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PFAS exposure is associated with an unfavourable metabolic profile in infants six months of age

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ABSTRACT

Exposure to perfluoroalkyl substances (PFAS) are reported to have numerous negative health effects and children are especially vulnerable. The aim of this study was to investigate whether maternal and infant PFAS burden have any impact on prenatal and postnatal growth, liver and lipid parameters in infants at age six months. Data on diet and growth parameters, as well as blood samples were collected from healthy pregnant women in week 18 and in the women and their infants at six months postpartum. The blood samples were analysed for liver enzymes, blood lipids and PFAS. Maternal perfluoroalkyl carboxylic acids (PFCA) and fish for dinner $\geq$ 3 days per week in pregnancy week 18 were associated with reduced birth weight and increased percent weight gain the first six months of life. Infant PFCA concentrations were positively associated with serum alanine aminotransferase and total- and LDL-cholesterol concentrations at six months of age. Our data demonstrate that prenatal and postnatal PFAS exposure are associated with an unfavourable metabolic profile at a very young age. This pattern is concerning as it may be linked to early conditioning of later metabolic disease. It is vital to reduce PFAS exposure in women of fertile age in order to prevent development of metabolic disease in the next generation.

1. Introduction

During the last 70 years, thousands of perfluoroalkyl substances (PFAS) have been produced for use in consumer and industrial applications (Salvatore et al. 2022). PFAS are environmentally persistent and tend to accumulate in the ocean and marine food chains and contaminate the groundwater, consequently, diet and drinking water are the major human exposure pathways (De Silva et al. 2021; Sunderland et al. 2019). Studies show that high seafood consumers may be exposed to PFAS concentrations that potentially may pose a health risk (Casals-Casas and Desvergne 2011; Crawford et al. 2024).

We have documented a linear transfer of PFAS from the mother to the infant during pregnancy and lactation, resulting in higher infant concentrations than observed in never-pregnant women (Varsi et al. 2022). Infants, toddlers and older children are reported to have a high body burden of different PFAS with peak serum concentrations occurring before the child reaches 20 months (Koponen et al. 2018). Serum PFAS concentrations are reported to be higher in infants compared to their mothers(Varsi et al. 2022). In infants aged six months median serum perfluorooctanoate (PFOA) concentration was 4.9 times higher than the maternal level (Varsi et al. 2022).

Studies indicate that PFAS are related to a range of negative health effects (Zheng et al. 2023), and particularly fertile and pregnant women, infants, children and adolescents are vulnerable to PFAS exposure (Liew et al. 2018). Prenatal PFAS exposure has been associated with decreased birth weight and increased risk of childhood overweight or adiposity (Chen et al. 2023; Gao et al. 2022; Gyllenhammar et al. 2018; Maisonet et al. 2012; Starling et al. 2019). There are evidence for PFAS hepatotoxicity from both rodent studies and epidemiological studies in humans (Costello et al. 2022), including children (Stratakis et al. 2020). In addition, higher levels of cholesterol and triglycerides have been associated with PFAS in both cord blood and in children (Frisbee et al. 2010; Geiger et al. 2014; Jain and Ducatman 2018; Spratlen et al. 2020).

The unfavourable profile related to PFAS exposure resembles the

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profile seen in metabolic syndrome, a multifactorial disease, particularly linked to nutrition (van Ommen et al. 2009). There is currently no clear understanding of the linkage between PFAS and these health effects, but studies suggest that prenatal exposure to PFAS may be involved in epigenetic modifications in loci related to growth and development, lipid metabolism, and nutrient metabolism (Perng et al. 2023), which are factors associated with metabolic syndrome (Eckel et al. 2005).

In order to prevent metabolic disease, we need to understand and control the factors associated with development of the metabolic syndrome. The aim of this study was to investigate whether diet and PFAS status in the mother and infant had any impact on infant growth parameters and biochemical markers related to metabolic syndrome at age six months.

2. Material and methods

2.1. Study population and design

Healthy women with a singleton pregnancy were recruited in pregnancy week 18 at routine ultrasound examination at the Obstetrical Department at Haukeland University Hospital, Bergen, Norway, during the period of 2011 to 2015. All women were invited for follow up during pregnancy (pregnancy week 28 and 36) through six months postpartum (6 weeks, 4 and 6 months postpartum) and the last visit also included the infant.

Women with pregnancy related or chronic disease were excluded, and of initially 140 recruited pregnant women, 114 women met the inclusion criteria. Maternal and infant health status and growth parameters were recorded at her general practitioner or at the local Maternity and Child Health Care Centre. The participants completed a questionnaire concerning maternal age, parity, education, diet preferences, including intake of fish, and weight during pregnancy and postpartum, in addition to infant growth parameters and nutrition postpartum in an interview with either Kristin Holstad or Anne-Lise Bjørke-Monsen at each time point of the study. Detailed reports on changes in PFAS status during pregnancy and the postpartum period have formerly been published (Varsi et al. 2021; Varsi et al. 2022).

