

# Diet as a Source of Exposure to Environmental Contaminants for Pregnant Women and Children from Six European Countries

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**BACKGROUND:** Pregnant women and children are especially vulnerable to exposures to food contaminants, and a balanced diet during these periods is critical for optimal nutritional status.

**OBJECTIVES:** Our objective was to study the association between diet and measured blood and urinary levels of environmental contaminants in mother–child pairs from six European birth cohorts ( $n = 818$  mothers and 1,288 children).

**METHODS:** We assessed the consumption of seven food groups and the blood levels of organochlorine pesticides, polybrominated diphenyl ethers, polychlorinated biphenyls (PCBs), per- and polyfluoroalkyl substances (PFAS), and heavy metals and urinary levels of phthalate metabolites, phenolic compounds, and organophosphate pesticide (OP) metabolites. Organic food consumption during childhood was also studied. We applied multivariable linear regressions and targeted maximum likelihood based estimation (TMLE).

**RESULTS:** Maternal high ( $\geq 4$  times/week) versus low ( $< 2$  times/week) fish consumption was associated with 15% higher PCBs [geometric mean (GM) ratio = 1.15; 95% confidence interval (CI): 1.02, 1.29], 42% higher perfluoroundecanoate (PFUnDA) (GM ratio = 1.42; 95% CI: 1.20, 1.68), 89% higher mercury (Hg) (GM ratio = 1.89; 95% CI: 1.47, 2.41) and a 487% increase in arsenic (As) (GM ratio = 4.87; 95% CI: 2.57, 9.23) levels. In children, high ( $\geq 3$  times/week) versus low ( $< 1.5$  times/week) fish consumption was associated with 23% higher perfluorononanoate (PFNA) (GM ratio = 1.23; 95% CI: 1.08, 1.40), 36% higher PFUnDA (GM ratio = 1.36; 95% CI: 1.12, 1.64), 37% higher perfluorooctane sulfonate (PFOS) (GM ratio = 1.37; 95% CI: 1.22, 1.54), and  $> 200\%$  higher Hg and As [GM ratio = 3.87 (95% CI: 1.91, 4.31) and GM ratio = 2.68 (95% CI: 2.23, 3.21)] concentrations. Using TMLE analysis, we estimated that fish consumption within the recommended 2–3 times/week resulted in lower PFAS, Hg, and As compared with higher consumption. Fruit consumption was positively associated with OP metabolites. Organic food consumption was negatively associated with OP metabolites.

**DISCUSSION:** Fish consumption is related to higher PFAS, Hg, and As exposures. In addition, fruit consumption is a source of exposure to OPs. <https://doi.org/10.1289/EHP5324>

## Introduction

During gestation and early postnatal development, the fetus and the child, respectively, are vulnerable to the effects of environmental chemicals due to rapid cellular differentiation and tissue development and the incomplete development of protective mechanisms (Heindel et al. 2015a). More specifically, developmental low-dose exposure to persistent organic pollutants, such as organochlorine compounds and polybrominated diphenyl ethers (PBDEs), has been consistently linked to restricted fetal growth, neurotoxicity, immunotoxicity, and reduced fertility, and

robust evidence is emerging on their obesogenic effects (Heindel et al. 2015b; Johansson et al. 2017; Linares et al. 2015; Vrijheid et al. 2016; Vuong et al. 2018). In addition, early life exposure to per- and polyfluoroalkyl substances (PFAS), commonly used in a wide variety of products, can induce carcinogenic, hepatotoxic, and immunotoxic effects, as well as adverse birth outcomes, childhood obesity, and type 2 diabetes (Alderete et al. 2019; Braun 2017; Heindel et al. 2015b; Johansson et al. 2017; Liew et al. 2018; Lim 2019). Prenatal exposure to toxic metals, such as mercury (Hg), cadmium (Cd), and lead (Pb) in early life, can disrupt the development of the nervous system, and such exposures can affect the child's cognitive, motor, and behavioral development. In addition, evidence is building on the immunotoxic effects of metal exposure (Claus Henn et al. 2014; Farzan et al. 2016; Valeri et al. 2017). On the other hand, early life exposure to nonpersistent pollutants such as phthalates, environmental phenols, and organophosphate pesticides (OPs) has been also linked to adverse neurobehavioral outcomes, obesity, and asthma (Braun 2017; Heindel et al. 2015b; Hertz-Picciotto et al. 2018; Philippat et al. 2017; Philips et al. 2017; Raanan et al. 2015). In summary, early life exposure to several environmental chemical hazards has been linked to adverse health outcomes, and even though acute high exposures can induce such effects, continuous low-dose exposures have been consistently linked to toxic effects (Myers et al. 2009; Taylor et al. 2013; Vandenberg et al. 2012). Hence, determining the sources of exposure and eliminating

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exposure to environmental hazards at critical developmental stages is a major public health issue.

Diet is a major source of exposure to many hazardous environmental factors. Food can be contaminated via transfer of substances from contaminated marine and/or agricultural food chains, during food production or food processing, or as a result of leakage from food packaging (Domingo and Nadal 2017; Ng and von Goetz 2017). Dietary exposure to persistent organic pollutants (POPs), including polychlorinated dioxins/furans and biphenyls (PCDDs/PCDFs and PCBs), dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), PBDEs and PFASs is driven mainly by consumption of foods of marine or terrestrial animal origin (Domingo and Nadal 2017; EFSA 2006a, 2006b, 2012b). Such contaminants are found in biological samples from pregnant women worldwide, and positive associations between blood concentrations of POPs and consumption of fish and seafood, meat, and dairy products have been consistently reported (Brantsæter et al. 2013; Cao et al. 2011; Cequier et al. 2015; Llop et al. 2010; Manzano-Salgado et al. 2016; Miyashita et al. 2015; Papadopoulou et al. 2014). Similarly, seafood and other foods of animal origin have been identified as sources of exposure to POPs for children although fewer studies have focused on this age group (Caspersen et al. 2016; González-Alzaga et al. 2018; Jain 2018; Wu et al. 2015).

Fish and seafood are an established dietary source of Hg and arsenic (As). Dietary determinants of other toxic elements, such as Cd and Pb are more diverse (Baeyens et al. 2014; Berglund et al. 2015; Castaño et al. 2015; Li et al. 2014; Llop et al. 2014; Miyashita et al. 2015). Regarding exposure to nonpersistent contaminants, consumption of canned food has been related to increased urinary levels of bisphenol A (BPA) (Casas et al. 2013; Covaci et al. 2015), and consumption of food stored in plastic packaging has been related to higher urinary levels of phthalate metabolites (Giovanoulis et al. 2016). For other nonpersistent compounds, such as parabens and triclosan (TCS), the dietary sources are unclear (Larsson et al. 2014; Sakhi et al. 2018). For nonoccupationally exposed populations, contaminated fruit and vegetable consumption has been identified as a major contributor to OP exposure, monitored as increased concentrations of urinary nonspecific OP metabolites (Cequier et al. 2017; Katsikantami et al. 2019; van den Dries et al. 2018).

Most earlier studies have focused on the dietary determinants of exposure to single contaminants, even though several contaminants frequently share common sources of exposure. Few studies have reported contaminants' patterns and their association with nutrients and the consumption of specific foods (Birgisdottir et al. 2013; Dassuncao et al. 2018; Hu et al. 2018; Veyhe et al. 2015). The identification of such common dietary sources of exposure can assist in designing and delivering effective dietary advice. Dietary recommendations must be balanced between the health risks related to dietary exposure to environmental contaminants and the health benefits of important nutrients.

