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PFAS levels and exposure determinants in sensitive population groups

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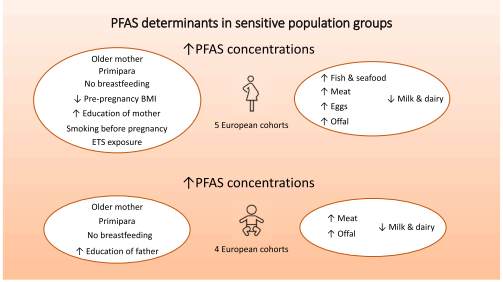
HIGHLIGHTS

- High detection rates of PFAS were observed in the blood of pregnant women and newborns.
- Higher educational level of father was associated with higher PFAS in cord blood.
- Dietary factors were associated with PFAS concentrations in pregnant women.
- Daily milk and dairy consumption was associated with lower PFAS in both populations.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Per- and polyfluoroalkyl substances (PFAS) are persistent organic pollutants. The first exposure to PFAS occurs *in utero*, after birth it continues via breast milk, food intake, environment, and consumer products

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that contain these chemicals. Our aim was to identify determinants of PFAS concentrations in sensitive population subgroups– pregnant women and newborns.

Methods: Nine European birth cohorts provided exposure data on PFAS in pregnant women (INMA-Gipuzkoa, Sabadell, Valencia, ELFE and MoBa; total N = 5897) or newborns (3xG study, FLEHS 2, FLEHS 3 and PRENATAL; total N = 940). PFOS, PFOA, PFHxS and PFNA concentrations were measured in maternal or cord blood, depending on the cohort (FLEHS 2 measured only PFOS and PFOA). PFAS concentrations were analysed according to maternal characteristics (age, BMI, parity, previous breastfeeding, smoking, and food consumption during pregnancy) and parental educational level. The association between potential determinants and PFAS concentrations was evaluated using multiple linear regression models.

Results: We observed significant variations in PFAS concentrations among cohorts. Higher PFAS concentrations were associated with higher maternal age, primipara birth, and educational level, both for maternal blood and cord blood. Higher PFAS concentrations in maternal blood were associated with higher consumption of fish and seafood, meat, offal and eggs. In cord blood, higher PFHxS concentrations were associated with daily meat consumption and higher PFNA with offal consumption. Daily milk and dairy consumption were associated with lower concentrations of PFAS in both, pregnant women and newborns.

Conclusion: High detection rates of the four most abundant PFAS demonstrate ubiquitous exposure of sensitive populations, which is of concern. This study identified several determinants of PFAS exposure in pregnant women and newborns, including dietary factors, and these findings can be used for proposing measures to reduce PFAS exposure, particularly from dietary sources.

Credit author statement

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1. Introduction

Per- and polyfluoroalkyl substances (PFAS) belong to the group of persistent organic pollutants (Stockholm Convention on persistent organic pollutants, 2009). First exposure to these substances occurs *in utero*. After birth exposure continues via breast milk and the environment, as these chemicals have been found in air, dust, surface and ground water, soil and sediment all around the world, and thus end up amongst others in our food and drinking water (ATSDR, 2018). Despite the regulation of the two most widespread PFAS, perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), serum concentrations of these legacy PFAS in humans are decreasing slowly, due to their persistence in the environment (EEA – European Environment Agency, 2019). On the other hand, many novel PFAS are emerging as alternatives to the restricted PFAS and could also be present in human organisms (Brase et al., 2021).

Dietary exposure has been suggested as the main route of exposure to PFAS. Besides environmentally-contaminated food, such as fish, meat, offal, eggs, fruit and fruit products (EFSA, 2020), PFAS can migrate into food from food packaging (e.g., PFOA-containing paper or cardboard) or from PTFE-coated cookware (ATSDR, 2018). Another route of exposure in regions contaminated by PFAS is ingestion of drinking water contaminated by PFAS (ATSDR, 2018). Breast milk is the dominant exposure source for breastfed infants. Other possible PFAS exposure pathways include ingestion of house dust, hand-to-mouth transfer from treated carpets, clothes and upholstery, inhalation of indoor and ambient air, inhalation of impregnation spray aerosols and dermal exposure from wearing treated clothes and contact with personal care products (Thépaut et al., 2021; Trudel et al., 2008).

Pregnant women and newborns represent sensitive subgroups of the population (ATSDR, 2018). PFAS bioaccumulate in the body of a woman throughout her life and during pregnancy they can be transferred to the fetus. PFOS and PFOA have been detected in 99–100% of cord blood samples in several studies (Apelberg et al., 2007; Cariou et al., 2015; Fei et al., 2007; Manzano-Salgado et al., 2015; Ode et al., 2013; Richterová et al., 2018), which indicates that PFAS can cross the placental barrier, causing the exposure of fetus in the sensitive period of *in utero* development.

Prenatal exposure to PFAS might have long-lasting health consequences, as exposure to PFOS and PFOA has been previously associated with various health outcomes in childhood and adolescence. Maternal PFOS and PFOA concentration was associated with increased body weight, BMI, and body fat in children (Braun et al., 2016; Maisonet et al., 2012) and with higher total and LDL cholesterol (Frisbee et al., 2010; Geiger et al., 2014; Maisonet et al., 2015; Zeng et al., 2015). PFAS may also affect antibody response to vaccination and asthma and infections (Abraham et al., 2020; Dalsager et al., 2016; Dong et al., 2013; Grandjean et al., 2012; Stein et al., 2016). There is some evidence of an association between PFAS and alteration of thyroid function (Kim et al., 2011a, 2016; Lopez-Espinosa et al., 2012), decreased glomerular filtration rate (Watkins et al., 2013), behavioral and learning problems (Stein and Savitz, 2011; Vuong et al., 2016) and attention-deficit/hyperactivity disorder (Hoffman et al., 2010; Liew et al., 2015; Stein and Savitz, 2011; Strøm et al., 2014). Current evidence from studies on PFAS and the onset of puberty suggests that PFAS may have an influence on delayed menarche, decreased serum estradiol in girls and testosterone in boys (Kristensen et al., 2013; Lopez-Espinosa et al., 2011).

To reduce exposure to PFAS, it is important to know which external factors contribute to body burden. Knowledge of determinants of PFAS exposure can also help to develop appropriate prevention strategies and to identify population groups at risk of higher PFAS exposure. Some determinants of PFAS exposure, such as parity, breastfeeding, or fish consumption, are well documented (Kato et al., 2014; Park et al., 2019; Sagiv et al., 2015; Christensen et al., 2017; Jain, 2014), while less is known about other factors that might contribute to PFAS concentrations in human. PFAS have been detected in various food items, especially animal-based products (EFSA, 2020). However, specific information on the effects of consumption of these products on PFAS blood concentrations is lacking.

