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# Maternal diet quality during pregnancy and biomarkers of potentially toxic trace element exposure: Data from the ELFE cohort

Courtney Dow [a,*], Manik Kadawathagedara [a], Manel Ghozal [a], Marie-Aline Charles [a], Karine Adel-Patient [b], Clémentine Dereumeaux [c], Blandine de Lauzon-Guillain [a]

[a] *Université Paris Cité and Université Sorbonne Paris Nord, Inserm, INRAE, CRESS, Paris, France*
[b] *Universié Paris Saclay, CEA, INRAE, MTS/Laboratoire d'Immuno-Allergie Alimentaire, Gif-sur-Yvette, France*
[c] *Santé Publique France, Direction Santé Environnement Travail, Saint-Maurice, France*

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ABSTRACT

The contribution of the diet to potentially toxic trace element exposure in pregnancy has been rarely addressed. The objective of the present study was to determine the association between the maternal diet during pregnancy and biomarkers of exposure for arsenic (As), mercury (Hg) and lead (Pb) at delivery. As was assessed in maternal urine, Hg in maternal hair, and Pb in cord blood, as a proxy for *in utero* exposure. Based on 2995 women from the ELFE nationwide birth cohort, higher scores for dietary patterns considered healthy were associated with higher concentrations of As and Hg in maternal matrices. Levels of cord blood Pb were inconsistently associated with dietary patterns considered healthy, and lower with a dietary pattern driven by milk and breakfast cereals. Lower levels of Hg were associated with higher Western dietary pattern scores. In conclusion, higher levels of maternal urinary As and hair Hg are associated with diets considered as "Healthy", while cord blood Pb was not strongly correlated with dietary exposure.

## 1. Introduction

Both the World Health Organization (WHO) and the Agency for Toxic Substances and Disease Registry (ASTDR) recognize arsenic (As), lead (Pb) and mercury (Hg) as the "most toxic elements or substances of concern for threats posed to human health" (World Health Organization, 2010; Registry A for TS and D). Besides direct, multi-organ effects, these elements also alter genetic and epigenetic programming (Balali-Mood et al., 2021). All three elements readily cross the placenta, (Punshon et al., 2015; Chen et al., 2014) and can bioaccumulate in fetal tissues (Balali-Mood et al., 2021) with half-lives from 3 to 4 days (inorganic As [iAs]) up to an estimated 20 years (Hg), (Park and Zheng, 2012; Hughes, 2006) and thus can affect both maternal and offspring health.

In fact, arsenic and arsenic compounds are classified as Group 1 carcinogens, as sufficient evidence supports their role in the development of several types of cancers (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012). At exposure levels observed in the general population, maternal As exposure has also been associated with adverse pregnancy and birth-related outcomes such as spontaneous abortion, stillbirth, preterm birth, and low birth weight (Rahaman et al., 2021). Additionally, studies have found long-term effects on the offspring after prenatal exposure, such as the development of cancers, increased risk of both infectious and noncommunicable diseases, and impaired neurodevelopment (Rahaman et al., 2021; Farzan et al., 2016; Tsuji et al., 2015). Meanwhile, the toxic effects of Pb have been recognized since ancient times in Rome and Greece (Waldron, 1973). Lead's poisonous effects target almost every organ in the body, with the nervous system taking the greatest hit (Wani et al., 2015). There is no safe level of Pb exposure (Vorvolakos et al., 2016). In the general population, fetal Pb exposure has detrimental effects on offspring neurodevelopment (Hu et al., 2006; Thomason et al., 2019) and both children and adults have shown various consequences after Pb exposure, most notably, decreased cognitive functioning, kidney damage, and behavioural disorders (Olufemi et al., 2022). Similarly, high levels of Hg have destructive effects on the whole body, including, but not limited to the nervous, digestive, renal, immune, and cardiovascular systems (Rice et al., 2014). Maternal Hg exposure in the general population has been associated with adverse birth outcomes such as stillbirth, spontaneous abortion, and congenital malformations, (Rice et al., 2014) as well as negative effects on offspring neurodevelopment (Kim et al., 2020; Saavedra et al., 2022).

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* Corresponding author. 16 Avenue Paul Vaillant-Couturier, Bâtiment Leriche, 94807, Villejuif, France.
*E-mail address:* courtney.dow@inserm.fr (C. Dow).

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**Abbreviations**

| | |
|---|---|
| ATSDR | Agency for Toxic Substances and Disease Registry |
| ANSES | French Agency for Food, Environmental and Occupational Health and Safety |
| As | arsenic |
| BMI | body mass index |
| CI | confidence interval |
| DAG | directed acyclic graph |
| EFSA | European Food Safety Authority |
| FFQ | food frequency questionnaire |
| TDS | French total diet study |
| Hg | mercury |
| iAs | inorganic arsenic |
| LOD | limit of detection |
| LOQ | limit of quantification |
| OR | odds ratio |
| PCA | principal component analysis |
| PANDiet Score | Probability of Adequate Nutrient intake Diet quality index |
| Pb | lead |
| INCA 2 | Second French National Food Consumption Survey |
| WHO | World Health Organization |

Due to their non-biodegradable nature, these trace elements will accumulate in the environment and are thus ubiquitous in nature. Exposure will then occur via both natural (geothermal activity, coal, volcanic activity) and anthropogenic sources (industrial activity, mining, insecticides, herbicides, burning fossil fuels, paint, gasoline, dental amalgams), however, for those not exposed occupationally or as smokers, the major source of exposure is through the diet (Olufemi et al., 2022; Rice et al., 2014).