In the present analyses within a multicenter study, we aimed to systematically investigate and identify the dietary determinants of blood and urinary biomarkers of a wide range of ubiquitous environmental contaminants in pregnant mothers and their children. We further evaluated the effect of dietary recommendations on the concentrations of several environmental contaminants using targeted maximum likelihood based estimation (TMLE).

## Methods

### Study Population

This study was conducted within the Human Early Life Exposome (HELIX) project (Maitre et al. 2018; Vrijheid et al. 2014), which

draws resources from six existing European longitudinal population-based birth cohorts: Born in Bradford (United Kingdom; BiB) (Wright et al. 2013); Étude des Déterminants pré et postnataux du développement et de la santé de l'ENfant (France; EDEN) (Drouillet et al. 2009); Infancia y Medio Ambiente (Spain; INMA) (Guxens et al. 2012); Kaunas Cohort (Lithuania; KANC) (Grazuleviciene et al. 2009); Norwegian Mother and Child Cohort Study (Norway; MoBa) (Magnus et al. 2016), and Rhea (Greece) (Chatzi et al. 2017). Our study consisted of 818 mothers and 1,288 children and included information on maternal diet, child's diet, and measured levels of environmental contaminants during pregnancy and childhood. This subsample, called the HELIX subcohort, is nested within the entire HELIX cohort ( $n=32,000$  mother-child pairs) by inclusion of approximately 200 pairs from each cohort (Maitre et al. 2018). The detailed description of the study design and population is provided by Maitre et al. (2018). In brief, the included children were between 6 and 11 y of age, and the data and biological sample collection was conducted from 2013 to 2015. Eligibility criteria for inclusion in the subcohort were *a*) age 6–11 y at the time of the visit, with a preference for ages 7–9 y if possible; *b*) sufficient stored pregnancy blood and urine samples available for analysis of prenatal exposure biomarkers; *c*) complete address history available from first to last follow-up point; and *d*) no serious health problems that may affect the performance of the clinical testing or impact the volunteer's safety (e.g., acute respiratory infection). Each cohort selected participants at random from the eligible pool within the entire cohort and invited them to participate in this subcohort until the required number of participants was reached.

### Dietary Assessment

Information on maternal diet during pregnancy was collected using validated semiquantitative cohort-specific food frequency questionnaires (FFQs) (Brantsæter et al. 2008; Chatzi et al. 2011; Deschamps et al. 2009; Raynor and Born in Bradford Collaborative Group 2008; Vioque et al. 2013). Information about maternal diet during pregnancy was not available for the KANC cohort. For the BiB cohort, the collected information on maternal diet was via a short questionnaire and was limited to some but not all food groups (the missing food groups were fruits, vegetables, pulses, and dairy products). Hence, women from the KANC and BiB cohort were not included in our analysis. Detailed information on each FFQ is presented in Excel Table S1 for the included cohorts. Information about the children's diet was collected during the HELIX follow-up, when children were called to attend detailed examinations (Maitre et al. 2018) via a semiquantitative FFQ covering the child's habitual diet, which was filled in by the parent attending the examination appointment. The FFQ was developed by the HELIX research group and translated and was applied to all cohorts. We defined weekly consumption frequency of seven food groups: three foods of animal origin (meat and meat products, fish and seafood, and dairy products) and four foods of plant origin (vegetables, fruits, bread and cereals, and pulses such as dry beans, dry peas, chickpeas, and lentils). In addition, the children's organic food consumption was assessed by one question asking the parent to report their child's frequency of eating organic food. The answers were aggregated into a three-category variable: no organic consumption, once a week or less, and more than once a week.

### Chemical Analysis

The concentrations of several environmental contaminants were measured in maternal biological samples collected prenatally or at birth and in children's biological samples collected during the

HELIX follow-up. A detailed description of the analytical methods, the quality assurance and quality control, and the measured maternal and child concentrations have been published previously (Haug et al. 2018).

As presented in Excel Table S2, the environmental contaminants measured in blood were organochlorine compounds including PCBs (CB 118, CB 138, CB 153, CB 170, CB 180), dichlorodiphenyl trichloroethane (DDT), DDE, HCB, PBDEs (BDE 47, BDE 153), and PFASs [perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorononanoate (PFNA), perfluoroundecanoate (PFUnDA)] as well as the toxic elements Hg, Cd, Pb, and As. Notably, only concentrations of PFASs and toxic elements were available for mothers in the KANC cohort, with PFAS measured in whole blood rather than in serum or plasma as in the other cohorts. In addition, maternal toxic elements in the INMA cohort were measured in cord blood samples, rather than in maternal perinatal samples as in the other cohorts. The contaminants measured in urine were phthalate metabolites [Monoethyl phthalate (MEP), Mono-isobutyl phthalate (MiBP), Mono-n-butyl phthalate (MnBP), Mono benzyl phthalate (MBzP), Mono-2-ethylhexyl phthalate (MEHP), Mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), Mono-2-ethyl-5-oxohexyl phthalate (MEOHP), Mono-2-ethyl 5-carboxypentyl phthalate (MECPP), Mono-4-methyl-7-hydroxyoctyl phthalate (oh-MiNP), Mono-4-methyl-7-oxooctyl phthalate (oxo-MiNP)], phenols [MEPA, ETPA, propylparaben (PRPA), butylparaben (BUPA) BPA, OXBE, TCS] and OP metabolites [dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP), dimethyl dithiophosphate (DMDTP), diethyl phosphate (DEP), thiophosphate (DETP), diethyl dithiophosphate (DEDTP)]. Urinary creatinine and plasma or serum lipids concentrations were measured to facilitate adjustment for the urinary metabolites of phthalates, phenols, and OPs and the lipophilic compounds (PCBs, DDT, DDE, HCB, PBDEs), respectively. The maternal urinary metabolite concentrations for phthalates, phenols, and OPs as well as the maternal concentrations of the lipophilic compounds were not available in the KANC cohort. Values below the limit of quantitation were replaced with the observed values whenever available (Haug et al. 2018). For nonobserved concentrations, singly imputed values were obtained using a quantile regression approach. The detailed numbers of measured, quantified and included samples, overall and by cohort, are presented in Excel Tables S3 and S4 for maternal and child samples, respectively. The OP metabolites, DMDTP and DEDTP were not included in our analysis due to low detection frequencies in maternal and children samples. In addition, the individual concentrations of the four nonspecific OP metabolites were converted to their molar concentrations (nanomoles/gram of creatinine) and summarized to the total dialkylphosphate metabolites (sumDAPs; sum of DMP, DMTP, DEP, DETP), total dimethylphosphate metabolites (sumDM; sum of DMP and DMTP), and total diethylphosphate metabolites (sumDE; sum of DEP and DETP). Last, because common food sources were suspected sources, PCBs were analyzed as a summarized concentration (sumPCBs) rather than single congeners, and the di(2-ethylhexyl) phthalate (DEHP) metabolites, MEHP, MEHHP, MEOHP, and MECPP, were also included as a summed molar concentration (i.e., sumDEHP metabolites).

### Statistical Analysis

To identify dietary determinants of measured concentrations of environmental contaminants, we conducted complete case linear regression analysis for single contaminants adjusted for covariates. Based on *a priori* knowledge on covariates suspected to be related to both dietary habits and maternal levels of contaminants, the following variables were included in the pregnancy models: cohort, maternal age (in years), educational level (low/middle/

high), parity (nulliparous/multiparous), prepregnancy body mass index (in kilograms per meter squared), gestational weight gain (in kilograms), active smoking during pregnancy (yes/no), year of delivery [minimum–maximum (min-max) = 2003–2009]. Finally, child's ethnicity (white European/other) was used as a proxy for maternal ethnicity, as the later was not available (see Excel Table S5). The associations reported for pregnant women did not include women from the KANC and BiB cohorts because of missing maternal dietary information. For associations between child's diet and measured levels of environmental contaminants, the following *a priori* covariates were included in the multivariable models: cohort, age (years), body mass index (in kilograms per meter squared), Family Affluence Score (low/middle/high), year of birth (min-max = 2003–2009) and firstborn (yes/no).

