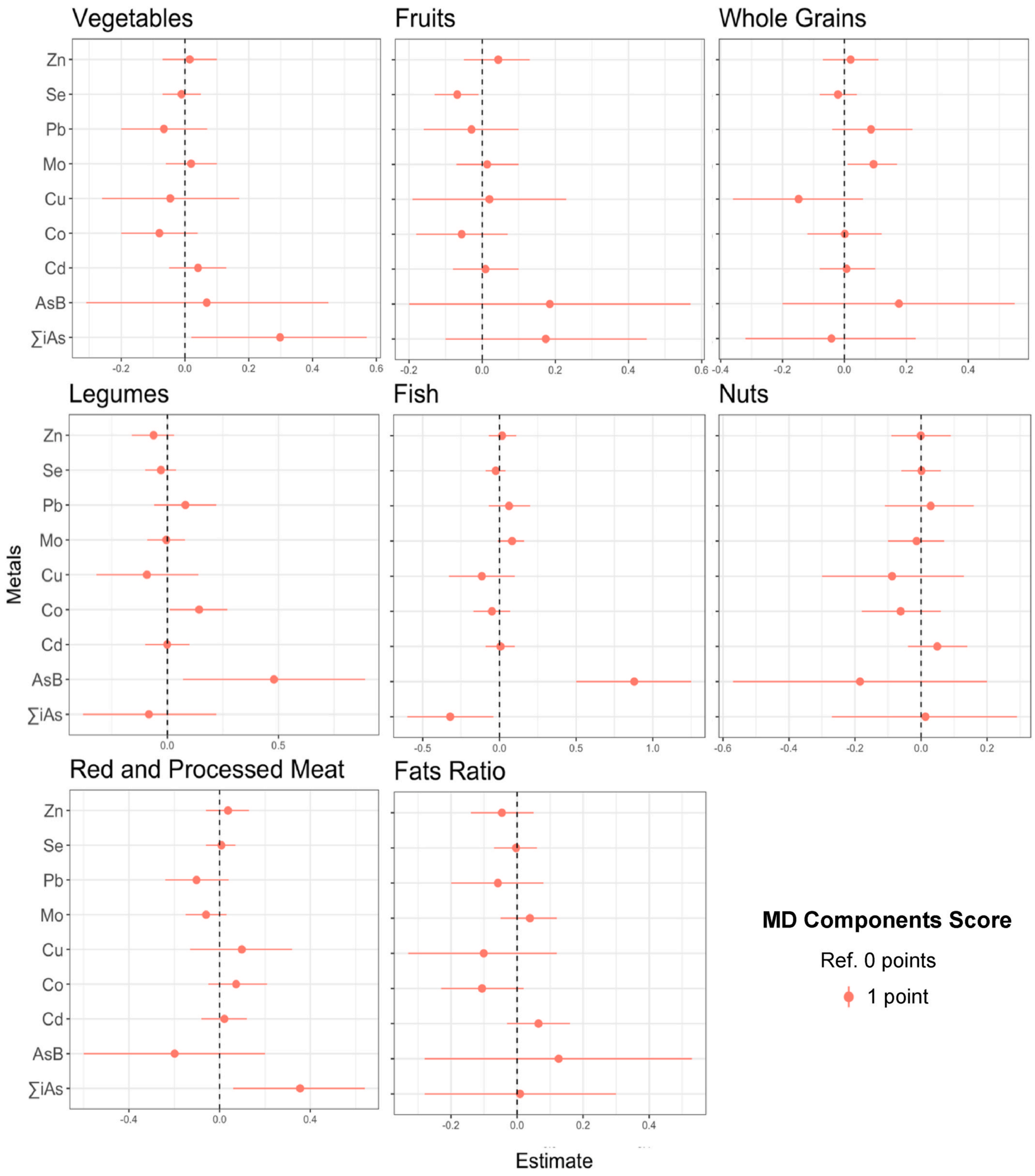

**Fig. 2.** Multiple linear regression estimates (CI) between the aMED index components and urine metals concentrations in children of 4–5 years of age. Models are adjusted for child sex (male or female), child age (years), maternal education (primary, secondary or university), maternal social class (I-II, III or IV-V), sub-cohort (Asturias, Gipuzkoa, Sabadell or Valencia), child body mass index (kg/m$^2$), total calorie intake (kcals/day) and urine specific gravity. In aMED index a score of 1 point was assigned to intakes above the median, intakes below the median were scored with 0 points. Bear in mind that the scoring of the red/processed meat component was reverted. Notice that the scale of the y-axis varies to facilitate the visualisation of the estimates in each plot.