Not only is the diet the major source of exposure to these potentially toxic trace elements, but evidence suggests that the diet and nutrition can modify the toxic effects on birth outcomes (Hennig et al., 2012; Okubo and Nakayama, 2023). Yet, very few studies address how the diet contributes to exposure in pregnant populations, (Golding et al., 2013; Lozano et al., 2022; Ashrap et al., 2020; Gustin et al., 2020) though pregnancy represents a physiologically unique situation where the influence of the diet may be distinct. In addition, studies often focus on a single nutrient or food group (Golding et al., 2013; Lozano et al., 2022; Ashrap et al., 2020; Gustin et al., 2020; Saoudi et al., 2018). However, actual dietary patterns reflecting the complex interplay of foods and nutrients on biomarkers of trace elements would provide a more complete understanding of the relationship. Among the few studies that have attempted to characterize the relationship between maternal diet quality and biomarkers of potentially toxic trace element exposure, (Okubo and Nakayama, 2023; Lin et al., 2021; Taylor et al., 2019) one is based on a single *a priori* defined healthy diet score (Okubo and Nakayama, 2023) and another on dietary patterns and food groups (Taylor et al., 2019). Only one study used a diet wide approach and analyzed both *a priori* defined scores and dietary patterns, (Lin et al., 2021) but this study was carried out in the US, where food habits and dietary sources of potentially toxic trace element exposure likely differ greatly from those in Europe (EFSA, 2009; EFSA. and Scientific Opinion on Lead in Food, 2010; EFSA, 2012; Powell et al., 2010; Schmidhuber and Traill, 2006).

Given the paucity of the literature, fetotoxic and long-term adverse effects on both maternal and offspring health, combined with the widespread exposure through the diet, our objective was to determine the association between the maternal diet during pregnancy, characterized using both *a priori* defined dietary scores and *a posteriori* dietary patterns, and the detection of As and Hg in maternal matrices at delivery, and Pb in cord blood, thus reflecting the *in utero* exposure of the offspring.

## 2. Methods

### 2.1. Study population

The ELFE cohort was initiated in 2011 to study the determinants of child health, development, and socialization (Charles et al., 2021). Mother-infant pairs were recruited over a 25-day period spread throughout the year from 349 randomly selected maternities in metropolitan France. Participants were approached after delivery and were considered eligible if: births ≥33 weeks of gestation, mothers were ≥18 years old and had no plan to leave metropolitan France in the following 3 years. Participating mothers had to provide written consent for their own and their child's participation. Fathers signed the consent form for the child's participation when present at inclusion or were informed about their rights to oppose it. A total of 18,040 mothers agreed to participate in the ELFE study, giving rise to 18,329 infants.

The ELFE study received approval from the Advisory Committee for the Processing of Information for Health Research (Comité Consultatif sur le Traitement des Informations pour la Recherche en Santé: CCTIRS; authorization 10.623), the committee for protection of persons engaged in research (CPP: Comité de Protection des Personnes; authorization CPP-IDF IX-11-024), the National Data Protection Authority (Commission National Informatique et Libertés: CNIL, authorization 910504) and the National Council for Statistical Information (CNIS).

### 2.2. Dietary assessment

#### 2.2.1. Dietary data

Dietary information was collected through a validated, self-administered food frequency questionnaire (FFQ) during the mother's stay at the maternity, as previously described (Kadawathagedara et al., 2021). Briefly, the FFQ estimated the consumption of 125 foods and beverages over the last 3 months of pregnancy. Frequency was assessed using a 7-item scale ranging from "never" to "more than once a day". Usual portion sizes were indicated with the aid of photographs picturing five possible sizes or the mid-portion was automatically assigned (Hercberg et al., 2002). Daily intake was then estimated by combining the consumption frequency with the portion size. This allowed food items to be categorized into 48 food groups and energy intake to be estimated. Nutrient intakes were calculated by multiplying each woman's daily intake of each food item by nutritional values from a French nutrient composition database (Hercberg, 2006). Women having more than 10 missing answers to the FFQ were excluded, otherwise, missing values were imputed with the sample median. Women who were likely misreporting food intake (<3rd or >97th percentile of estimated total energy intake, corresponding to <933 kcal/day >5072 kcal/day) were also excluded.

Both *a priori* and *a posteriori* approaches have benefits and drawbacks that may complement each other. The *a priori* approach estimates a dietary score based on previous knowledge between food and disease relationships. The *a posteriori* method uses data-reduction applications such as principal component analysis to derive patterns based on the dietary intake of the study population. The *a priori* approach is restricted by current knowledge of the diet-disease relationship, but the *a posteriori* approach is based on the collected data without a dietary hypothesis and may not be a valid representation of true dietary patterns. Thus, using both approaches can be complementary and provide different information.