In the multivariate regression analysis, blood and urinary concentrations of environmental contaminants were the dependent variables and were log-transformed to approach normal distribution. Food intakes were the independent variables and were categorized into tertiles. Hence, beta coefficients from all models were exponentiated (base 10) to produce the ratio of the geometric mean (GM) of contaminant concentrations of each category in respect to the GM of the reference category. Because food group intakes tend to correlate, the variance inflation factor (VIF) was used to assess multicollinearity, and for all the models, an  $IVF < 10$  was observed. Hence, the final models presented for pregnant women as well as for children were mutually adjusted for all food groups. Because multiple testing can be an issue, we have also reported the observed associations after correction for multiple comparisons with a false discovery rate controlled at  $< 5\%$  (Benjamini and Yekutieli 2005).

Because smoking is a major nondietary source of exposure to Cd, dietary determinants of Cd were explored in the whole population as well as in nonsmokers. As a secondary analysis and in order to explore the effect of prenatal exposure to contaminants on the postnatal dietary exposure, we adjusted the children's models for the corresponding contaminant concentration in the mother's sample during pregnancy.

For children, the associations between the frequency of organic food consumption with the measured environmental contaminants in blood and urine were also examined in multivariable linear regression models, adjusted for the same covariates as the analysis of child's diet, including all the food groups.

Finally, we performed TMLE analysis (Schuler and Rose 2017), aiming to estimate the marginal GM difference in environmental contaminants levels (Y) that were previously identified to be related with fish and fruit consumption if all HELIX mothers and children were given a hypothetical intervention ( $A = 1$ ) relative to a scenario in which none of the mothers and children were given that intervention ( $A = 0$ ):  $E[E(Y|A = 1, W) - E(Y|A = 0, W)]$ , where W is a matrix of covariates. To estimate  $E(Y|A, W)$  and  $E(A|W)$ , we used the Super Learner algorithm, an ensemble machine learning algorithm that uses a weighted combination of algorithms to return a prediction function that minimizes cross-validated mean squared error (van der Laan et al. 2007). Covariates used in the TMLE analysis were the same as those included in the regression analyses and are described above. The potential interventions of fish and fruit intake evaluated were based on international dietary recommendations (AHA/ASA 2017; WHO 2006): for fish, consuming fish according to the dietary recommendations (mothers: up to 3 meals/week, children: up to 2 meals/week) versus exceeding the dietary recommendation, and for fruit, consuming fruits according to the recommendation (both mothers and children: at least 2 servings/d) versus not reaching the recommendation for daily fruit intake.

Hence, the marginal GM difference of PCBs, PFASs, As, and Hg concentrations for the different fish intakes and of OPs

metabolites for the different fruit intakes were evaluated in separate TMLE models. These chemicals were chosen based on statistical significant and dose–response associations derived from the linear regression analysis and were consistent in mothers and children.

Statistical analyses were performed using Stata statistical software (release 14; Stata Corporation) and R (version 3.2.2; R Development Core Team). We used  $\alpha = 0.05$  as the level of significance in our analyses.

## Results

### Maternal and Child Diet in the HELIX Subcohort

The median intake of meat and fish during pregnancy was 8 and 3 times/week, respectively (Table 1). The median intake of meat and fish in children was 8 and 2 times/week, respectively. Both mothers and children consumed vegetables, fruits, dairy, and cereals much more frequently (>10 times/week).

By cohort, the women from the Norwegian and British cohorts reported the highest median intake of meat, and those from the Norwegian and Spanish cohort the highest median intake of fish (See Excel Table S6). Among the four cohorts with available dietary information, the women from the French cohort reported the lowest median intake of fruits and vegetables, but they had the highest median intake of pulses. Regarding the children, British and Norwegian children had higher median fish consumption than the other cohorts, whereas Lithuanian children had a median intake of dairy products at half of the overall median (see Excel Table S6). The frequency of consumption differed by cohort for all food groups ( $p < 0.001$ , Kruskal-Wallis test). Higher maternal education was related to higher maternal dairy and cereal intake and higher child vegetable intake (see Excel Table S7). Women with medium education had lower fish intake than low- and high-educated women.

In addition, 33% of the children reported no consumption of organic food, and 25% of the children were consuming organic food more than 1 time/week (Table 1). Organic food consumption was

**Table 1.** Weekly consumption of major food groups (in times per week) in women during pregnancy and children as assessed at 5–12 y of age, at the HELIX follow-up.

Food groups (times/week)	N	Non-consumers (%)	Median	P25	P75
<b>Maternal diet<sup>a</sup></b>					
Meat	929	0.5	8	6	12
Fish and seafood	940	2	3	2	5
Vegetables <sup>b</sup>	827	0.2	12	8	20
Fruits <sup>b</sup>	832	0.6	14	8	21
Dairy products <sup>b</sup>	829	0.1	21	15	31
Bread and cereals	944	0	17	6	33
Pulses <sup>b</sup>	832	25	1	0	3
<b>Child diet at 5–12 y of age<sup>c</sup></b>					
Meat	1,291	0.2	8	5	10
Fish and seafood	1,291	4	2	1	4
Vegetables	1,290	1	7	4	10
Fruits	1,289	0.3	9	6	18
Dairy products	1,291	0.3	20	13	28
Bread and cereals	1,289	0	19	13	26
Pulses	1,290	11	1	1	3
<b>Organic food consumption</b>					
No	427	33	—	—	—
Once a week	534	42	—	—	—
More than once a week	325	25	—	—	—

Note: —, Not applicable; BiB, Born in Bradford; EDEN, Étude des Déterminants pré et postnatals du développement et de la santé de l'ENfant; France; HELIX, Human Early-Life Exposome; INMA, Infancia y Medio Ambiente; KANC, Kaunas Cohort; MoBa, Norwegian Mother and Child Cohort Study; P, percentile.

<sup>a</sup>No information for KANC cohort.

<sup>b</sup>No information for the BiB cohort.

<sup>c</sup> $n = 203$  from BiB,  $n = 197$  from EDEN,  $n = 201$  from KANC,  $n = 272$  from MoBa,  $n = 199$  from Rhea,  $n = 219$  from INMA.

much more frequent in children of high-educated mothers than of low-educated mothers (see Excel Table S7).

### Food Consumption and Measured Environmental Contaminants in Blood during Pregnancy and Childhood

Fish consumption during pregnancy was positively associated with maternal concentrations of PCBs, PFUnDA, As, and Hg in a dose–response manner (Figure 1; see also Excel Table S8). More specifically, high fish intake (>4 times/week) was associated with 15% higher sumPCBs [GM ratio = 1.15; 95% confidence interval (CI): 1.02, 1.29], 42% higher PFUnDA and 89% higher Hg blood concentrations compared with the lowest intake (<2 times/week). The largest difference was observed for As, with a 201% increase in the blood concentration for medium fish intake (2–4 times/week) and 487% increase for high fish intake. These results remained significant after controlling for multiple comparisons.