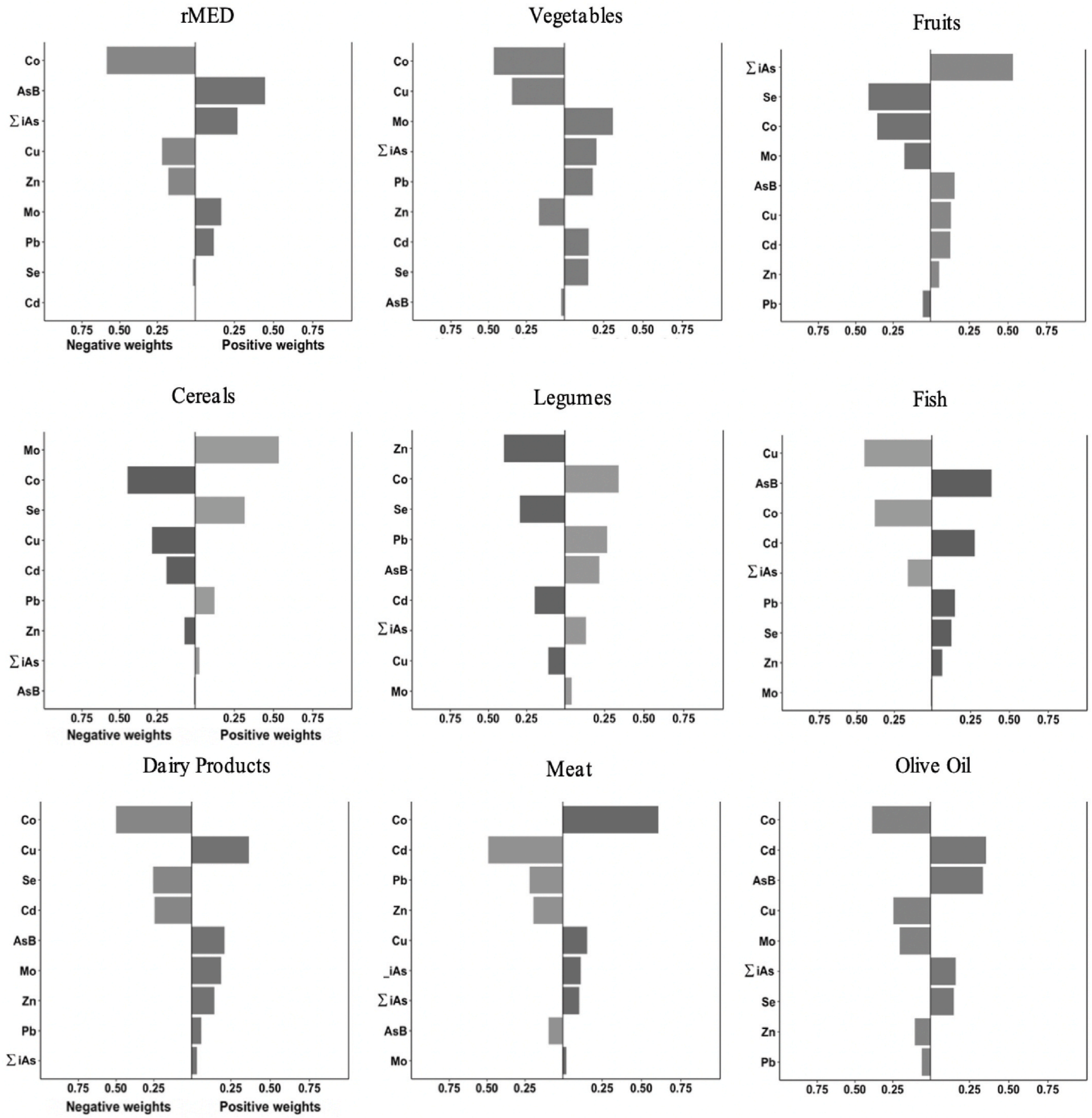

**Fig. 3.** Quantile g-computation between metal concentrations and rMED index components in children of 4–5 years of age. Models are adjusted for child sex (male or female), child age (years), maternal education (primary, secondary or university), maternal social class (I-II, III or IV-V), sub-cohort (Asturias, Gipuzkoa, Sabadell or Valencia), child body mass index (kg/m$^2$) and urine specific gravity.

(Soler-Blasco et al., 2021). Meat is an important source of vitamin B12, which is involved in iAs metabolism being an important cofactor in the synthesis of the methyl donor S-adenosylmethionine (SAM) in combination with folate in form of 5-methyltetrahydrofolate. A previous study carried out with adult population in Bangladesh showed a positive correlation between vitamin B12 and SAM concentrations (Howe et al., 2014). When SAM levels are deficient, the body's ability to methylate iAs into MMA and DMA before excretion in the urine is reduced, which weakens the iAs detoxification process (Abuawad et al., 2021; Bottiglieri, 2013; Lin et al., 2019). Cobalt is one of the main components of the vitamin B12, and thus meat consumption relates to exposure to Co (Leyssens et al., 2017; Osman et al., 2021).

The concentrations of Mo in cereals are generally higher compared to other food groups (Hattori et al., 2004; Noël et al., 2012), thus the consumption of cereals and whole grains in our child population related to high levels of Mo exposure. Previous studies showed that grain products are the primary source of dietary molybdenum. In a study carried out in US, cereals grains were the secondary Mo source for toddlers and adolescents (Hunt and Meacham, 2001) after dairy products. In this study, we did not observe an association between dairy