#### 2.2.2. Dietary patterns

Exploratory dietary patterns were derived using principal component analyses (PCA) of the 46 food groups consumed by the majority of the sample. The dietary patterns have been detailed previously (Kadawathagedara et al., 2021). The number of factors to retain was determined using the diagram of eigenvalues and the interpretability of the factors. Five dietary patterns were identified, together explaining 28% of the total variance: “Western” (7.9%), “Balanced” (6.8%), “Bread and Toppings” (4.7%), “Processed Products” (3.7%) and “Milk and Breakfast Cereals” (3.5%). Therefore, for each participant, a score was determined for each dietary pattern. The “Balanced” dietary pattern was characterized by high intakes of vegetables, fruit, fish, whole-grain bread, legumes, yogurt and cottage cheese, but low intakes of sugar-sweetened beverages, while the “Western” dietary pattern was characterized by high intakes of fast food, potatoes, cakes/pastries, red and processed meat. The “Bread and Toppings” pattern was characterized by high intakes of honey/jam, chocolate, butter, and to a lesser extent, bread and cheese; the “Processed Products” pattern by high intakes of prepackaged foods, ready-prepared dishes, canned foods and diet foods; and finally, the “Milk and Breakfast Cereals” pattern was characterized by high intakes of milk, cocoa powder, breakfast cereals and low intakes of coffee.

#### 2.2.3. *Dietary scores*

Two *a priori* defined dietary scores were computed previously (Kadawathagedara et al., 2021). Briefly, the Probability of Adequate Nutrient intake Diet quality index (PANDiet Score) measures the overall diet quality based on nutrient intake. For each nutrient, the probability of adequate intake (ie. intake sufficient to satisfy the requirement, but not excessive – based off nutrient reference values for the third trimester of pregnancy) was calculated. Then, all probabilities were summed to produce the PANDiet score. This dietary score has been previously validated among pregnant French women and ranges from 0 to 100 (Bianchi et al., 2016). The Diet Quality score is a score of compliance to dietary guidelines based on recommendations for French adults and pregnant women (Kadawathagedara et al., 2021). The percentage of each guideline followed by women were summed for each of 17 quantitative benchmarks to produce a score ranging from 0 to 17. For both dietary scores, a higher score indicates better compliance to dietary guidelines or nutrient reference values.

#### 2.2.4. *Food groups*

Finally, 16 food groups were included in this study. Depending on the food group, they were characterized either in terms of frequency or quantity, as the French dietary guidelines are expressed. Nine food groups were characterized by daily frequencies (fruit and vegetables, legumes, grains/cereals and legumes, whole grains (as a percentage), dairy products, animal products, fish and seafood, soy products, and coffee) while seven were characterized by daily quantities consumed (red meat, processed meat, nuts and seeds, added fats, water (all sources), sugar-sweetened beverages, and tea).

#### 2.2.5. *Estimates of dietary exposure to trace elements*

Food intake data obtained from the FFQ was combined with contamination data from the second French total diet study (TDS2), which provided concentration levels of contaminants in 212 core foods among 38 food groups (Sirot et al., 2009; ANSES French Agency for Food E and OH and S, 2011).

Following guidelines from the GEMS/Food-EURO (2013), values below the limit of detection (LOD) were replaced with 0 and values below the limit of quantification (LOQ) were replaced with the value of the LOD (GEMS/Food-EURO, 2013). This corresponds to the “lower bound” scenario.

### 2.3. *Biomarker assessment*

#### 2.3.1. *Biological sample collection*

Biological samples were collected from a subsample of participants who agreed to participate in the biological component of the study. A total of 4145 women had at least one biomarker measured. Samples were obtained from participating mothers just after admission to the maternity (urine: As), in the delivery room (cord blood: Pb), or within the first few days after birth (hair: Hg) (Dereumeaux et al., 2016).

Spot urine samples were collected in 150 mL polypropylene containers before the use of any medical devices to avoid external contamination. Cord blood was collected using venous catheters and stored in 6 mL EDTA tubes. All samples were maintained at a temperature of +4 °C in the hospital until transfer to biobanks via refrigerated trucks. After aliquotation into polypropylene cryotubes at the biobanks, urine samples were stored at −80 °C, while cord blood was stored at −196 °C. Selected samples were sent to laboratories for biomarker determination.

Hair samples were collected from the occipital area of the mother’s head. Each sample was stapled to a paper card and deposited into an envelope. Samples selected for biomarker determination were sent by air post to the laboratory for analysis.

#### 2.3.2. *Trace element concentration determination*

Determination of As and Pb were performed by Chemtox, Illkirch, France and quantified by inductively coupled plasma mass spectrometry. This method has been detailed previously (Dereumeaux et al., 2016). Hg was determined by the Toxicology Center of the National Institute of Public Health of Québec, Canada, using atomic absorption spectroscopy coupled with cold vapor generation, after an acid digestion. The methods of trace element determination have been previously validated (Esteban et al., 2015; Goullé et al., 2003).

Biomarker estimates were available for 1669 (Pb), 1941 (Hg) and 868 (As) participants. Like the dietary contamination estimates, the lower bound scenario was employed according to the GEMS/Food-EURO recommendations (GEMS/Food-EURO, 2013). LODs and LOQs for the trace elements of interest have been previously reported (Dereumeaux et al., 2016). Samples for which there was a manipulation problem or analytic interference were coded as missing (Supplementary Table 1).

### 2.4. *Other variables*

Data on covariates were collected via questionnaires during the mother’s stay at the maternity or in the follow-up telephone interview 2 months after birth. Demographic and socioeconomic covariates included in this study were maternal: age at delivery (years), migration history (migrant/descendent of migrant; rest of the population), education (lower to upper secondary; intermediate; ≥5y university degree), and employment status (employed; unemployed; out of the labour force). Household characteristics included the household income (€/Month/Unit Consumption quartiles), region (Paris; North; East; Eastern Paris Basin; Western Paris Basin; West; South-West; South-East; Mediterranean), and city size (rural; urban). Maternal characteristics were body mass index (BMI) before pregnancy (underweight/normal [$<25$ kg/m$^2$]; overweight [25.0–30.0 kg/m$^2$]; obese [$\geq 30.0$ kg/m$^2$]), parity (first child; one other child; ≥2 children), gestational weight gain (kg), gestational diabetes (yes; no), smoking during pregnancy (never smoker; smoker before pregnancy; smoking during pregnancy), and post-partum depression score (Edinburgh Postnatal Depression Score (EPDS)) (Guédeney and Jeammet, 2001; Cox et al., 1987). Variables related to the child or birth were: sex (male; female), cesarean birth (yes; no), gestational age (weeks), birth weight (kg), and any breastfeeding duration (months).