Previous studies analysed a limited number of PFAS determinants at

a national level or in areas contaminated by PFAS. Although determinants of PFAS exposure may differ among European countries as environment, lifestyle and food habits or implementation of chemical policies may differ, some PFAS determinants might be common on the European or global level. Pregnant women and newborns are particularly vulnerable to the adverse health effects of PFAS exposure and a joint European strategy is needed to protect these sensitive population groups. This study aims to investigate determinants of PFAS exposure common for the population of European pregnant women and newborns using pooled data from nine European cohorts to provide evidence for targeted strategies for reduction of PFAS exposure on a European level.

2. Methods

2.1. Population

This study was conducted within the European Human Biomonitoring Initiative HBM4EU (2017). We identified 19 European cohorts with data on PFAS concentrations measured either in the blood of pregnant women or in cord blood. In our study, we included cohorts with available measurements of at least PFOS and PFOA concentrations, and applied exclusion criteria, by which cohorts with small sample size ($n < 120$), as well as cohorts with exposure data collected before the year 2000 were excluded from the study. In total 9 cohorts signed bilateral contract for sharing their data. All studies had obtained ethical approval and all participants had signed informed consents. The cohort studies were divided into 2 groups based on the type of population. The first group (named "Study Population Pregnant Women") consisted of 5 cohorts with PFAS concentrations measured in pregnant women between 2003 and 2011 (French Longitudinal Study of Children – ELFE (Charles et al., 2020); Environment and Childhood Project – INMA -Gipuzkoa, Sabadell, Valencia (Guxens et al., 2012); The Norwegian Mother, Father and Child Cohort Study - MOBA (Magnus et al., 2016)), with the total number of participants $n = 5897$. The second group (named "Study Population Newborns") consisted of 4 cohorts with PFAS concentrations measured in cord blood between 2008 and 2014 (a regional birth cohort: 3xG (https://studie3xg.be/nl); Flemish Environment and Health Study - FLEHS 2 and FLEHS 3 (Colles et al., 2020); Prospective cohort study of developmental origins of adult diseases in the Slovak population - PRENATAL (Richterová et al., 2018)), with a total number of participants $n = 940$. Some studies were representative of a country (ELFE) or a region (INMA cohorts, FLEHS 2 and FLEHS 3) and others were recruited or selected for specific research purposes (MoBa sub-populations, 3xG, PRENATAL). General characteristics of the participating cohorts are available in the Supplementary material (Supplementary Tables S1 and S2).

2.2. Exposure assessment

Blood samples of pregnant women were obtained during the examination in the first (INMA cohorts), second (MoBa) or third (ELFE) trimesters and cord blood samples were taken at delivery (3xG, FLEHS 2, FLEHS 3, PRENATAL). Concentrations of the four most abundant PFAS: PFOS, PFOA, perfluorohexanesulfonic acid (PFHxS) and perfluorononanoic acid (PFNA) were analysed in maternal plasma (4 cohorts) or serum (1 cohort) and in cord blood plasma (3 cohorts) or serum (1 cohort) (Table 1). In the FLEHS 2 cohort, PFHxS and PFNA were not analysed. Details on chemical analyses in each cohort have been described elsewhere (Colles et al., 2020; Dereumeaux et al., 2016; Haug et al., 2009; Manzano-Salgado et al., 2015; Richterová et al., 2018; Schoeters et al., 2022).

2.3. Maternal and newborn characteristics

The influence of maternal and newborn characteristics on PFAS concentrations was examined together with various socio-demographic and lifestyle factors. The information on these variables was obtained from clinical records and from questionnaires, either self-administered or administered by trained personnel, depending on the cohort. Each study was asked to provide data harmonised according to a codebook developed within the HBM4EU project. The maternal characteristics included were: age at delivery (for cord blood analysis) and age at sampling (for pregnant women blood analysis) in years, parity (primipara yes/no) and previous breastfeeding (yes/no, and duration in weeks only in newborns) of pregnant women and mothers of newborns, pre-pregnancy body mass index (BMI) ($\leq$25 vs. >25 kg/m^2) and lifestyle factors: smoking before (yes/no) and during pregnancy (yes/no) and exposure to environmental tobacco smoke (ETS) during pregnancy (yes/no). The newborn variables were: sex and gestational age (weeks). Information on the educational level of both the mothers and fathers of newborns, and the educational level of pregnant women were categorised based on The International Standard Classification of Education (International, 2012): low education (ISCED 0–2), medium education (ISCED 3–4), high education (ISCED $\geq$5).

2.4. Dietary factors

Besides the maternal and newborn characteristics, we analysed

Table 1
General information on sampling by cohort.

Cohort	Country	Population	N	Sampling year	Matrix	Biomarkers	Method	LOQ µg/L
INMA-Gipuzkoa INMA-Sabadell INMA-Valencia	Spain	Pregnant women	1243	2003–2008	Blood - plasma	PFOS, PFOA, PFHxS, PFNA	column-switching HPLC-MS/MS	0.2 (0.1 for PFNA)
MOBA	Norway	Pregnant women	4413	2003–2009	Blood - plasma	PFOS, PFOA, PFHxS, PFNA	column-switching HPLC-MS/MS	0.05
ELFE	France	Pregnant women	241	2011	Blood - serum	PFOS, PFOA, PFHxS, PFNA	LC-HR-MS	0.15
FLEHS 2	Belgium	Newborns	220	2008–2009	Cord blood - plasma	PFOS, PFOA	HPLC-MS/MS	0.3
3xG	Belgium	Newborns	128	2010–2012	Cord blood - plasma	PFOS, PFOA, PFHxS, PFNA	HPLC-MS/MS	0.2
PRENATAL	Slovakia	Newborns	323	2010–2012	Cord blood - serum	PFOS, PFOA, PFHxS, PFNA	U-HPLC–MS/MS	0.2
FLEHS 3	Belgium	Newborns	269	2013–2014	Cord blood - plasma	PFOS, PFOA, PFHxS, PFNA	HPLC-MS/MS	0.2

LC-HR-MS: Liquid chromatography–high resolution–mass spectrometry; HPLC-MS/MS: High-performance liquid chromatography with tandem mass spectrometry; LOQ: Limit of quantification.
PFOS: Perfluorooctanesulfonic acid; PFOA: Perfluorooctanoic acid; PFHxS: Perfluorohexanesulfonic acid; PFNA: Perfluorononanoic acid.

dietary factors as potential determinants of PFAS exposure in pregnancy as well. In each cohort, food frequency questionnaires (FFQ) were used to obtain information about the frequency of consumption of different types of food during pregnancy. These data were available for both study populations: pregnant women and newborns. Cohorts were asked for additional data post-harmonisation to deal with inconsistency among the cohorts in food items used in the questions and also in categories of consumption frequency. Data on food consumption were grouped into 5 variables: seafood and fish (including freshwater and sea fish when available), meat, offal, milk and dairy products, and eggs. The frequency of consumption for each variable was divided into 4 categories: never, <1x/week, at least 1x/week but not daily, and daily. Since we observed a low percentage of subjects in some categories of food consumption (Table 2), we decided to dichotomise dietary variables based on the proportion of subjects in each category of frequency. Seafood and fish consumption and egg consumption was categorised as <1x/week or at least 1x/week, meat and milk and dairy consumption was categorised as not daily or daily and offal consumption was categorised as never or sometimes. No data on offal consumption were available in FLEHS 2 cohort. Data on the main source of drinking water were missing in MoBa, 3xG and FLEHS 2; thus this variable was not included in the multiple linear regression models.