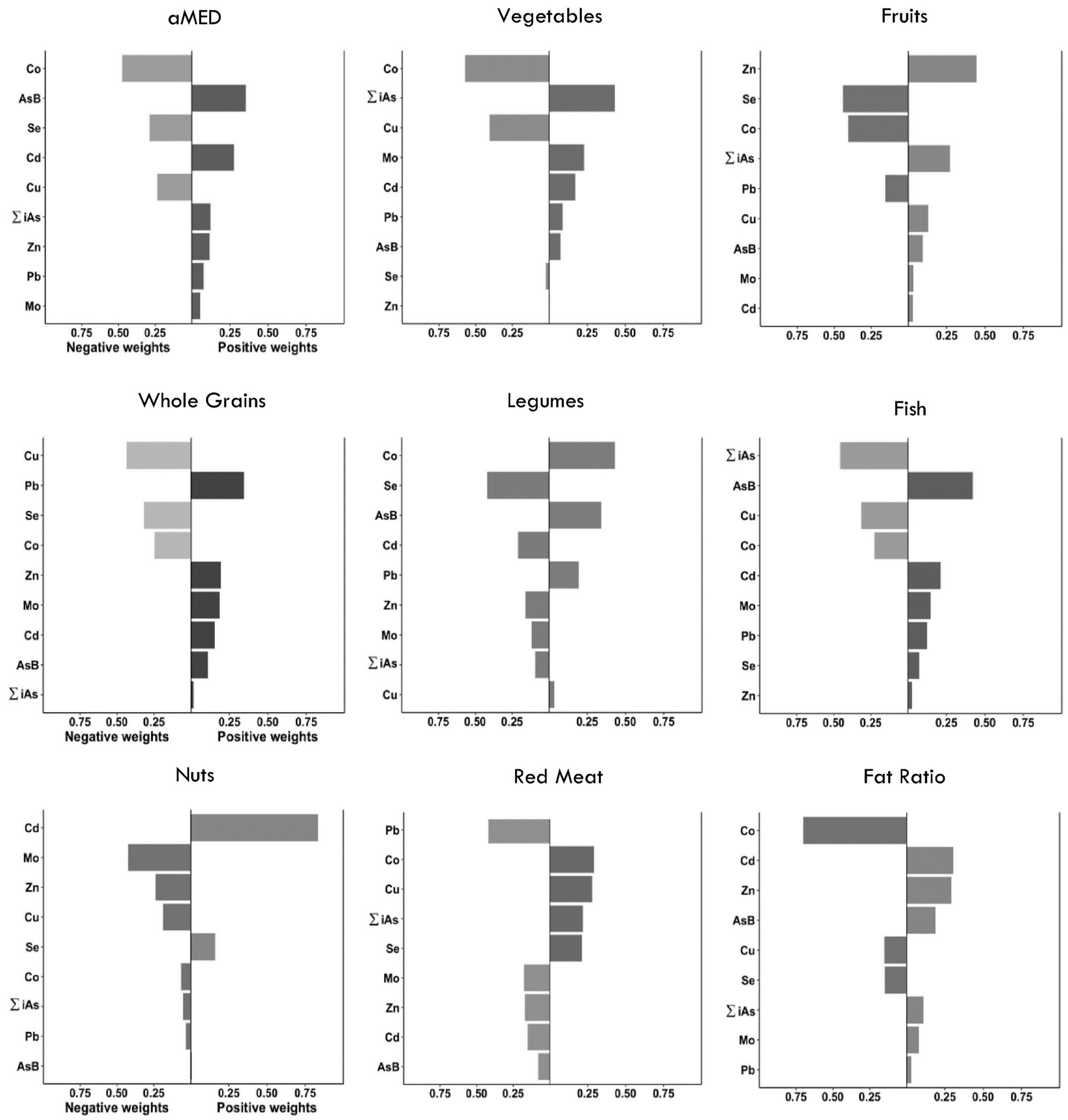

**Fig. 4.** Quantile g-computation between metal concentrations and aMED index components in children of 4–5 years of age. Models are adjusted for child sex (male or female), child age (years), maternal education (primary, secondary or university), maternal social class (I-II, III or IV-V), sub-cohort (Asturias, Gipuzkoa, Sabadell or Valencia), child body mass index (kg/m$^2$), total calorie intake (kcals/day) and urine specific gravity.

product consumption and exposure to Mo. This lack of association could potentially be attributed to the lower intake of dairy products in the studied population when compared to the general population in the US (Emond et al., 2018). In another study conducted in France where 116 typical foods of the diet of children and adults were analysed, it was observed that cereals and cereals products were one of the food groups with the highest Mo exposure (Noël et al., 2012). Rice and rice products may contain higher concentrations of iAs compared to other cereals (Williams et al., 2007); however, our children's rice consumption was not associated with iAs exposure. The rice consumption only referred to 13.5% of the cereals and whole grains component and was relatively low with an average daily intake of 16.3 g compared with Spanish children of the same age (AECOSAN, 2017). A reduced Co and Cu exposure was observed with the overall cereals component but not with whole grains. Food processing such as polishing reduces the cereals metals content (Wapnir, 1998). The association between olive oil consumption and increased Cd exposure could be explained by the processing of olives to produce olive oil. During the olive processing, the levels of metals may increase as a result of equipment corrosion, higher temperatures in metal containers, and the oil extraction process. Furthermore, the materials used for packaging and storage can also influence metal exposure (Pera et al., 2022). However, further studies are needed to gain a comprehensive understanding of these factors.