### 2.5. *Sample selection*

From the 18,329 participants in this study, women were excluded if they had no dietary information available ($n = 2250$) or no biomarker samples for any of the three potentially toxic trace elements of interest ($n = 13{,}084$) (Supplementary Fig. 1). This resulted in a study population of 2995 participants with at least one measure available for any trace element ($n = 1633$ for Hg; $n = 1530$ for Pb; $n = 798$ for As). Only 106 participants had measures available for all three trace elements.

### 2.6. Statistical analyses

#### 2.6.1. Main analyses

A detailed statistical procedure on the descriptive analyses can be found in **Annex 1a**. Multiple imputation with chained equations were used to impute missing data for covariates (Sterne et al., 2009). Further details on the procedure are presented in **Annex 1b**.

Trace element concentrations were classified into tertile groups for multinomial logistic regression, as the distribution of Hg was still skewed after log2-transformation. Four primary models were constructed with different exposures of interest: i) 5 dietary patterns considered simultaneously; ii) PANDiet score; iii) Dietary Quality score; iv) food groups (fruit and vegetables, legumes, whole wheat bread, nuts and seeds, fish, dairy, red meat, processed meat, soy products, added fats, water, coffee, tea, and sugar-sweetened, beverages considered simultaneously).

The categorization of food groups is detailed in **Annex 1c**.

A directed acyclic graph (DAG) was used to determine the necessary covariates to include in the models (Shrier and Platt, 2008). Finally, models were adjusted for the following: maternal age, education, employment status, household income, immigration history, city size, pre-pregnancy BMI, smoking during pregnancy and parity (Supplementary Fig. 2). All models were also adjusted for the maternity ward size and recruitment wave to account for the sampling design. We tested for an interaction with smoking during pregnancy, as the dietary sources of trace elements may contribute less to exposure in smokers than in non-smokers. The interaction was not significant ($p > 0.10$).

All statistical analyses were performed on SAS Version 9.4 [SAS Institute, Cary, NC, USA].

#### 2.6.2. Sensitivity analyses

First, linear regression was conducted for each of the models with dietary patterns/scores and biomarkers for As and Pb. As the distribution of Hg was highly skewed, we did not perform linear regression in this case. Second, complete case analyses were performed on the population without missing data for covariates: Hg ($n = 1270$), Pb ($n = 1165$) and As ($n = 615$).

## 3. Results

### 3.1. Population description

Descriptive characteristics of the study population are presented in Table 1. Women in the study population were an average of 30.4 years old, with 16.5% having spent ≥5 years in university. The majority of women were employed (71.8%) during pregnancy and were mainly not migrants or descendants of migrants (84.7%). More than half of the women had a pre-pregnancy BMI <25 kg/m$^2$ (69.3%) and 22.7% smoked during pregnancy. Almost half of the women (45.4%), were primiparous.

Excluded women were slightly older, with higher education and household income, more likely a migrant or descendent of a migrant, more likely living in an urban area, had a lower pre-pregnancy BMI and were less likely to smoke during pregnancy than included women (Supplementary Table 2).

### 3.2. Trace element description

Sample summary statistics for trace element concentrations and dietary estimates of contaminant exposure can be found in Table 2. The geometric means for each trace element concentration according to tertiles of dietary score/pattern are displayed in Supplementary Table 3. Exposure to As and Hg appear higher in tertile 3 compared to tertile 1 of the Diet Quality Score and lower for the “Western” dietary pattern. Exposure to As, Hg and Pb all seem to be higher in tertile 3 compared to tertile 1 of the “Balanced” dietary pattern.

**Table 1**
Descriptive characteristics of the study population ($n = 2995$).

| Variable | | N (%) or mean ± [SD] | Range |
|---|---|---|---|
| *Sociodemographic Factors* | | | |
| Maternal Age (Y) | | 30.4 [4.9] | 18.0; 48.0 |
| Maternal Education | Lower to upper secondary | 1076 (40.3) | |
| | Intermediate | 1153 (43.2) | |
| | ≥5Y university degree | 440 (16.5) | |
| Household Income (€/Month/Unit Consumption) | ≤1111 | 641 (23.9) | |
| | 1112–1500 | 802 (30.0) | |
| | 1501–1944 | 659 (24.6) | |
| | >1945 | 575 (21.5) | |
| Maternal Employment Status | Employed | 1997 (71.8) | |
| | Unemployed | 356 (12.8) | |
| | Out of the labour force | 428 (15.4) | |
| Migration History (Maternal) | Immigrant/ Descendent of Migrant | 426 (15.3) | |
| | Rest of population | 2362 (84.7) | |
| Number of Habitants in the Urban Unit | Rural (<2000 inhabitants) | 830 (27.7) | |
| | Urban | 2163 (72.3) | |
| Maternal Characteristics | | | |
| Parity | First child | 1305 (45.4) | |
| | One other child | 1026 (35.7) | |
| | Two or more children | 541 (18.8) | |
| BMI (kg/m$^2$)[a] | | 23.9 [5.1] | 13.6; 52.5 |
| Gestational Weight Gain (kg) | | 13.0 [5.6] | −22.0; 42.0 |
| Gestational Diabetes | No | 2660 (92.7) | |
| | Yes | 208 (7.3) | |
| Maternal Smoking during Pregnancy | Never smoker | 1579 (53.0) | |
| | Smoker only before pregnancy | 725 (24.4) | |
| | Smoker in pregnancy | 673 (22.6) | |
| *Birth/Child Characteristics* | | | |
| Cesarean Birth | No | 2590 (86.9) | |
| | Yes | 392 (13.1) | |
| Sex of Child | Male | 1574 (52.6) | |
| | Female | 1421 (47.4) | |
| Gestational Age (weeks) | | 39.3 [1.3] | 33.0; 42.0 |
| Birth Weight (kg) | | 3.4 [0.5] | 1.34; 5.1 |