2.5. Statistical analysis

All statistical analyses were performed using STATA 13.0. Concentrations below LOQ were checked in each cohort separately and then imputed based on the percentage of values < LOQ in the cohort: by LOQ/$\sqrt{2}$ if <20% values were below LOQ or by LOQ/2 if ≥ 20% values were below LOQ (Park et al., 2010). The distribution of PFAS concentrations was right-skewed and concentrations were log-transformed using natural logarithm. Associations between each chemical substance and each variable, as well as associations between covariates, were examined by linear regression and by chi-square test. Based on directed acyclic graphs (DAG) (Greenland et al., 1999) and the significance of variables in bivariate analyses ($p \leq 0.200$), variables were included in multiple linear regression (MLR) and then the stepwise selection method was used to remove non-significant variables one by one, starting with the least significant. We also added those variables that were not significant in bivariate analysis one by one into the MLR model as a sensitivity analysis. Selection of the best model was based on the adjusted R^2 and Akaike's information criterion (AIC) and a different final model was chosen for each of the four PFAS. K-fold cross-validation (k = 10) was applied as a data splitting method for model validation (Xu and Goodacre, 2018). The variable cohort was included as a fixed factor in the final models for all PFAS (except PFNA in newborns). Beta coefficients presented in Figs. 1 and 2 were exponentiated (estimate = e^{β}) to transfer the estimates from ln-scale. The effect estimates (Fig. 3, Supplementary Tables S5 and S6) represent proportional changes (in %) in PFAS concentrations in each category of variable compared to the reference category. For the variable cohort, we used as a reference category the cohort with the most recent sample collection – FLEHS 3 for newborns and ELFE for pregnant women.

In newborns, the educational level of the mother and the educational level of the father were used in the multiple linear regression analyses. As a sensitivity analysis, the highest educational level of the household was included in the models instead of the educational level of the mother and father. However, the highest educational level of the household was not significantly associated with PFAS concentrations, while the educational level of the father appeared to be a strong determinant of all PFAS concentrations in cord blood. In pregnant women, the variable "smoke exposure in pregnancy", which combines information about smoking in pregnancy and exposure to ETS during pregnancy, was used as a sensitivity analysis in the MLR model instead of the two variables, smoking during pregnancy and ETS exposure in pregnancy, but we did not observe any improvement in the model. Moreover, the inclusion/exclusion of outliers did not change the models and we decided to keep outliers in the models. Since there is a disproportion in the size of cohorts of pregnant women, with the MoBa cohort being the largest (n = 4413), we examined bivariate associations between potential determinants and PFAS concentrations in each cohort separately and the selected MLR model was applied on the MoBa dataset to check if the results could be driven by MoBa cohort solely.

Table 2
General characteristics of the study population.

	Study population NEWBORNS (n = 940)		Study population PREGNANT WOMEN (n = 5897)	
	% or mean ± SD	missing %	% or mean ± SD	missing %
Characteristics of newborn				
Sex		1.0	–	–
Boys	52.1			
Girls	47.9			
Gestational age (weeks)	39.4 ± 1.3	1.9		
Characteristics of mother				
Maternal age				
At delivery	30.0 ± 4.3	4.0	30.2 ± 4.5	0.2
At sampling (years)	–		30.1 ± 4.5	0.1
Primipara (yes)	43.7	2.9	58.5	1.8
Previous breastfeeding (yes)	46.3	6.4	37.0	2.5
- Duration (weeks)	30.7 ± 37.9	7.3	–	–
Pre-pregnancy BMI (>25 kg/m^2)	26.5	1.4	33.6	2.6
Maternal smoking				
Before pregnancy (yes)	25.2	16.5	36.7	0.9
During pregnancy (yes)	9.8	5.1	14.2	1.1
ETS during pregnancy (yes)	43.8	19.3	24.3	1.1
Educational level				
Mother		3.6		2.5
Low (ISCED 0–2)	12.0		10.9	
Medium (ISCED 3–4)	36.6		30.8	
High (ISCED ≥5)	51.4		58.3	
Father		5.9	–	–
Low (ISCED 0–2)	20.3			
Medium (ISCED 3–4)	41.9			
High (ISCED ≥5)	37.8			
Food consumption				
Fish		3.1		5.9
Never	8.6		5.7	
<1x/week	39.0		20.3	
At least 1x/week but not daily	48.0		68.3	
Daily	4.4		5.7	
Meat		1.0		5.8
Never	2.0		0.8	
<1x/week	8.0		0.6	
At least 1x/week but not daily	45.3		29.6	
Daily	44.7		69.0	
Offal		28.8		5.9
Never	72.2		37.0	
<1x/week	27.1		34.7	
At least 1x/week but not daily	0.7		26.8	
Daily	0.0		1.5	
Milk and dairy products		1.3		5.6
Never	0.1		1.0	
<1x/week	5.2		0.8	
At least 1x/week but not daily	22.2		11.5	
Daily	72.5		86.7	
Eggs		1.8		5.8
Never	2.2		4.0	
<1x/week	34.8		24.1	
At least 1x/week but not daily	61.0		69.8	
Daily	2.0		2.1	

SD: Standard deviation; BMI: Body mass index; ISCED: The International Standard Classification of Education.