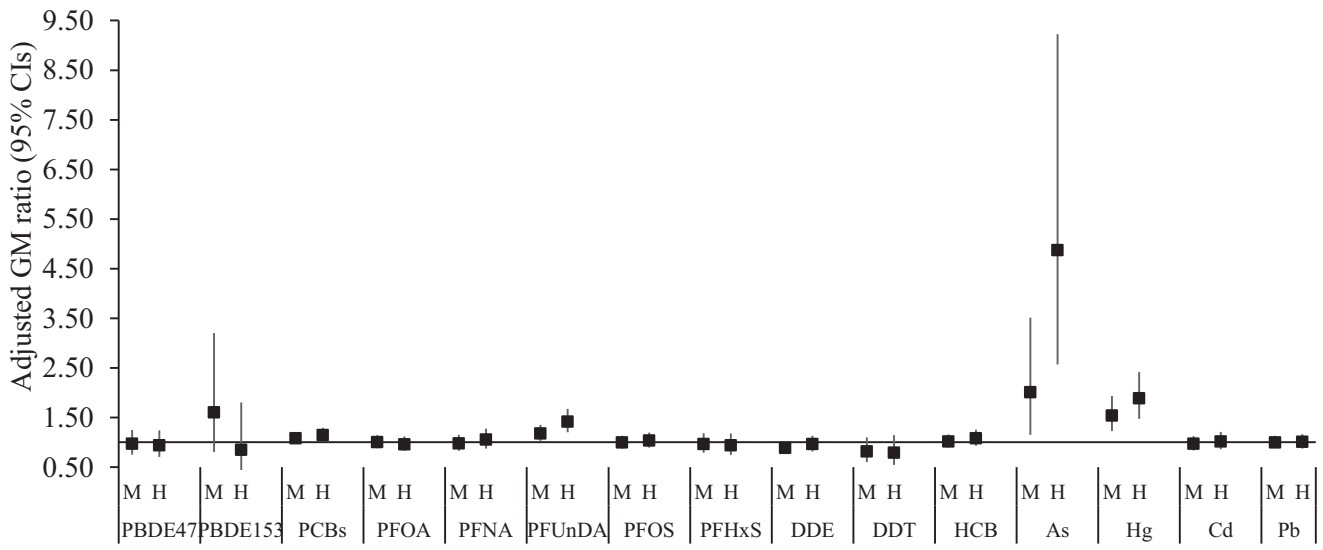
In children, medium fish intake (1.5–3 times/week) was associated with 11% higher PCBs, 21% higher PFNA, 33% higher PFOS, 8% higher HCB, 77% higher As, and 82% higher Hg. High fish intake (>3 times/week) was associated with 23% higher PFNA, 36% higher PFUnDA, 37% higher PFOS, and >200% higher As and Hg concentrations in child's blood. These results remained significant after controlling for multiple comparisons (Figure 2; see also Excel Table S9).

In a secondary analysis, after adjustment for the prenatal exposure to the respective environmental contaminants (by including maternal levels measured in pregnancy), similar results were obtained for high fish intake in childhood and PFAS, As, and Hg levels (see Excel Table S11).

In children, although we had detailed information of consumption of different types of seafood, this information was not available for mothers. Most children reported consumption of white fish more than 1 time/week (64%), of oily fish more than 1 time/week (37%), and of any shellfish (crustaceans and bivalves) (53%). Any shellfish consumption was associated with higher blood levels of PCBs, all PFASs, As, and Hg (Figure 3; see also Excel Table S12). Consumption of oily fish more than once a week was associated with higher blood levels of PCBs, PFNA, PFUnDA, PFOS, As, and Hg, and similar results were found for white fish consumption of more than 1 time/week, but not for PFUnDA and PCBs.

Regarding other foods of animal origin, high meat intake during pregnancy ( $\geq 10$  times/week) was associated with lower prenatal levels of DDE and DDT, whereas high meat intake in childhood (>9 times/week) was associated with lower blood Hg (see Excel Tables S8 and S9). In nonsmoking mothers and all children, high meat intake was associated with lower Cd levels in blood [GM = 0.80 (95% CI: 0.66, 0.96) and GM = 0.87 (95% CI: 0.77, 0.98), respectively] (see Excel Tables S9 and S10). High dairy intake was associated with lower PFUnDA in maternal blood and lower PCBs, DDT, and As in children's blood. Consistently for both populations, high dairy intake was associated with approximately 20% lower Hg levels and 11–14% lower Pb levels. After controlling for multiple comparisons, only the association between dairy and lower Pb in children remained significant.

When exploring the associations between consumption of foods of plant origin—namely vegetables, fruits, cereals, and pulses—much fewer and less consistent associations were observed than those for foods of animal origin (see Excel Tables S13 and S14). High vegetable intake in pregnancy was associated with higher maternal PFOA levels, whereas high consumption of fruit and pulses in children was associated with higher PFUnDA levels. These associations were not significant after controlling for multiple comparisons.



### Maternal weekly frequency of fish & seafood intake

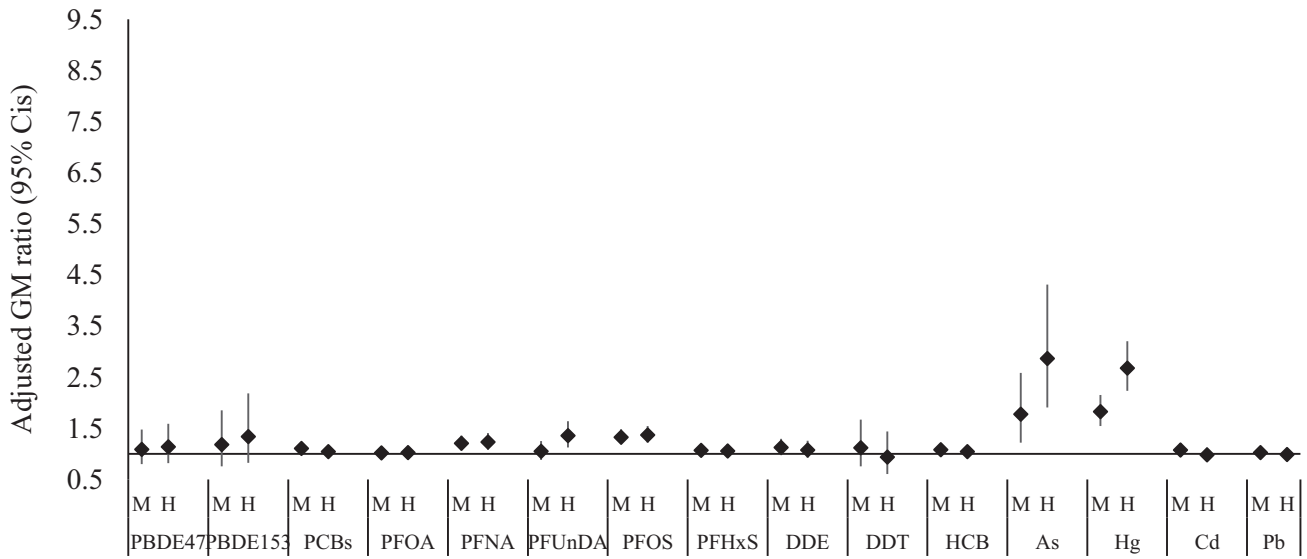
*Low (Reference): <2 times/week; Medium (M): 2-4 times/week; High (H): >4 times/week*

**Figure 1.** Adjusted linear regression associations between weekly consumption of fish and seafood and measured levels of contaminants in maternal blood collected during pregnancy ( $n = 409-722$ ). Models are mutually adjusted for all food groups and for cohort, maternal age, educational level, parity, prepregnancy body mass index, gestational weight gain, active smoking during pregnancy, and year of delivery. Women from KANC and BiB cohorts are not included. Corresponding numeric data are reported in Excel Table S8. As, arsenic; BiB, Born in Bradford cohort; Cd, cadmium; CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; GM, geometric mean; HCB, hexachlorobenzene; Hg, mercury; KANC, Kaunas Cohort; Pb, lead; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PFHxs, perfluorohexane sulfonate; PFNA, Perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PFUnDA, perfluoroundecanoate.