[a] BMI: body mass index; EPDS: Edinburgh Postnatal Depression Score.

Higher scores for the “Milk and Breakfast Cereal” Pattern corresponded to a lower average Pb cord blood level, while higher “Processed Products” scores corresponded with higher average urinary As levels. Finally, a higher “Bread and Toppings” score corresponded to higher average levels of hair Hg. The correlation between As and Hg was 0.20 (Spearman correlation coefficient (r); $p < 0.001$), however the correlations between the other trace element pairs were $r < 0.06$.

Trace element concentrations of urinary As moderately correlated with dietary exposure to total, organic and inorganic As ($r = 0.12$, $p < 0.0001$; $r = -0.08$, $p = 0.03$; $r = 0.19$, $p < 0.0001$, respectively). Maternal hair concentrations of Hg also positively correlated with dietary exposure to inorganic and total Hg ($r = 0.12$, $p < 0.0001$; $r = 0.27$, $p < 0.0001$, respectively), while the correlation between the Pb concentrations in cord blood and dietary exposure to Pb was weaker ($r = 0.05$, $p = 0.08$).

**Table 2**

Summary statistics of arsenic, mercury and lead in biological matrices at delivery and estimated exposure via the diet during pregnancy in women from the ELFE study.

| Trace Element | Matrices | N | GM [95% CI] | P25 | P50 | P75 | P95 |
|---|---|---|---|---|---|---|---|
| *Trace Element Concentrations*[c] | | | | | | | |
| As (μg/L) | Urine | 798 | 10.70 [10.00, 11.50] | 5.42 | 9.78 | 19.2 | 64.9 |
| Hg (μg/g) | Hair | 1530 | 0.27 [0.24, 0.31] | 0.26 | 0.45 | 0.73 | 1.30 |
| Pb (μg/L) | Cord blood | 1633 | 7.59 [7.39, 7.80] | 5.40 | 7.40 | 10.3 | 19.5 |
| *Dietary Exposure (μg/d)* | Maternal diet | | | | | | |
| Total As | | 798 | 64.26 [61.72, 66.90] | 42.53 | 62.51 | 90.71 | 162.41 |
| Inorganic As | | 798 | 28.21 [27.32, 29.14] | 20.89 | 27.67 | 38.30 | 59.21 |
| Organic As | | 798 | 31.43 [29.62, 33.35] | 16.78 | 30.19 | 56.36 | 123.13 |
| Total Hg | | 1530 | 1.74 [1.68, 1.81] | 1.00 | 1.64 | 3.10 | 5.98 |
| Inorganic Hg | | 1530 | 0.93 [0.91, 0.96] | 0.67 | 0.94 | 1.32 | 2.11 |
| Pb | | 1633 | 14.20 [13.89, 14.52] | 10.92 | 13.89 | 18.21 | 28.75 |

aGM: geometric mean; P25: 25th percentile; P50: 50th percentile; P75: 75th percentile; P95: 95th percentile.

bAs: arsenic; Hg: mercury; Pb: lead.

[c] Values under the limit of detection and limit of quantification have been imputed.

### 3.3. Dietary patterns and trace element concentrations

Higher "Balanced" dietary pattern and Diet Quality scores during pregnancy were both associated with higher concentrations of As in urine and Hg in hair at delivery (Fig. 1; Supplementary Table 4). On the other hand, higher "Western" dietary pattern scores were associated with lower concentrations of hair Hg. Higher scores on the "Balanced" dietary pattern were also associated with higher concentrations of Pb measured in cord blood, while both the Diet Quality score and the "Milk and Breakfast Cereals" pattern were negatively associated with concentrations of cord blood Pb.

A higher score on the "Processed Products" dietary pattern was associated with higher concentrations of Pb for the 2nd tertile, but the association did not reach statistical significance for the 3rd tertile. Neither the PANDiet score nor the dietary pattern "Bread and Toppings" were associated with concentrations of As, Hg or Pb.

### 3.4. Food groups and trace element concentrations

In analyses using food groups, higher intake of fish and seafood was associated with higher urinary As and hair Hg, but lower concentrations of cord blood Pb (Supplementary Table 5). Higher consumption of whole grains was also associated with increased concentrations of hair Hg, while a negative association was observed with processed meat and sugar-sweetened beverages. Large intakes of tea were associated with both increased concentrations of hair Hg and cord blood Pb. Intakes of fruit and vegetables and coffee were positively associated with concentrations of cord blood Pb, while fish and seafood, whole grains and dairy were negatively associated with concentrations of Pb.