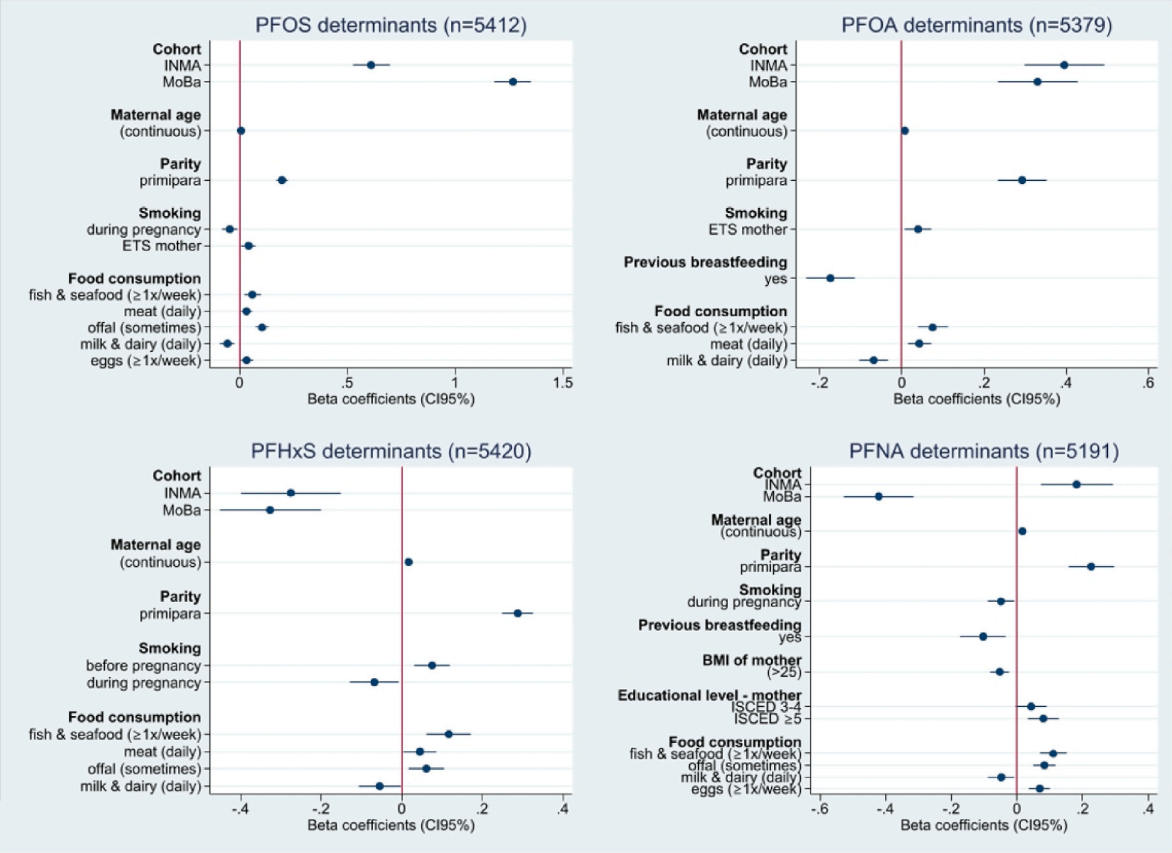

Fig. 1. Associations between PFAS concentrations in blood of pregnant women (ln-transformed) and study population characteristics
Reference category: cohort – ELFE; parity – multipara; smoking before and during pregnancy and ETS – no; educational level of father – ISCED 1–2; fish & seafood consumption – less than 1x/week; meat consumption – less than 1x/day; offal consumption – never; milk & dairy consumption – less than 1x/day; egg consumption – less than 1x/week.

As a sensitivity analysis, missing data on variables significant at least in one model (maternal age, breastfeeding, parity, smoking and ETS exposure in pregnancy, educational level of father, and dietary variables) were imputed by multiple imputation model based on cohort and educational level of the mother. The number of imputations was selected according to the percentage of missing values (newborns - 30 imputations, pregnant women - 10 imputations).

3. Results

The general characteristics of both study populations are described in Table 2. Briefly, the mean age of mothers at delivery in the newborn study population and the age of pregnant women at sampling was 30 years. In the pregnant women study population, there was a higher percentage of primiparas (58.5%), overweight or obese women (33.6%) and smokers before (36.7%) and during pregnancy (14.2%) compared to mothers of newborns (43.7% primiparas; 26.5% obese or overweight; 25.2% smokers before and 9.8% during pregnancy). In the newborn study population, 46.3% of mothers have breastfed previous children and the mean duration of previous breastfeeding was 30 weeks. Almost half of the mothers of newborns were exposed to ETS during pregnancy (43.8%), while only one quarter of pregnant women answered that they were exposed to ETS during pregnancy (24.3%). We observed disparities in the proportion of women in each category of educational level among cohorts (Supplementary Tables S1 and S2). Such disparities were also observed in categories of parity, especially among cohorts of pregnant women (22.6% primiparas in ELFE vs 56.1 and 60.4% in INMA and MoBa respectively; Supplementary Table S1). Food consumption varied strongly between the cohorts, even within the same country. For example, daily consumption of meat in the Flemish cohorts varied from 14.9% in 3xG cohort to 67.3% and 88.1% in FLEHS 3 and FLEHS 2, respectively (Supplementary Table S2). Regarding dietary variables, almost half of the mothers of newborns and around two thirds of pregnant women ate fish or seafood at least once a week but not daily (Table 1). 44.7% of mothers of newborns and 69% of pregnant women consumed meat daily; on the other hand 72.2% of mothers never consumed offal. Most of the mothers of newborns and pregnant women consumed milk and dairy products every day (72.5% and 86.7%, respectively). Consumption of eggs was similar in both, mothers of newborns and pregnant women, with the highest percentage of women consuming eggs at least once a week but not daily (61.0% of mothers and 69.8% of pregnant women) (Table 2).

Among all four PFAS analysed, the highest median concentration in blood of pregnant women was observed for PFOS (10.87 μg/L), followed by PFOA (2.34 μg/L), PFHxS (0.63 μg/L) and PFNA (0.45 μg/L). In cord blood, the highest median concentration was observed for PFOA (1.27 μg/L), followed by PFOS (0.99 μg/L), PFNA (0.22 μg/L) and PFHxS (0.15 μg/L) (Table 3). Concentrations of all four PFAS showed strong positive correlations (data not shown). PFAS concentrations in blood of pregnant women and in cord blood by cohort are shown in the Supplementary material (Supplementary Figs. S1 and S2). The median concentrations of the four PFAS in blood of pregnant women and cord blood by socio-demographic characteristics are described in Supplementary material (Supplementary Tables S3 and S4).