### TMLE Analysis—Fish Recommendations and Levels of Environmental Contaminants

Using TMLE analysis, we estimated that a population of pregnant women in which everyone was consuming fish in an amount equal

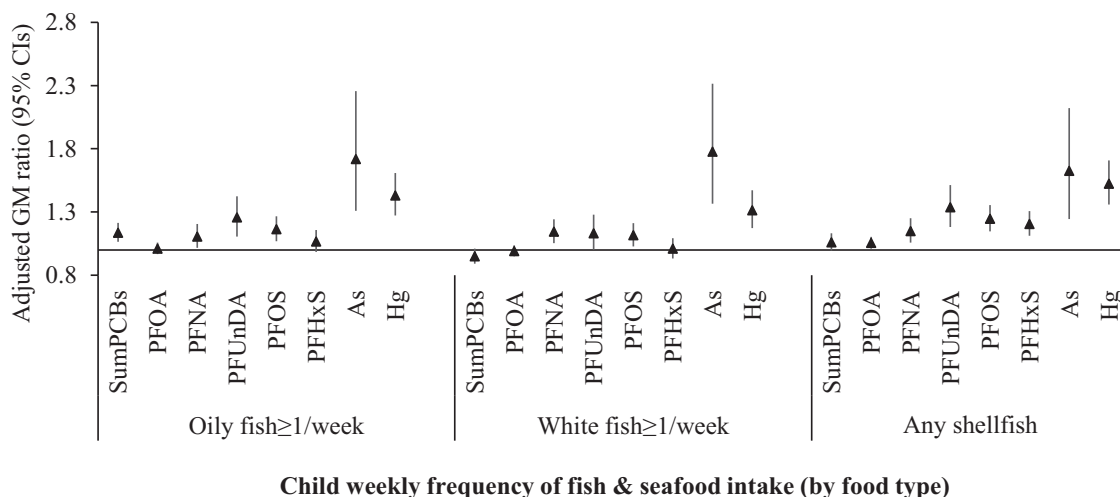
to or lower than the dietary recommendation (up to 3 servings/week) would have marginal GM PFNA, As, and Hg blood concentrations of  $0.17 \mu\text{g/L}$  (95% CI:  $-0.26, -0.07 \mu\text{g/L}$ ),  $2.08 \mu\text{g/L}$  (95% CI:  $-2.62, -1.54 \mu\text{g/L}$ ), and  $1.02 \mu\text{g/L}$  (95% CI:  $-1.39, -0.65 \mu\text{g/L}$ ) lower than in a population of pregnant women where



### Child weekly frequency of fish & seafood intake (total)

*Low (Reference): <1.5 times/week; Medium (M): 1.5-3 times/week; High (H): >3 times/week*

**Figure 2.** Adjusted linear regression associations between weekly consumption of fish and measured levels of contaminants in child blood ( $n = 1,265-1,286$ ). Models are mutually adjusted for all food groups and for cohort, age, body mass index, Family Affluence Score, year of birth, and firstborn. Corresponding numeric data are reported in Excel Table S9. As, arsenic; Cd, cadmium; CI, confidence interval; DDE, dichlorodiphenyl dichloroethylene; DDT, dichlorodiphenyl trichloroethane; GM, geometric mean; HCB, hexachlorobenzene; Hg, mercury; Pb, lead; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PFHxs, perfluorohexane sulfonate; PFNA, Perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PFUnDA, perfluoroundecanoate.



Reference groups: Oilyfish: <1 time/week; White fish: <1 time/week; Shellfish: No intake.

**Figure 3.** Adjusted linear regression associations between consumption of different seafood types and blood levels of PFAS, As, and Hg in childhood ( $n = 1,265-1,286$ ). Models are mutually adjusted for all food groups and for cohort, age, body mass index, Family Affluence Score, year of birth, and firstborn. Corresponding numeric data are reported in Excel Table S12. As, arsenic; CI, confidence interval; GM, geometric mean; Hg, mercury; PFHxS, perfluorohexane sulfonate; PFNA, Perfluorononanoate; PFOA, perfluorooctanoate; PFUnDA, perfluoroundecanoate; sumPCB, summarized concentration of polychlorinated biphenyls.

everyone was consuming fish >3 times/week (Table 2). Regarding children, if the whole population were consuming fish equal to or lower than the dietary recommendation (up to 2 servings/week) they would have  $-0.03 \mu\text{g/L}$  and  $-0.46 \mu\text{g/L}$  lower PFUnDA and PFOS blood levels and  $-0.81 \mu\text{g/L}$  and  $-0.73 \mu\text{g/L}$  lower As and Hg levels than if the whole population were consuming more fish meals per week. Nonsignificant associations were observed for other PFAS.

**Table 2.** Estimation of the marginal geometric mean difference in sumPCBs, PFAS, As, and Hg concentrations in mothers and children from a hypothetical intervention scenario of weekly fish consumption.

Pollutants	Exposed/total (n/N)	Intervention scenario	
		$\Psi$	95% CI
<b>Women (pregnancy)<sup>a</sup></b>			
SumPCBs (ng/g lipid)	347/516	1.13	-15.19, 17.46
PFOA ( $\mu\text{g/L}$ )	377/722	-0.13	-0.44, 0.17
PFNA ( $\mu\text{g/L}$ )	377/722	-0.17	-0.26, -0.07
PFUnDA ( $\mu\text{g/L}$ )	340/524	-0.02	-0.04, 0.00
PFOS ( $\mu\text{g/L}$ )	377/722	0.83	-0.01, 1.68
PFHxS ( $\mu\text{g/L}$ )	377/722	0.04	-0.08, 0.15
As ( $\mu\text{g/L}$ )	256/409	-2.08	-2.62, -1.54
Hg ( $\mu\text{g/L}$ )	289/590	-1.02	-1.39, -0.65
<b>Children (5–12 y of age)<sup>b</sup></b>			
SumPCBs (ng/g lipid)	817/1,265	1.63	-1.09, 4.36
PFOA ( $\mu\text{g/L}$ )	835/1,286	-0.04	-0.11, 0.04
PFNA ( $\mu\text{g/L}$ )	835/1,286	-0.05	-0.13, 0.03
PFUnDA ( $\mu\text{g/L}$ )	835/1,286	-0.03	-0.05, -0.02
PFOS ( $\mu\text{g/L}$ )	835/1,286	-0.46	-0.71, -0.21
PFHxS ( $\mu\text{g/L}$ )	835/1,286	0.05	-0.21, 0.30
As ( $\mu\text{g/L}$ )	833/1,283	-0.81	-1.19, -0.44
Hg ( $\mu\text{g/L}$ )	833/1,283	-0.73	-0.91, -0.55

Intervention scenario: A = 1: following the dietary recommendation for weekly fish consumption (women: up to 3 meals/week and children: up to 2 meals/week); A = 0: exceeding the dietary recommendation for weekly fish consumption. As, arsenic; BiB, Born in Bradford cohort; CI, confidence interval; Hg, mercury; KANC, Kaunas Cohort; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PFUnDA, perfluoroundecanoate; SumPCBs, summarized concentration of polychlorinated biphenyls;  $\Psi$ : marginal geometric mean difference between exposed and unexposed.

<sup>a</sup>Models are adjusted for all food groups and for cohort, maternal age, educational level, parity, prepregnancy body mass index, gestational weight gain, active smoking during pregnancy, and year of delivery. Women from KANC and BiB are not included.

<sup>b</sup>Models are adjusted for all food groups and for cohort, age, body mass index, Family Affluence Score, year of birth, and firstborn.