### 3.5. Sensitivity analyses

In linear regression between dietary patterns/scores and concentrations of trace elements measured in maternal matrices or cord blood, results were similar to those observed in multinomial regression except that a higher Diet Quality score was no longer associated with lower concentrations of Pb (Supplementary Table 6).

Similar results were observed between dietary patterns/scores and hair Hg concentrations in complete case analysis (Supplementary Table 7). However, with regards to As, the association between the "Balanced" dietary pattern and the Diet Quality score did not reach statistical significance, as it did not between the "Balanced" dietary pattern and concentrations of Pb. Finally, we found no interaction with smoking during pregnancy (p > 0.10).

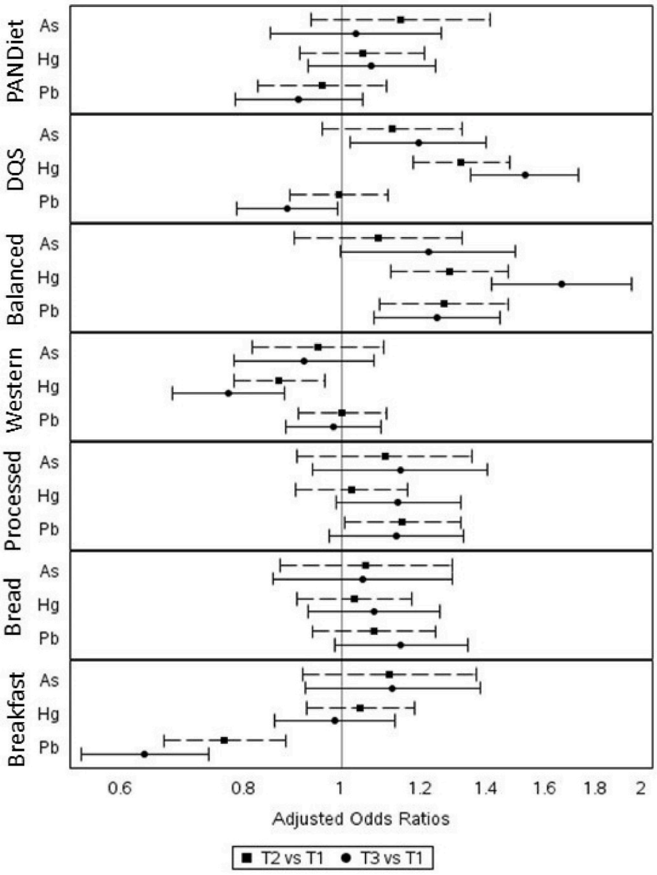

**Fig. 1.** Association between dietary patterns/scores and concentrations of arsenic (As), mercury (Hg) and lead (Pb) in women from the ELFE study ($n = 798$ As; $n = 1530$ Hg; $n = 1633$ Pb)

[a]Values are odds ratios (OR) and [95% confidence intervals] per 1 point increase in dietary score/pattern, with the exception of the PANDiet score, which is displayed per 10 point increase. Adjusted for recruitment wave, maternity size, maternal age, education, immigration history, employment status, household revenue, parity, pre-pregnancy BMI, smoking during pregnancy and size of the urban unit). All dietary patterns (Balanced, Western, Processed, Bread, Breakfast) were considered simultaneously in a single model, while the two dietary scores were in individual models (PANDiet and DQS: Diet Quality Score).

## 4. Discussion

We characterized the relationship between *a priori* defined dietary scores, *a* posteriori defined dietary patterns, and food groups during pregnancy with concentrations of potentially toxic trace elements in maternal matrices collected at delivery or in cord blood. Higher "Balanced" dietary pattern and Diet Quality scores were associated with higher concentrations of As in urine and Hg in hair. Concentrations of Pb in cord blood were also positively associated with "Balanced" dietary pattern scores, while they were negatively associated with Diet Quality and the "Milk and Breakfast Cereals" scores. Lower concentrations of hair Hg were associated with higher "Western" dietary pattern scores.

Our results concerning the positive association between the Diet Quality score with Hg and Pb are in accordance with findings from a Japanese cohort (Okubo and Nakayama, 2023). Okubo et al. calculated *a priori* balanced diet scores based on the Japanese Food Guide Spinning Top and found higher scores were positively associated with second/third trimester maternal blood Hg and negatively associated with Pb concentrations. Overall, the Japanese balanced diet score was somewhat similar to ours though food groups and scoring were slightly different (ie. the Japanese score separated fruit and vegetables but combined fish, meat and eggs). On the other hand, among five PCA-derived dietary patterns (i) "Health Conscious"; ii) "Traditional"; iii) "Processed"; iv) "Confectionary" and v) "Vegetarian"), no associations were observed with 1st trimester maternal blood Pb concentrations in a UK cohort (Taylor et al., 2019). Finally, in a US cohort, Lin et al. performed a diet-wide association study using two *a priori* diet scores: i) the Alternate Healthy Eating Index for Pregnancy [AHEI-P] (based on modified national recommendations for pregnant women); ii) a traditional Mediterranean diet [MD] score; as well as two PCA-derived dietary patterns: i) "Prudent"; ii) "Western" (Lin et al., 2021). Higher AHEI-P scores were associated with higher first trimester erythrocyte Hg concentrations, while the MD and Prudent scores were positively associated with both As and Hg and the Western dietary pattern was negatively associated with Hg. The findings concerning As and Hg correlate with ours, where we observe higher concentrations with higher scores for healthy diets and lower concentrations of Hg with a Western dietary pattern. However, both previously mentioned cohorts did not observe any associations with Pb (Lin et al., 2021; Taylor et al., 2019). These differences may stem from the mediums used to measure Pb; the previous cohorts used blood/erythrocytes, but in ELFE, Pb was measured in cord blood.