The consumption of legumes in our study population was a 26% higher compared to data reported by AECOSAN for children aged 3–9 years with a mean consumption of 19.9 g/day (AECOSAN, 2017). Co plays an important role in nitrogen fixation, and thus the concentrations of Co in legumes are relatively high (Gad, 2012; Hu et al., 2021). In our child population, an increased legumes consumption was associated with higher Co and lower Cu exposure in line with a prior study also carried out in Spain (Junqué et al., 2022). Fruits are not an important source of Se compared to meat, cereals, or dairy products (Kieliszek, 2019), and thus we observed that an increased consumption of fruits related to reduced exposure to Se. The fruits consumption level in our study population was similar to the mean consumption of 145.1 g/day reported for children aged 3–9 years in Spain (AECOSAN, 2017).

Numerous studies have demonstrated the multiple health benefits of the MD due to its nutrient composition, which includes antioxidants and anti-inflammatory properties. In this study, we observed associations between certain components of the MD and higher concentrations of toxic metals. However, when considering the diet as a whole, we found no association with these metals. Therefore, the MD as a dietary pattern could provide an adequate balance in metal exposure.

Our study has a cross-sectional design limiting the inference on cause-effect, and the sample size is modest, which may limit the statistical power of the analyses. We adjusted for a wide range of potential confounding factors, yet the effects of residual confounding factors remain a possibility. The MD indexes were calculated based on data gathered with a previously validated FFQ. This FFQ was validated with 24 h dietary recalls and biochemical samples displaying acceptable reproducibility and validity for assessing dietary intake among children of the same age (Vioque et al., 2016). The FFQ is also considered a reliable method to assess diet over a long period of time (Willett, 2013). Although urinary metal concentrations are considered an adequate biomarker of exposure and widely used in epidemiological studies, it is important to bear in mind that the rate of excretion may vary across metals (Fort et al., 2014). For Co, Mo, As and Cd there is evidence that urine as matrix is acceptable to assess exposure. As, Mo and Co in urine are considered biomarkers of short-term exposure, while Cd is a biomarker of long-term exposure (Faroon and Keith, 2004; Todd et al., 2020; Chou and Harper, 2007; Faroon et al., 2012). However, for Cu, Pb and Zn, urine might not the ideal matrix to evaluate their exposure, so conclusions must be drawn with caution. For this analysis we only used one-time spot urine sample to assess metal concentrations that may lead to an increased risk of exposure misclassification. The associations obtained with Pb and Se may be underestimated due to the relatively low recovery of these metals. On the other hand, the quantile g-computation is a novel multi-pollutant method that was applied in our study to estimate the main contributors of the metal mixtures on the MD.

## 5. Conclusion

Our study on Spanish children aged 4–5 suggests that MD adherence decreases exposure to certain metals but increases exposure to others. The non-toxic AsB exposure highlights the significant impact of fish/seafood on MD adherence. However, it is important to emphasize the importance of choosing healthy options with low toxic concentrations of metals within the typical foods of the MD to avoid metal exposure. Additional longitudinal studies are needed to confirm our findings on the association between MD adherence and metal mixture exposure and to explore the long-term health effects of early-life MD adherence.

## Author contribution statement

LN-B contributed to methodology, formal statistical analysis and writing; AJS-P contributed to conceptualisation, methodology, visualisation, reviewing of manuscript and obtaining funding; AM, MC, CM, KR, McC and GJO contributed performed urinary metals concentrations analysis and reviewing of the manuscript; JV contributed to methodology and reviewing of the manuscript; AI, MB-Z, RS-B, GR-M, AF-S, AT, MC, MV and GJO were responsible for the acquisition of data and made a critical revision of the manuscript for intellectual content and approved the final manuscript.

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## 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.

## Data availability

Data will be made available on request.

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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.2023.116508.

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