The strong association between the variable cohort and PFAS concentrations observed in bivariate analysis remained significant in multivariable analysis for all PFAS except for PFNA in newborns (Figs. 1 and 2). Primipara birth was associated with a significantly higher

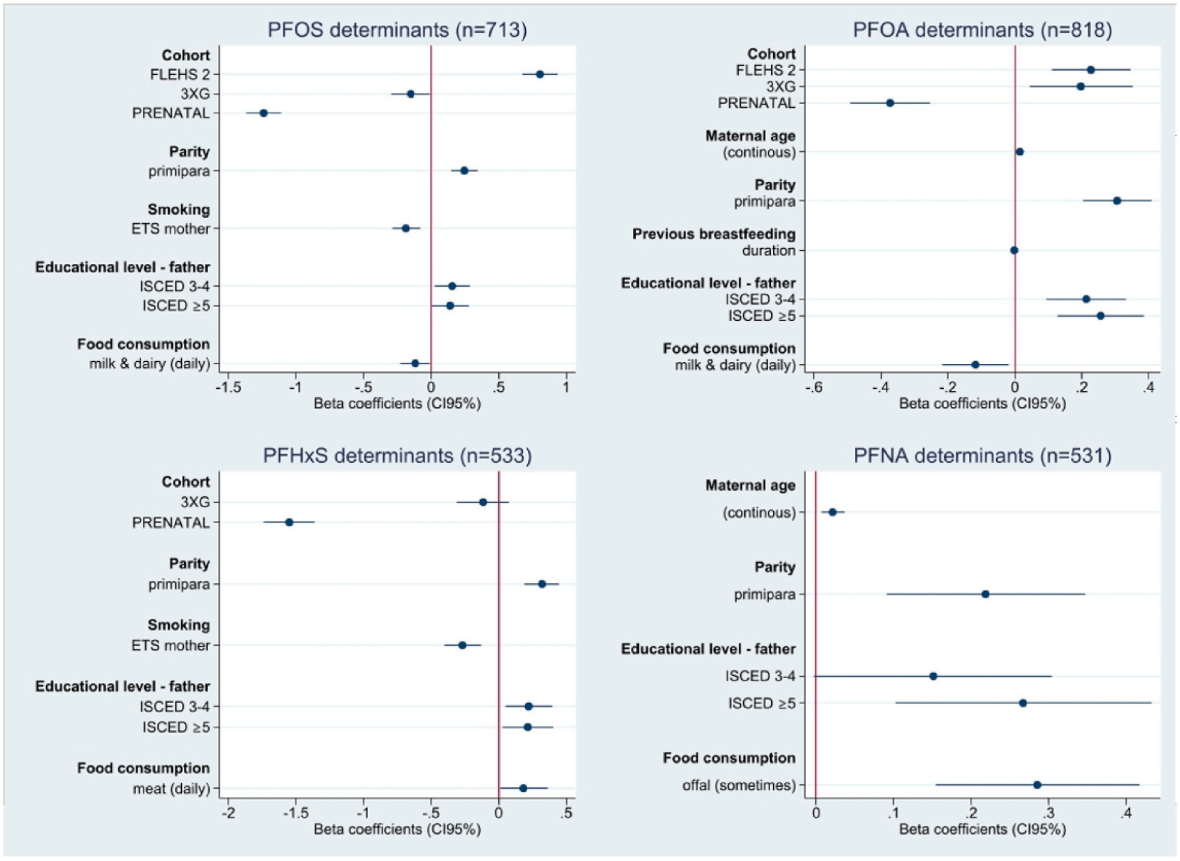

Fig. 2. Associations between cord blood PFAS concentrations (ln-transformed) and study population characteristics
Reference category: cohort – FLEHS 3; parity – multipara; smoking ETS – no; educational level of father – ISCED 1–2; milk & dairy consumption – less than 1x/day; meat consumption – less than 1x/day; offal consumption – never.

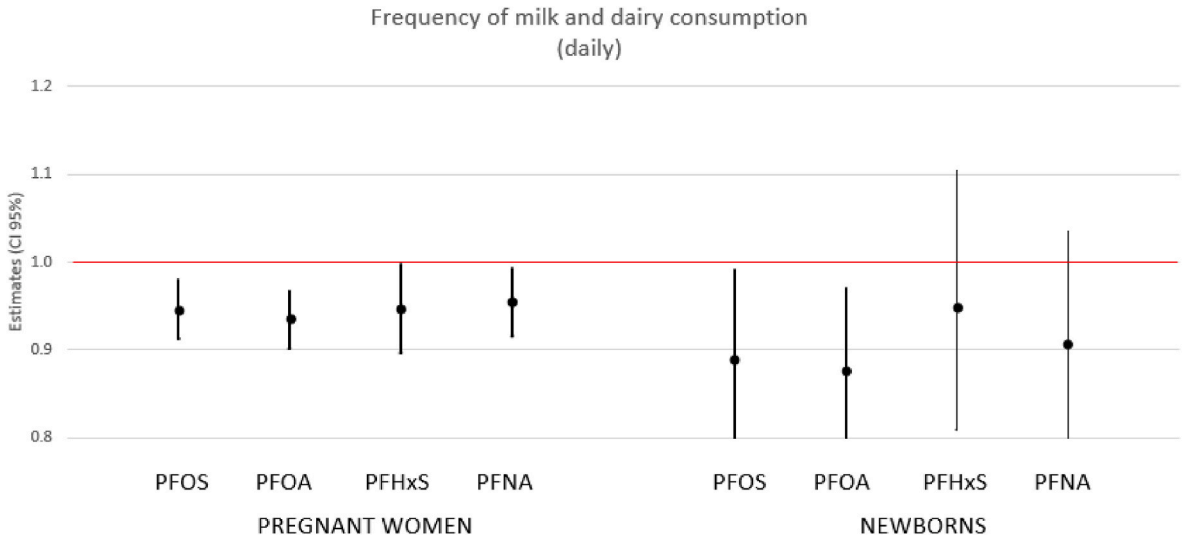

Fig. 3. Associations between PFAS concentrations in blood of pregnant women and cord blood (ln-transformed) and milk consumption
Reference category: milk & dairy consumption – less than 1x/day.

concentrations of all PFAS in both study populations ($p < 0.001$). The observed increase in PFAS concentrations was from 22% to 34% in pregnant women and 25%–36% in newborns of primiparas compared to multiparas. A higher age of mother at delivery was associated with significantly higher PFAS concentrations in pregnant women ($p < 0.001$) and PFOA and PFNA concentrations in newborns ($p = 0.008$ and $p = 0.006$, respectively). Previous breastfeeding was associated with lower PFOA and PFNA blood concentrations in pregnant women ($p < 0.001$ and $p = 0.003$, respectively) and a longer duration of previous breastfeeding was associated with lower cord blood concentrations of PFOA in newborns ($p = 0.030$). Pre-pregnancy BMI above 25 was associated with lower PFNA concentrations in pregnant women ($p < 0.001$). In newborns, we observed medium and higher educational levels of the father to be associated with increased concentrations of all four PFAS analysed

Table 3
PFAS serum/plasma concentrations in blood of pregnant women and cord blood.