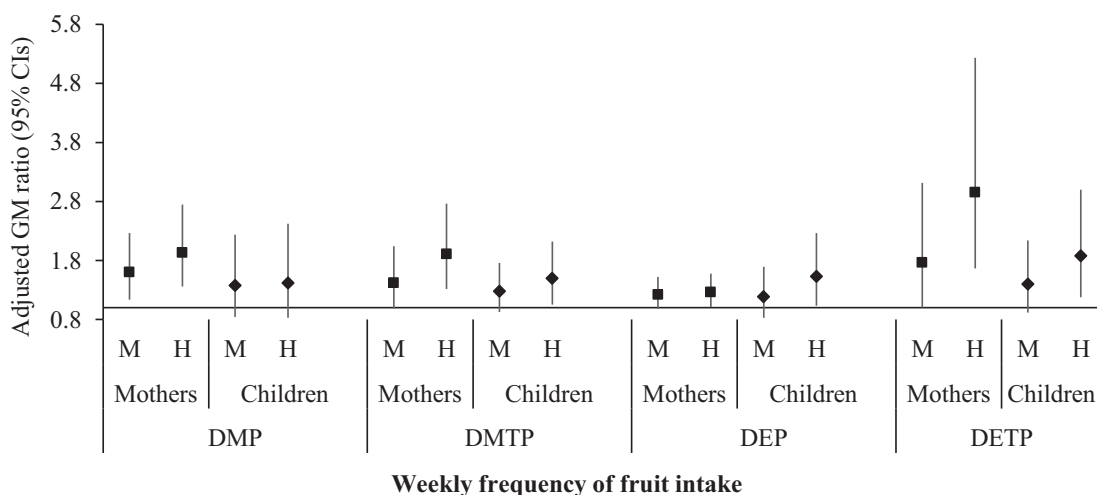
### Food Consumption and Measured Environmental Contaminants in Urine during Pregnancy and Childhood

During pregnancy, consumption of meat was associated with higher levels of BPA and lower levels of oxo-MiNP, and high consumption of fish was associated with higher levels of PRPA and BUPA (see Excel Table S8). Medium fish intake in childhood (1.5–3 times/week) was associated with higher urinary BPA, whereas higher fish intake (>3 times/week) was associated with lower OXBE levels. Finally, dairy consumption in the medium tertile (15–26 times/week) was associated with higher urinary BUPA levels. Only the associations between maternal meat intake and BPA remained significant after controlling for multiple comparisons.

Regarding foods of plant origin, fruit intake was consistently associated with higher levels of urinary OP metabolites in both populations, in a dose–response manner (Figure 4; see also Excel Tables S13 and S14). More specifically, high fruit intake during pregnancy (>18 times/week) was associated with more than 90% higher DMP and DMTP, 26% higher DEP, and a 295% increase in DETP urinary levels in pregnancy. Only associations with DEP did not remain significant after accounting for multiple comparisons. Although similar results were obtained when using the summarized OP concentrations as sumDAPs, sumDMs, and sumDEs, the effect estimates were attenuated (see Excel Table S15).

In children, only the highest fruit intake (>14 times/week) was associated with increased urinary levels of OP metabolites (Figure 4; see also Excel Table S14). The highest increase, by 88%, was observed for DETP, as for the pregnant women, followed by approximately 50% increase in DMTP and DEP. When OP metabolites were analyzed in sums, the effect estimates were significant although some were attenuated (see Excel Table S15).

Regarding other foods of plant origin, vegetable consumption was positively associated with PRPA and MEP urinary levels in pregnancy, as well as with BPA and TCS levels in childhood (see Excel Tables S13 and S14). Cereal consumption was negatively associated with BPA, DEHP metabolites, and OH-MiNP in pregnancy. In children, fruit intake was negatively associated with BPA, whereas cereal intake was positively associated with MBzP and negatively associated with OH-MiNP levels. None of these associations remained significant after controlling for multiple comparisons.



Mothers: Low (Reference): <10 times/week; Medium (M): 10-18 times/week; High: (H)>18 times/week.  
 Children: Low (Reference): <7 times/week; Medium (M): 7-14 times/week; High (H): >17 times/week.

**Figure 4.** Adjusted linear regression associations between weekly consumption of fruit and measured levels of organophosphate pesticide (OP) metabolites in maternal ( $n = 712\text{--}747$ ) and child urine ( $n = 1,286$ ). Maternal models are mutually adjusted for all food groups and for cohort, maternal age, educational level, parity, prepregnancy body mass index, gestational weight gain, active smoking during pregnancy, and year of delivery. Child models are mutually adjusted for all food groups and for cohort, age, body mass index, Family Affluence Score, year of birth, and firstborn. Women from KANC and BiB cohorts are not included. Corresponding numeric data are reported in Excel Tables S13 and S14. BiB, Born in Bradford cohort; CI, confidence interval; DEP, diethyl phosphate; DETP; diethyl thiophosphate; DMP, dimethyl phosphate; DMTP, dimethyl thiophosphate; GM, geometric mean; KANC, Kaunas Cohort.

### TMLE Analysis—Fruit Recommendations and Levels of Environmental Contaminants

Using TMLE analysis, we estimated that if the whole population of pregnant women were following the recommendation of consuming at least two servings of any fruit per day (2 fruits/d), it would result in 4.51  $\mu\text{g/g}$  creatinine higher DMP levels, compared with women consuming <2 fruits/d (Table 3). Under a

**Table 3.** Estimation of the marginal geometric mean difference in urinary organophosphate pesticide metabolites concentrations in mothers and children from a hypothetical intervention scenario of weekly fruit consumption.

Pollutants	Exposed/total ( $n/N$ )	Intervention scenario	
		$\Psi$	95% CI
<b>Women (pregnancy)<sup>a</sup></b>			
DMP ( $\mu\text{g/g}$ creatinine)	182/745	4.51	0.77, 8.26
DMTP ( $\mu\text{g/g}$ creatinine)	184/747	3.96	-0.23, 8.15
DEP ( $\mu\text{g/g}$ creatinine)	184/745	1.16	-0.57, 2.88
DETP ( $\mu\text{g/g}$ creatinine)	178/712	0.88	-0.01, 1.77
sumDAPs (nmol/g creatinine)	176/708	77.5	18.5, 136.5
sumDM (nmol/g creatinine)	176/708	63.0	9.1, 116.8
sumDE (nmol/g creatinine)	176/708	12.7	-2.2, 27.6
<b>Children (5–12 y of age)<sup>b</sup></b>			
DMP ( $\mu\text{g/g}$ creatinine)	184/1,286	0.55	-0.43, 1.52
DMTP ( $\mu\text{g/g}$ creatinine)	184/1,286	0.43	-1.63, 2.49
DEP ( $\mu\text{g/g}$ creatinine)	184/1,286	3.97	-2.76, 10.69
DETP ( $\mu\text{g/g}$ creatinine)	184/1,286	0.56	-0.03, 1.14
sumDAPs (nmol/g creatinine)	184/1,286	36.4	-11.9, 84.7
sumDM (nmol/g creatinine)	184/1,286	7.5	-11.8, 26.7
sumDE (nmol/g creatinine)	184/1,286	29.2	-14.9, 75.3

Intervention scenario: A = 1: following the dietary recommendation for daily fruit consumption (women and children: at least 2 servings of fruits/day); A = 0: not reaching the dietary recommendation for daily fruit consumption. BIB, Born in Bradford cohort; CI, confidence interval; DEP, diethyl phosphate; DETP; diethyl thiophosphate; DMP, dimethyl phosphate; DMTP, dimethyl thiophosphate; KANC, Kaunas Cohort; sumDAPs, total dialkylphosphate metabolites (DMP, DMTP, DEP, DETP); sumDE, total diethylphosphate metabolites (DEP and DETP); sumDM, total dimethylphosphate metabolites (DMP and DMTP);  $\Psi$ : marginal geometric mean difference between exposed and unexposed.