We observed higher concentrations of urinary As in women with higher "Balanced" dietary pattern and Diet Quality scores. These associations are most likely explained by the contribution of fish and seafood to these scores. Besides contaminated drinking water, fish and seafood are widely recognized as the food group with the highest total As (tAs) concentrations, mainly in the form of the relatively non-toxic organic As (oAs) (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; Rahaman et al., 2021). In the present study, fish and seafood is an important contributor to the "Balanced" dietary pattern and its intake contributes positively to the Diet Quality score. Accordingly, this food group was the sole group positively related to urinary As concentrations in our study. In the US cohort where the MD and Prudent scores were also positively associated with maternal As levels, Lin et al. likewise observed a strong positive association between seafood intake and erythrocyte As concentrations, but additionally observed positive associations with fresh fruit and white rice and negative associations with dairy and other grain items (white bread, French fries, potato, crackers) (Lin et al., 2021). The positive association between fish and seafood intake with urinary As, as well as the positive correlation between urinary As and dietary exposure to tAs and oAs, support our hypothesis that the diet is an important source of tAs exposure.

Both high "Balanced" dietary pattern and Diet Quality scores were associated with higher concentrations of hair Hg. Almost 20% of the variation in maternal total blood Hg concentrations may be attributed to the diet (Golding et al., 2013). As was the case with arsenic, this association may be primarily driven by intakes of fish and seafood, and to a lesser extent, by the intakes of whole grains and tea, which are all important contributors to the "Balanced" dietary pattern and contribute positively to the Diet Quality score. Like As, fish and seafood are the primary source of Hg in seafood consumers, accounting for 44% of the dietary variation in total blood Hg in a UK population and for 77% in a Korean population (Golding et al., 2013; Kim et al., 2016). Fish consumption also explained 20% of the variation in Hg concentrations in cord blood from a population living along the St. Lawrence river (Morrissette et al., 2004). Findings from the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) state that almost all dietary Hg in the French population originates from fish and seafood intake (ANSES French Agency for Food E and OH and S, 2013). However, wine, rice, vegetables/vegetable oil, liquor, and beans/nuts/soy may be contributors in non-seafood consumers (Lin et al., 2021; Wells et al., 2020; Airaksinen et al., 2011). Similar to our study, tea, whole grains and soy products have been positively associated with tHg, (Golding et al., 2013; Airaksinen et al., 2011; Kwon et al., 2009; Shao et al., 2013) such that grains contributed to 10% of tHg intake in a Korean study (Kim et al., 2016).

We observed a negative association between Hg concentrations and the "Western" dietary pattern. This association was similarly observed between the "Western" dietary pattern and erythrocyte Hg concentrations in a US cohort (Lin et al., 2021). The negative association with the "Western" dietary pattern in this study could be explained by the negative associations between processed meat and sugar sweetened beverage consumption with Hg concentrations. It is unclear why we observed these negative associations, but they may reflect the effects of other dietary or lifestyle factors that limit the absorption/bioavailability of mercury or speed up its elimination (Abdullah, 2020).

Hair concentrations of Hg correlated significantly with dietary exposure to both iHg and tHg in this study. Hair Hg represents chronic long-term exposure, however, tHg concentrations are also influenced by other factors, such as smoking and age. In one Chinese study, smoking accounted for 11–18% of estimated tHg in hair (Shao et al., 2013), but we found no interaction with smoking in this study. Overall, our results suggest that the maternal diet may be a major contributor to total hair Hg concentrations in this study.

According to ANSES, the major contributors to Pb exposure in the adult French population are alcoholic drinks (14%), bread and bread products (13%) and water (11%) (ANSES French Agency for Food E and OH and S, 2013). More recent results from the cross-sectional Esteban study have found that alcoholic beverages (20.1%), homegrown meat, poultry and eggs (11.7%), tap water (11.2%), and bread and bread products (6.1%) were the key dietary intakes responsible for the variation in adult French Pb blood concentrations (Oleko et al., 2022). A previous study in ELFE supports these findings as dietary factors associated with cord blood Pb concentrations were maternal tap water, shellfish, vegetable, and bread consumption (Saoudi et al., 2018). In the present study, considering dietary patterns and larger food groups, larger consumptions of coffee, tea, and fruit and vegetables were associated with increased concentrations of Pb in cord blood, while dairy products, whole grains and fish and seafood were negatively associated with cord blood Pb. The Esteban study similarly found a negative association between the intake of milk/milk products and chocolate with blood Pb concentrations in adults, (Oleko et al., 2022) while European data have found fruit and vegetables and tea to be large contributors to dietary Pb intake (European Food Safety Authority, 2012; Schneider et al., 2014). One other study has also found coffee to contain low concentrations of Pb (Winiarska-Mieczan et al., 2021).