	n	% <LOQ	AM ± SD	GM [95% CI]	P25	P50	P75
PREGNANT WOMEN – blood							
PFOS (μg/L)	5897	0	11.82 ± 7.09	10.05 [9.89; 10.20]	7.15	10.87	15.22
PFOA (μg/L)	5897	0	2.54 ± 1.30	2.26 [2.23; 2.29]	1.66	2.34	3.16
PFHxS (μg/L)	5897	2.2	0.78 ± 0.83	0.62 [0.61; 0.63]	0.44	0.63	0.88
PFNA (μg/L)	5897	0.3	0.52 ± 0.33	0.45 [0.44; 0.45]	0.32	0.45	0.64
NEWBORNS – cord blood							
PFOS (μg/L)	939	0	1.45 ± 1.53	0.92 [0.87; 0.99]	0.49	0.99	1.84
PFOA (μg/L)	939	0	1.43 ± 1.21	1.14 [1.09; 1.19]	0.82	1.27	1.78
PFHxS (μg/L)	719	13.1	0.26 ± 0.24	0.16 [0.15; 0.17]	0.09	0.15	0.39
PFNA (μg/L)	632	4.7	0.26 ± 0.20	0.21 [0.19; 0.22]	0.14	0.22	0.33

AM: Arithmetic mean; GM: Geometric mean; P25: 25th percentile; P50: 50th percentile; P75: 75th percentile.

($p < 0.001$ to 0.054 for medium educational level and $p < 0.001$ to 0.049 for high educational level) compared to low educational level. The observed increase in PFAS concentrations was 16–28% for medium educational level and 15–31% for high educational level, compared to low educational level. In comparison, the educational level of pregnant women was significantly associated only with increased PFNA blood concentrations ($p = 0.070$ and $p = 0.001$, for medium and high levels respectively). Smoking during pregnancy was associated with lower PFOS, PFHxS and PFNA concentrations ($p = 0.014$, $p = 0.035$ and $p = 0.018$, respectively) and exposure to tobacco smoke during pregnancy with higher PFOS and PFOA concentrations in the blood of pregnant women ($p = 0.016$ and $p = 0.017$, respectively). The opposite direction of association was observed between exposure to tobacco smoke during pregnancy and PFOS and PFHxS concentrations in cord blood ($p < 0.001$ for both).

In the pregnant women study population, we observed significant associations between PFAS concentrations in the blood of pregnant women and all dietary variables. Seafood and fish consumption at least once a week was associated with higher concentrations of all PFAS (exp. β from 1.063 to 1.122; $p < 0.001$). Daily consumption of meat was associated with higher concentrations of PFOS, PFOA and PFHxS (exp. $\beta = 1.034$, $p = 0.021$; exp. $\beta = 1.044$, $p = 0.002$, exp. $\beta = 1.045$, $p = 0.034$, respectively). Pregnant women who consumed offal had higher concentrations of PFOS, PFHxS and PFNA (exp. $\beta = 1.111$, $p < 0.001$; exp. $\beta = 1.061$, $p = 0.009$; exp. $\beta = 1.088$, $p < 0.001$, respectively). Egg consumption at least once a week was associated with higher concentrations of PFOS and PFNA ($\beta = 1.035$, $p = 0.018$; exp. $\beta = 1.071$, $p < 0.001$, respectively).

On the other hand, only a few significant associations were observed between PFAS concentrations and dietary variables in the study population of newborns. We observed significant positive associations between PFHxS cord blood concentrations and daily consumption of meat (exp. $\beta = 1.202$, $p = 0.039$) and between PFNA cord blood concentrations and consumption of offal (exp. $\beta = 1.330$, $p < 0.001$). We did not find any significant association between cord blood PFAS concentrations and consumption of seafood and fish or offal.

Daily milk and dairy consumption were associated with lower concentrations of all PFAS (exp. β from 0.934 to 0.954, $p < 0.001$ to 0.042) in pregnant women and with lower PFOS and PFOA concentrations in newborns (exp. $\beta = 0.889$, $p = 0.035$; exp. $\beta = 0.876$, $p = 0.011$, respectively). The observed decrease in PFOS and PFOA concentrations ranged from 5% to 7% for pregnant women and from 11% to 12% for newborns (Fig. 3). Detailed results of multiple linear regression analyses are presented in Supplementary Tables S5 and S6. In a sensitivity analysis, we did not observe any improvement in the MLR models for pregnant women and newborns when imputed data on potential determinants were used.

4. Discussion

In our study, we observed associations between PFAS concentrations in cord blood and several maternal characteristics, such as parity, maternal age, as well as with the educational level of the father. In addition, PFAS concentrations in pregnant women were associated not only with maternal age, parity or previous breastfeeding, but also with the consumption of different types of animal-based food.

In our population of pregnant women, the geometric mean (GM) of PFOS was 10.1 μg/L, mainly due to a higher concentration in the MoBa cohort (12.5 μg/L) compared to INMA and ELFE (5.8 and 3.2 μg/L, respectively). The GM of our population was comparable to the mean concentration in pregnant women in the Multiethnic Cohort of Cincinnati (GM: 11.6 μg/L) (Kato et al., 2014) and higher than concentrations found in some European studies, such as the MISA study in Norway (arithmetic mean: 8.0 μg/L), the SELMA study in Sweden (GM: 5.2 μg/L) or the Aarhus Birth Cohort in Denmark (median: 8.2 μg/L) (Berg et al., 2014; Shu et al., 2018; Bjerregaard-Olesen et al., 2016), as well as in the Hokkaido Study in Japan (GM: 4.9 μg/L), the Child study in Canada (median: 2.2 μg/L) or a recent US study (median: 1.9 μg/L) (Tsai et al., 2018; Workman et al., 2019; Eick et al., 2021) (Supplementary Table S7). Similarly, concentrations of PFOA were higher in our population (GM: 2.3 μg/L) compared to the three above-mentioned European cohorts (from 1.5 to 2.0 μg/L) and the Canadian and US studies (median: 0.9 and 0.8 μg/L, respectively). For PFHxS, the Cincinnati study and the SELMA study showed higher GM concentrations (both 1.3 μg/L) than our study (0.6 μg/L) and other studies mentioned above (0.3–0.5 μg/L). PFNA concentrations were similar across the studies (0.3–0.75 μg/L), with the exception of the Hokkaido study (GM: 1.2 μg/L), and were comparable with our study (GM: 0.45 μg/L). GM of cord blood concentration of PFOS and PFNA was lower in our study (0.9 and 0.2 μg/L, respectively) compared to the Cincinnati cohort (3.3 and 0.5 μg/L, respectively) (Kato et al., 2014) and a Chinese study (median: 1.5 and 0.3 μg/L, respectively) (Liu et al., 2011) (Supplementary Table S8). GM of PFOA cord blood concentration in our study and in the Chinese study was 1.1 μg/L, while in the Cincinnati cohort it was 2.9 μg/L. GM of cord blood concentration of PFHxS in our study (0.2 μg/L) was lower than in the Cincinnati cohort (0.6 μg/L) but higher than in the Chinese study (0.1 μg/L).