<sup>a</sup>Models are adjusted for all food groups and for cohort, maternal age, educational level, parity, prepregnancy body mass index, gestational weight gain, active smoking during pregnancy, and year of delivery. Women from KANC and BiB are not included.

<sup>b</sup>Models are adjusted for all food groups and for cohort, age, body mass index, Family Affluence Score, year of birth, and firstborn.

similar scenario, maternal DAPs would be 77.52 nmol/g creatinine higher, and maternal DMs, 62.95 nmol/g creatinine higher, than the levels of women consuming <2 fruits/d. Regarding the children, we found no significant increase of urinary OP metabolites related to the recommended fruit consumption.

### Organic Food Consumption in Childhood

Organic food consumption in childhood was associated with blood and urine levels of several environmental contaminants in children samples, in a dose-related manner (see Excel Table S16). Regarding positive associations, the largest increase was found for PBDEs, with 50% and 80% higher PBDE47 and PBDE153 levels associated with organic food consumption more than once per week, compared with no organic food consumption. Similarly, 28% higher PCBs and 9% higher PFOA levels were found. Regarding negative associations, the largest effect estimate was found for DEP, with 38% lower levels reported for consumers of organic food of >1 time/week compared with no organic food consumers. In addition, organic food consumption >1 time/week was associated with 8% lower Pb, 26% lower MEP, and 11% lower DEHP metabolites.

### Discussion

In this international, multicenter study, we systematically analyzed the dietary predictors of exposure to a wide range of environmental contaminants in pregnancy and childhood. We found that fish consumption was positively associated with exposure to multiple contaminants, including PFASs, As, and Hg. Using TMLE analysis, we estimated that adherence to the dietary recommendations (pregnant women:  $\leq 3$  servings/week, children  $\leq 2$  servings/week) for fish intake would result in lower exposure to PFASs, As, and Hg compared with those exceeding these recommendation. Fruit consumption was associated with increased levels of urinary OP metabolites concentrations in both pregnant women and children. Using TMLE analysis, we found that consuming more than 2 fruits/d could increase the exposure of pregnant women to OPs, compared with lower fruit intake.

Previous research has showed that fish consumption is a major source of exposure to PFASs for several adult populations worldwide (Christensen et al. 2017; Domingo and Nadal 2017; Ericson et al. 2008; Haug et al. 2010), including pregnant women and women of reproductive age (Berg et al. 2014; Brantsæter et al. 2013; Jain 2013; Manzano-Salgado et al. 2016). Nevertheless, studies in children have failed to find an association between fish intake and blood PFASs, attributing the absence of association to lower fish intake in children than in adults (Jain 2018; Wu et al. 2015). In the present study, fish consumption was positively associated with maternal PFUnDA levels, in a dose–response manner, whereas in children only high fish intake (>3 times/week) were significantly associated with increased PFUnDA. In addition, we found that the association between oily fish consumption and PFUnDA in children was stronger than for white fish. Fish consumption was identified as a major contributor to PFUnDA exposure in a study analyzing foods from European markets (Klenow et al. 2013). The higher bioaccumulation potential in the aquatic food webs of long-chain PFASs (C9–C12), like PFUnDA, compared with the short-chain PFASs, as well as the nondecreasing environmental levels of PFUnDA, might explain why mainly PFUnDA was consistently associated with fish intake in both pregnant women and children (Bjerregaard-Olesen et al. 2016; Ng and Hungerbühler 2014). PFNA and PFOS levels were also positively associated with fish intake in children, whereas a similar increase was observed for medium and high intake. This might be explained by differences in the choices of specific fish species, meaning that the children in the high fish group chose fish that did not further contribute to PFOS and PFNA exposure. However, the analysis of oily and white fish consumption showed similar associations for PFNA and PFOS.

The strongest associations were found between fish consumption and blood levels of Hg and As in both pregnant women and children. Intake in the highest tertile ( $\geq 4$  times/week for pregnant women and  $\geq 3$  times/week for children) were associated with two- and five-times higher blood Hg and As levels. Fish consumption is an established source of human exposure to these toxic elements (Awata et al. 2017; Birgisdottir et al. 2013; Brantsæter et al. 2010; EFSA 2012a; Jin et al. 2014; Miklavčič et al. 2013; Outzen et al. 2015; Veyhe et al. 2015), even in infants (Choi et al. 2017). Although fish and other seafood can be high in total As, the contribution of the more toxic inorganic As is only 2–3.5% of the total As (EFSA 2009, 2014). Nevertheless, there are large knowledge gaps regarding the toxicological potential of individual organic As species, such as arsenosugars and arsenolipids, for which seafood is a major source of exposure (Molin et al. 2017; Taylor et al. 2017). Unfortunately, the exposure levels to As species, within the organic or inorganic fraction, was not available in our study. On the other hand, the more toxic methyl mercury contributes up to 100% of the total Hg in fish (EFSA 2015a).

By applying TMLE analysis, we found that diets that did not exceed the recommended fish intake were associated with significantly lower PFNA, As, and Hg exposure in pregnant women and lower PFUnDA, PFOS, As, and Hg exposure in children. Overall, the exposure levels of the assessed environmental contaminants in our study population were lower or within the previously reported ranges for European and American populations (Haug et al. 2018). Haug et al. (2018) assessed the exposure levels of the HELIX population by human biomonitoring (HBM) cutoffs based on human health risk (The Human Biomonitoring Commission, Germany, 2017). For blood Hg, 72 women and 31 children exceeded the cutoff (5  $\mu\text{g/L}$ ), indicating some health risk related to the exposure. Similar cutoffs have been used to assess levels of concern in the National Health and Nutrition Examination Survey (NHANES) population (5.8  $\mu\text{g/L}$ ) (Mahaffey et al. 2009). According to our

TMLE findings, fish consumption within the recommended levels, one fourth of the women and one third of the children who were above the cutoff will be below the cutoff. Not exceeding the recommended fish consumption could result in a reduction of maternal serum Hg and PFNA and child Hg concentrations in levels below the 25th percentile of the NHANES survey levels for the respective population groups (Jain and Ducatman 2019; Schober et al. 2003). Nevertheless, we note that these interpretations and extrapolations of our effect estimates need to be interpreted with caution. Our study population reported more frequent fish consumption than what has been previously reported in large population-based studies (Garaulet et al. 2011; Papanikolaou et al. 2014; Stratakis et al. 2017; Tognon et al. 2014). More than half of the included pregnant women and children were consuming fish up to the recommendation (see Excel Table S17). Overall, then, in a population of women of reproductive age and young children with relatively high fish intake, not exceeding the recommended weekly servings could effectively reduce their exposure as well as their child's prenatal and postnatal exposure to As, Hg, and some PFASs, without losing the health benefits associated with fish consumption (EFSA 2015a).

We found a positive association between fruit intake and concentrations of OP metabolites in urine for both pregnant women and children. Pesticides commonly used all over Europe and in other countries worldwide, such as chlorpyrifos, can contribute to such exposures, monitored as increased urinary levels of dialkyl phosphates metabolites (Cequier et al. 2017). Fruit consumption has been consistently related to higher exposure to OPs in adults and children (Berman et al. 2013; Cequier et al. 2017; Lewis et al. 2015; McKelvey et al. 2013; Muñoz-Quezada et al. 2012; Osaka et al. 2016; Sokoloff et al. 2016). In addition, organic food consumption in childhood was associated with lower levels of OP metabolites (i.e., DEP). This is line with several current studies, including an intervention study in Californian children and a randomized cross-over study in Australian adults (Berman et al. 2016; Bradman et al. 2015; Oates et al. 2014). Given the lower levels of pesticide residues in organic food compared with conventionally grown food (EFSA 2015b), organic food consumption may be an effective way to reduce the dietary exposure to OPs in European populations.