The negative association with the "Milk and Breakfast Cereal" pattern found in the present study may be driven by the strong positive contribution of milk to this pattern and the negative contribution of coffee. Similarly, the negative association between the Diet Quality score and Pb in cord blood may be attributed to the positive contributions of dairy, whole grains, and fish and seafood to the score. On the other hand, the positive association with the “Balanced” dietary pattern may appear more counter-intuitive, as similar associations were observed with the other trace elements for the Diet Quality score and the “Balanced” dietary pattern. However, coffee consumption is a negative contributor to the Diet Quality score, whereas it does not contribute to the “Balanced” dietary pattern. Moreover, some food groups were considered as a whole to calculate the Diet Quality score (dairy products, fish and seafood) but parts of these food groups don’t contribute to the “Balanced” dietary pattern (breaded fish, milk). Fruit and vegetables were important contributors to both the Diet Quality score and the “Balanced” dietary pattern.

However, total dietary Pb exposure was not found to correlate with cord blood Pb in this study. This may be for several reasons; first, it is possibly due to the skeletal mobilization of maternal Pb during pregnancy, (Gulson et al., 2003) which may provide a large contribution to fetal Pb levels (80%) (Agency for Toxic Substances and Disease Registry, 2020). Second, little is understood about maternal-fetal transfer, but it is believed to occur by simple diffusion (Rísová, 2019). Significantly higher levels of Pb have been found in cord blood than in maternal blood in the 1st or 3rd trimesters in a Canadian study, (Arbuckle et al., 2016) but the reverse was true in a Tawainese study (Lin et al., 2010). Third, lead exposure can occur through a variety of sources, but in France, the factors most associated with adult blood Pb levels appear to be the diet, smoking, living in an older residence (constructed before 1949 (due to the risk of lead paint)), and living in a town/village (vs in the inner city) (Oleko et al., 2022). Finally, the complex interplay between other nutrients has been shown to affect Pb levels by decreasing placental transfer or bone resorption during pregnancy (Rísová, 2019; Lin et al., 2010; Janakiraman et al., 2003). This could explain the complex associations between dietary exposure to Pb and cord blood Pb.

This study was conducted in a large, nationwide cohort with biomarkers dosed in many women and extensive information on confounding factors, even if analyses could not exclude residual confounding. Maternal diet was assessed using a validated food frequency questionnaire and was characterized using complementary approaches: *a priori* defined dietary scores based on dietary guidelines, *a posteriori* dietary patterns, and food groups. The analysis of dietary scores and patterns allowed us to take the synergistic and antagonistic effects of the diet as a whole into account. It also helps identify the dietary consumption patterns that could drive higher levels of potentially toxic trace elements, in order to orient public health measures and/or to adapt recommendations to the nutritional and chemical nature of foods. Meanwhile, analyzing food groups allowed to identify potential sources of dietary exposure to potentially toxic trace elements and/or detect food groups that affect their absorption or metabolism. We have to acknowledge that biomarkers of exposure were available only for total trace elements, and not levels of organic or inorganic subtypes. This would have provided interesting information, as for example, we could distinguish between whether the dietary patterns/scores were associated with the relatively non-toxic oAs or the more lethal iAs. We additionally had dietary exposure estimates available to compare the biomarkers of exposure with. Furthermore, we only possessed biomarkers of exposure collected at delivery and physiological changes during pregnancy may render trace element levels very different throughout pregnancy. For example, Pb mobilization from bone drastically increases in the third trimester compared to the first (Gulson et al., 2003). On the other hand, hair Hg is indicative of long-term exposure levels and may represent a more average and valid measure of exposure during pregnancy. Yet, As has a short half-life and urinary levels only represent exposure over the past few days. Finally, though Pb was measured in cord blood, As and Hg biomarkers of exposure were dosed from the mother, which may not precisely reflect fetal exposure. However, maternal hair Hg is highly predictive of oHg in cord blood, which is a valid measure for prenatal Hg exposure (Morrissette et al., 2004; Grandjean et al., 2005).

### 4.1. Conclusion

Higher diet quality during pregnancy appears associated with greater levels of maternal urinary As and maternal hair Hg at delivery. However, the increases in total As and Hg we observed may be driven by increases in the less toxic forms of oAs and iHg. Findings were more mixed for cord blood Pb. Some of these associations appear to be driven by a higher consumption of fish and seafood in healthy diets. Fish and seafood are an important source of nutrients, so pregnant women should take care to adhere to dietary guidelines and consume fish and seafood in moderate amounts and vary the types and origins to limit exposure to potentially toxic trace elements. However, the influence of individual nutrients on potentially toxic trace element metabolism, (Abdullah, 2020; Agency for Toxic Substances and Disease Registry, 2020; Sijko and Kozłowska, 2021) especially in pregnancy, should be studied further. Future interest should also be focused on speciation analyses to determine which species are driving the observed increases in total As and Hg. It is important to make this distinction to determine the health impact of these dietary consumption patterns and food groups and more clearly identify the associations with trace element toxicity.

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## Data sharing

The data underlying the findings cannot be made freely available for ethical and legal restrictions. This study includes a substantial number of variables that, together, could be used to re-identify the participants based on a few key characteristics and then be used to have access to other personal data. Therefore, the French ethics authority strictly forbids making these data freely available. However, some data can be obtained upon request from the ELFE principal investigator. Readers may contact marie-aline.charles@inserm.fr to request the data.

## CRediT authorship contribution statement

**Courtney Dow:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Manik Kadawathagedara:** Writing – review & editing. **Manel Ghozal:** Writing – review & editing. **Marie-Aline**

**Charles:** Writing – review & editing. **Karine Adel-Patient:** Writing – review & editing. **Clémentine Dereumeaux:** Writing – review & editing. **Blandine de Lauzon-Guillain:** Writing – review & editing, Validation, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

## 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

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