4.1. Maternal characteristics

We observed primiparity to be associated with higher concentrations of PFAS. Association between parity and PFAS concentrations has been well documented (Berg et al., 2014; Kato et al., 2014; Ode et al., 2013; Park et al., 2019; Sagiv et al., 2015; Tsai et al., 2018). Pregnancy is one of the routes of PFAS elimination from the body of a woman, when PFAS are transferred to the fetus. In the study of Zhang and Qin (2014), it was estimated that the average daily exposure of the fetus via placental transfer was 13.7 and 8.32 ng/day for PFOS and PFOA, respectively, and for pregnant woman, total daily elimination of PFOS and PFOA through pregnancy was 30.1 and 11.4 ng/day.

Another important way of PFAS elimination from the body of the mother is breastfeeding. An association between PFAS and breastfeeding

has been documented in several studies (Berg et al., 2014; Brantsæter et al., 2013; Kato et al., 2014; Sagiv et al., 2015). In our study, previous breastfeeding was associated with lower concentrations of PFOA in newborns, as well as with lower PFOA and PFNA concentrations in pregnant women. PFOA and PFNA were detected in 84 and 71% of breast milk samples from donors in Southern Spain, respectively, with median concentrations of 7.17 and 2.59 ng/L, while PFOS was detected in only 34% and PFHxS in 24% of samples (both medians < LOD) (Serrano et al., 2021). Kim et al. (2011b) observed a 2.3-fold lower transport efficiency of PFOS from maternal serum to breast milk compared to that of PFOA. The compound-specific transport of PFAS to breast milk suggested by these studies (Kim et al., 2011b; Serrano et al., 2021) might explain the fact that observed associations in our study were significant for PFOA and PFNA but not for PFOS and PFHxS.

We observed that higher maternal age was associated with a higher concentration of all four PFAS in pregnant women and higher PFOA and PFNA concentrations in cord blood. The studies on associations between age and PFAS concentrations reported mixed results. Similarly to our results, Kato et al. (2014) found lower cord blood PFAS concentrations for women under 25 years compared to women above 25 years of age and a Danish study observed a significant linear trend of increasing PFAS concentrations in pregnant women with increasing age (Bjerregaard-Olesen et al., 2016). In contradiction to these results, in some other studies, an older age of women was associated with lower blood concentrations of some PFAS (Sagiv et al., 2015) or the PFAS concentrations did not differ across the age groups (Calafat et al., 2007). The sources of exposure may differ according to age and together with elimination ways of PFAS via menstrual bleeding, pregnancy, and breastfeeding (Park et al., 2019), it can affect the association between age and PFAS concentrations. In our multiple linear regression models, we controlled for factors such as parity or breastfeeding by including them into the model. Also, exposure to PFAS, even though measured at the same age but not within the same time period, could differ as a result of changes in production and use over time as well as due to restrictions.

In agreement with our results, higher educational level was associated with higher PFOS and PFOA concentrations in US adults from the National Health and Nutrition Examination Survey (NHANES) and middle-aged women from the SWAN study (Calafat et al., 2007; Park et al., 2019). A significant positive association between PFHxS and PFOS and higher educational levels of pregnant women was reported by a Danish study, however PFOA and PFNA concentrations were similar for women with a high, upper middle, and lower middle educational level (Bjerregaard-Olesen et al., 2016). In newborns, we particularly observed an association with the educational level of the father, which could be a proxy variable of household socio-economic status (SES) or income. Seshasayee et al. (2021) observed household income to be associated with a higher consumption of packaged foods and fish in children and higher income has also been associated with higher exposure to PFAS in pregnant women (Fisher et al., 2016; Kato et al., 2014; Sagiv et al., 2015; Tsai et al., 2018). SES of family influences dietary patterns as well as the use of PFAS-containing products, such as personal care products, cookware, waterproof clothes, etc.

There is no consistency in the literature about the potential associations between active smoking and PFAS concentrations. In agreement with our results, Kato et al. (2014) reported lower PFOS concentrations in active smokers among pregnant women compared to non-smokers. Similar results have been shown in a Canadian study (Fisher et al., 2016) for PFOA concentrations in pregnant women and in a Danish study for all PFAS analysed (Bjerregaard-Olesen et al., 2016). On the other hand, smoking was positively associated with serum concentrations of PFNA and PFOA in 17–39 years old women from 2003 to 2008 NHANES study (Jain, 2013), with higher PFHxS in pregnant women who were smokers in the Swedish SELMA study (Shu et al., 2018) and with higher PFOS in pregnant women in the Hokkaido Study (Tsai et al., 2018). However, the potential mechanism behind these associations remains unknown. Smoking during pregnancy is usually associated with lower SES (Weaver et al., 2008), which also has an influence on other lifestyle factors, thus the association can also reflect the effect of SES on PFAS exposure and in our group, lower education was associated with lower PFAS exposure.

In our study, overweight and obese women had significantly lower PFNA blood concentrations compared to women with normal or lower BMI. Findings from the literature about the potential associations between exposure to PFAS and BMI are inconsistent. Kato et al. (2014) observed an association between lower PFOS and PFNA concentrations and higher BMI in pregnant women as well. Higher PFAS concentrations were inversely associated with BMI in Danish pregnant women (Bjerregaard-Olesen et al., 2016), but the Korean study of adolescents and adults showed a positive association between PFAS and BMI (Ji et al., 2012). However, higher BMI could also be an adverse outcome caused by exposure to high PFAS concentrations (Geiger et al., 2021), therefore it is not clear whether BMI is a determinant or outcome of PFAS exposure.

4.2. Dietary factors

Several studies reported associations between fish and seafood consumption and PFAS concentrations in human plasma or serum (Berg et al., 2014; Christensen et al., 2017; Jain, 2014; Rylander et al., 2010; Shu et al., 2018). In agreement with our results, a study in Poland (Falandysz et al., 2006) observed that higher consumption of Baltic fish and seafood was associated with higher concentrations of PFAS. Hradkova et al. (2010) determined the concentrations of PFOA and PFOS in imported canned fish and seafood products on the Czech retail market and found that several products originated in the Baltic Sea (including cod livers, sardines, and sprats) had the highest concentrations of PFAS. In the Norwegian Fish and Game Study, PFAS concentrations in serum of adults were significantly associated with the consumption of lean fish, fish liver, shrimp. Fish and shellfish were the major dietary source, contributing 81% of the estimated dietary intakes of PFOS and 38% of PFOA (Haug et al., 2010). The consumption of high Omega-3 fish (salmon, tuna, sardine) was associated with lower PFAS concentrations, while consumers of fried fish, and other fish/shellfish (trout, sole, halibut, shrimp, lobster, etc.) had higher plasma concentrations of PFOS, PFHxS and PFNA in US adults (Lin et al., 2020).