On the other hand, our TMLE analysis showed that adherence to the recommended fruit intake would result in higher OP exposure and that was significant for pregnant women only. In our study population, a fourth of the included women and 14% of the included children adhered to the fruit recommendation (see Excel Table S17) (WHO 2000). Hence, the diet quality of women of reproductive age and children can be improved by increasing the intake of fruit and vegetables and this is advisable. Nevertheless, a future intervention aiming to increase fruit intake in these population groups, could result in increased exposure to OPs, especially in women, consequently exposing the developing fetus to these chemicals. High prenatal OP exposure is of concern because it has been linked to restricted fetal growth and reduced neurodevelopment in children, including autism spectrum disorders (González-Alzaga et al. 2014; Harley et al. 2011; Naksen et al. 2015; Rauch et al. 2012; Sagiv et al. 2018). However, supporting the choice of organically over conventionally grown fruits might be an effective way to increase the dietary quality of a population and the related beneficial health effects without increasing the possible risks related to pesticide exposure.

Negative associations between food intake and levels of environmental contaminants are more challenging to interpret and are scarcely reported. Nevertheless, some associations may be explained by well-known biological interactions between essential nutrients and toxic elements. High meat intake was associated with a decrease in blood Cd levels in nonsmoking women and all



children. A similar finding was reported in nonsmoking women from 16 European countries (Berglund et al. 2015). In a status of low iron, the uptake and absorption of divalent metals, including Cd, is higher, resulting in increased Cd blood levels (Meltzer et al. 2010). Hence, meat eaters might have better iron status, resulting in lower uptake of Cd and lower concentrations in blood. Unfortunately, we could not explore this in more details because iron status assessment was not available in our study. In addition, we observed that dairy consumption was associated with lower Pb and Hg levels in both pregnant women and children. Pb absorption is enhanced under calcium (Ca) deficiency, whereas Pb can interfere the metabolism of Ca and disrupt the intercellular Ca homeostasis and functions (Kwong et al. 2004; Talpur et al. 2018). Hence, high dairy intake, resulting in high Ca intake, might reduce Pb absorption and its related neurotoxic effects (Gomes et al. 2017). Even though the Ca-Pb interaction is one of the most-studied essential nutrient–toxic element interactions, little evidence exists between dairy intake and Pb blood levels, especially in children. To our knowledge, only one study, of 5- to 8-y-old children ( $n = 300$ ) from Uruguay, found a negative trend between dairy consumption, mainly yogurt, and blood Pb concentrations, and between estimated Ca intake from diet and blood Pb (Kordas et al. 2018). Calcium homeostasis is also a target of Hg, along with Cd and Pb, and *in vitro* studies have shown that the toxic metals can disturb the intracellular Ca homeostasis and act on Ca-mediated cell functions (Hechtenberg and Beyersmann 1991; Kirk et al. 2003).

Fewer and less consistent associations were observed between food intake and urinary levels of nonpersistent contaminants. Fish and vegetable intake were identified as potential emerging dietary sources OXBE, TCS, and parabens. Some parabens are permitted to be applied on food in the European Union, whereas besides such uses, parabens, along with OXBE and TCS, are widely used in cosmetics, personal care products, and pharmaceuticals as antimicrobial preservatives (Andersen 2008; Dann and Hontela 2011; DiNardo and Downs 2018; EFSA 2004; Sakhi et al. 2018). Common to all the abovementioned environmental phenols, no dietary exposure sources have been identified (Sakhi et al. 2018), whereas their widespread use could result to the contamination of the aquatic biota and crops via wastewater and sewage effluent contamination (Dann and Hontela 2011; van Wijnen et al. 2018). For example, OXBE has been found globally in water, soil, sediments, sludge, and biota and can bioaccumulate in fish (Balmer et al. 2005; Brausch and Rand 2011; Gago-Ferrero et al. 2012). Taken together, our results suggest that vegetables and fish consumption might be an emerging source of human dietary exposure to environmental phenols commonly used in personal care products including parabens, OXBE and TCS. We acknowledge that the large contribution of nondietary exposure sources to several nonpersistent compounds might explain the weaker and fewer associations observed. In addition, several co-exposures from personal care products, rather than diet itself, might explain our findings.

### Strengths and Limitations

One of the main strengths of our study is the inclusion of biomarkers for a large number of contaminants from diverse groups of chemicals, including persistent and nonpersistent environmental chemicals. The large sample size as well as the focus on vulnerable groups, namely pregnant women and young children, are strengths of our study. Single-country studies with similar aims as ours have generated inconsistent results, even for well-known dietary exposures, resulting from many factors, including sample size and low variability in food intake. Small differences in the predictor variables across the population (food intake) might contribute to a lower

explained variation of the outcome (biomarkers of exposure to contaminants), even though diet still would be the main contributor to exposure (Pearce 2011). Hence, a multicountry design, with a wide span from north to south Europe, can increase the variation in both food intake and measured biomarkers, as well as the generalizability of the findings across Europe. Nevertheless, we acknowledge that by pooling data from different countries, country-specific dietary habits and differences in food contamination levels between countries are not fully acknowledged. Hence, the extrapolation of our findings for each country needs careful interpretation. In addition, the use of TMLE to test the effect on dietary recommendations on exposure to environmental chemicals is a strength of our study. Such methodologies can be used to better inform future public health policies.

On the other hand, a limitation related to this design is the different FFQs used for the assessment of maternal diet. However, in children, an identical FFQ was applied in all centers. The use of FFQs might not be an appropriate dietary assessment method, especially for exposure to contaminants with short half-lives, given that FFQs are made to capture long-term dietary habits that most probably do not reflect day-to-day variations (Papadopoulou et al. 2016). Estimated energy intake was not available in our study and is not included as a covariate in our models given that it is widely recommended for studies exploring diet–health associations (Rhee et al. 2014). Due to the multicountry design, we considered that energy calculations based on country-specific nutrition composition tables would induce bias in our estimates, rather than reduce it. On the other hand, body weight is an independent and objective marker that is strongly associated with energy expenditure and it has been taken into account in our analyses. Although in some respect, the HELIX cohorts were ideally suited for pooling because of similar data collection tools, there was also variability in confounders among the six cohorts, described in detail by Maitre et al. (2018). Thus, although our models are adjusted for cohort, maternal education, and family affluence, we cannot rule out the possibility of bias in our effect estimates due to residual confounding due to socioeconomic position. Montazeri et al. (2019) have reported and discussed the socioeconomic disparities in exposure to environmental contaminants in the HELIX population and in light of our results, such socioeconomic disparities can be partially explained by dietary behavior. Finally, for the TMLE analysis, although we used clinically based international dietary advice to estimate effects on blood and urinary biomarkers of contaminants, we acknowledge that country-specific dietary advice may exist, including detailed consumption advice for specific fish species (Oken et al. 2003; Oken 2015).

### Conclusion

In conclusion, high fish consumption during the critical developmental periods of pregnancy and early childhood was associated with higher concentrations of PFASs, As, and Hg in biological samples collected from pregnant women and children. These compounds have certain or probable health effects following early life exposures. Our findings suggest that exposure to these persistent compounds could be reduced by changes in dietary behaviors, such as not exceeding the current dietary recommendation for fish. In addition, high fruit consumption was related to increased exposure to pesticides, whereas the choice of organic over conventionally grown fruits contributed to lower exposures of pesticide residues. Overall, given that foods are a vessel of essential nutrients as well as toxic environmental contaminants, potential dietary interventions, focused on fruit and fish intake, may consider also accounting for the simultaneous increase in PFAS, As, and Hg exposure and balance the benefits of a healthy diet with the harms of exposure to toxic environmental chemicals.

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