In our study, meat consumption was associated with higher PFOS and PFOA concentrations in pregnant women and with higher PFHxS concentrations in both, pregnant women and newborns. Similarly, Halldorsson et al. (2008) observed higher intake of red meat and animal fats to be associated with higher plasma PFOS concentrations and, to a lesser extent, PFOA concentrations in Danish pregnant women. Meat consumption was positively associated with PFAS concentrations in adults from the NHANES 2003–2008 study (Jain, 2014) as well as in a Norwegian study (Haug et al., 2010). Increased PFAS concentrations were observed in high consumers of game (Berg et al., 2014), poultry (Berg et al., 2014; Eick et al., 2021; Liu et al., 2017; Lin et al., 2020) and red meat (Berg et al., 2014; Eick et al., 2021; Liu et al., 2017). Consumption of animal-based food showed a positive association with the risk of increased PFAS concentrations in Spanish adults (Arrebola et al., 2018), and it was mainly explained by fish (47%) and meat (44%) consumption. On the other hand, a Korean study conducted by Ji et al. (2012) did not find significant associations between meat consumption and PFAS concentrations in adolescents or adults.

We observed offal consumption to be associated with higher PFAS in pregnant women (PFOA not significant) and with higher PFNA concentrations in newborns. In line with our results, higher consumption of offal (liver, kidney, blood, and heart) was associated with higher PFAS concentrations (Tian et al., 2018). PFAS are absorbed in the gastrointestinal tract of mammals, then, distributed via plasma to the other parts of the body and tend to accumulate in the liver (EFSA, 2020). Offal is not consumed frequently in the population, thus the association with PFAS concentrations in humans is difficult to demonstrate in the

epidemiological studies based on food frequency questionnaires.

Literature on the association between PFAS concentrations and egg consumption is scarce. Some studies reported no association between egg consumption and PFAS concentrations (Halldorsson et al., 2008; Liu et al., 2017), while in a Spanish study, the effect of animal-based food on PFOA and PFHxS concentrations was explained not only by meat and fish but also by egg consumption (Arrebola et al., 2018). In a Flemish study (Colles et al., 2020), increased PFOS concentrations were associated with the consumption of locally produced eggs in adolescents and adults, and EFSA reported (2020) high concentrations of PFOS and PFOA in eggs and egg products. In our study, we observed significant association only for PFOS and PFNA concentrations in the pregnant women study population.

Interestingly, we observed significantly lower PFAS concentrations associated with daily consumption of milk and dairy products. Contradictory results have been published by Park et al. (2019), where higher concentrations of PFOA and PFHxS were observed in middle-aged women with daily consumption of dairy food, however, PFOS concentrations were lower among the daily consumers of dairy food. Cheese consumption more than 1x/week was associated with higher concentrations of PFNA in pregnant women (Eick et al., 2021). High-fat dairy products (butter and cheese) were associated with higher PFAS plasma concentrations in children (Seshasayee et al., 2021). On the contrary, low-fat milk was associated with lower PFNA concentrations in children and low-fat dairy food was associated with lower concentrations of PFOS, PFOA and PFNA in adults (Lin et al., 2020; Seshasayee et al., 2021). Italian milk monitoring study (Barbarossa et al., 2014) demonstrated relatively low PFOS concentrations (up to 97 ng/L) and rare PFOA contamination in different types of cow milk samples. These findings suggest that milk and dairy food, especially low-fat products, are not among the main contributors to PFAS body burdens.

4.3. Limitations and strengths

Our study has several limitations. First, most of the cohorts are regionally based, thus they are not nationally representative. In addition, the MoBa subsample used in our study does not represent a random sample from the entire MoBa cohort. The data have been compiled from three different data sets where participants have been selected for specific studies – subfecundity (Whitworth et al., 2012), preeclampsia among nulliparous women (Starling et al., 2014), and attention-deficit/hyperactivity disorder and cognitive functions in preschool children (Skogheim et al., 2020). Different sampling years also made the comparison of PFAS concentrations across cohorts difficult. Second, we had to deal with disproportion in the number of participants that varies largely between cohorts of pregnant women. We included the cohort as a fixed factor in our multiple linear regression models and applied the final model in each of the contributing cohorts separately. After a comparison of the results for the whole study population and individual cohort results, we could conclude that our results were not driven by the largest cohort. Third, PFHxS and PFNA were not measured in FLEHS 2, therefore the sample size for concentrations of these two PFAS in cord blood is reduced. In addition, some important factors, such as the type of drinking water or local food consumption, were not available in some of the cohorts and we had to exclude them from the analyses. Variables like fast food consumption or use of Teflon cookware were not available at all. This highlights the importance of coordinated approaches, particularly in the construction of questionnaires for future biomonitoring studies.

Despite these limitations, one of the main advantages of this study was its size (n = 5897 and 940, for pregnant women and newborns, respectively). Comparability of data on covariates from different cohorts was achieved by post-harmonisation of the data according to the codebook developed within HBM4EU project. Our statistical analysis was performed on harmonised pooled data and we observed some strong associations not only with maternal characteristics but also with the consumption of animal-based food during pregnancy. Observed disparities in some maternal characteristics (parity, educational level, smoking status, ETS exposure) and dietary patterns among cohorts of newborns as well as among cohorts of pregnant women were controlled by adding the cohort variable in the MLR models. Even though the cohort variable was significantly associated with PFAS concentrations, associations between dietary variables and PFAS concentrations remained significant. Pooling of data from nine cohorts from different European countries enabled us to identify common determinants for the European population of pregnant women and newborns. This approach can provide information on the strongest sources of PFAS exposure in the two very sensitive sub-populations to target common strategies for reduction of PFAS exposure at the European level.

5. Conclusion

High detection rates of the four most abundant PFAS demonstrate the ubiquitous exposure of sensitive populations, which is of concern. Besides the strong determinants of PFAS exposure, parity and maternal age, several other determinants have been identified by this study. The educational level of the father as a proxy for the socioeconomic status of the family and various dietary factors were associated with PFAS concentrations in cord blood and/or blood of pregnant women. Regarding dietary factors, fish and seafood consumption was associated with higher concentrations of all 4 PFAS in pregnant women but an association with higher PFAS concentrations was observed also for other types of food, such as meat, offal and eggs. A contrasting association was observed between daily milk and dairy consumption and lower PFAS in both pregnant women and newborns, suggesting that dairy products are not major sources of PFAS in this population. Based on the results of this study, a greater focus on dietary sources of PFAS is needed, including regular monitoring of PFAS concentrations in foodstuffs.

Credit author statement

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Declaration of competing interest

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

Data availability

The data that has been used is confidential.

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