Ethical approval of the protocol was granted by the Regional Committee on Medical Research Ethics, REK 2011/2447, and written informed consent was obtained from all women.

2.2. Blood sampling and analysis

Non-fasting blood samples were obtained by antecubital venipuncture and collected into vacutainer tubes without additives (Terumo), serum was transferred to Sarstedt tubes without additives with plastic pipettes and stored at − 80 °C. Background contamination of the sampling equipment was not present.

Twenty different PFAS were analysed in serum from all women (n = 114) and for only 94 of the 114 infants at age six months, due to unsuccessful venepuncture, at the University Hospital of North Norway (Tromsø, Norway) according to Huber and Brox (Huber and Brox 2015) by an automated fully validated high-throughput sample preparation method and analysis by ultrahigh pressure liquid chromatography tandem-quadrupole mass-spectrometry (UHPLC-MS/MS, Waters, Milford, MA, USA). Analysed PFAS consist of perfluorobutanoate (PFBA), perfluoropentanoate (PFPeA), perfluorohexanoate (PFHxA), perfluoroheptanoate (PFHpA), PFOA, perfluorononanoate (PFNA), perfluorodecanoate (PFDA), perfluoroundecanoate (PFUnDA), perfluorododecanoate (PFDoDA), perfluorotridecanoate (PFTrDA) and perfluorotetradecanoate (PFTeDA), perfluorobutane sulfonate (PFBS), perfluoropentane sulfonate (PFPS), perfluorohexane sulfonate (PFHxS), perfluoroheptane sulfonate (PFHpS) and perfluorooctane sulfonate (PFOS), perfluorononane sulfonate (PFNS), perfluorodecane sulfonate (PFDS), perfluorododecane sulfonate (PFDoDS) and perfluorooctane sulfonamide (PFOSA). Sum of perfluorocarboxylic acids (PFCA), sum of perfluorosulfonic acids (PFSA) and sum of all quantified perfluoroalkyl substances (PFAS = PFCA + PFSA) were calculated.

Analytical coefficients of variation (CVa) were ≤ 10 % for all the measured PFAS except for PFDA and PFUnDA with CVa of 12 % and 18 %, respectively. Detection frequency, range, median, mean and standard deviation (SD) of 18 of the 20 PFAS in infants, pregnant women in week 18 and women 6 months postpartum are given in Supplemental Table 1 and 2. PFBA and PFPeA were excluded due to non-optimal data quality related to analytical challenges for specificity, as described earlier (Huber and Brox 2015).

Serum for analysis of alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (**γ**-GT), total-, low density lipoprotein (LDL-) and high density lipoprotein (HDL-) cholesterol, and triglycerides was available for all mothers and for only 49 of the 94 infants, who were venipunctured, due to lack of volume. The samples were analysed in the routine accredited laboratory at Haukeland University Hospital, Bergen, Norway on Roche Cobas c702 (Roche Diagnostics, Basel, Switzerland) automated analyzer. CVa was 5 % for ALT, 3 % for ALP, 4 % for γ-GT, 3 % for total cholesterol, 2.5 % for LDL cholesterol 3 % for HDL cholesterol and 3 % for triglycerides.

2.3. Statistical analysis

Results are presented as mean and standard deviation (SD) and compared by Student's *t*-test, or median, interquartile range (IQR) and compared by Mann-Whitney *U* Test with Monte Carlo implementation. Spearman correlation was used to explore relationships between PFAS concentrations and maternal fish intake and infant growth parameters. Multiple linear regression models, additionally including gender and weight at six months, were used for validation of maternal PFAS status on infant growth parameters and for validation of the effect of infant PFAS status on serum markers of infant liver and lipid parameters.

Graphical illustrations of the relationships between infant PFAS concentrations and serum ALT, total- and LDL-cholesterol were obtained by generalized additive models (GAM) and adjusted for gender and weight at six months.

Limits of detection (LODs) for serum PFAS concentrations were set as concentrations calculated by the Targetlynx-software for each individual sample (LOD*i*) and each individual analyte with a signal to noise ratio of 3 divided by the related sample amount. Where blank contamination was detected (background contribution during sample preparation), LOD was calculated as an average of the blanks multiplied by three times of their standard deviation. If the LOD calculated from the blank contamination was higher than the LOD*i* of the sample, the LOD calculated based on the blank samples was used. Limit of quantification (LOQ) was defined as three times the LOD. To reduce possible bias of left censored data analyses we have used the actual values between LOQ and LOD. PFAS concentrations below the LOD were not quantified (in most cases there was only noise visible in the chromatogram) and these data

Table 1
Baseline characteristics of infants at age six months and their mothers in pregnancy week 18.

Infant data (n = 114)	
Boys, n (%)	60 (53 %)
Gestational age at birth, weeks, mean (SD)	40.0 (1.0)
Birth weight, g, mean (SD)	3573 (418)
Weight at 6 months, g, mean (SD)	7969 (987)
Months of exclusive breastfeeding, months, mean (SD)	3.8 (1.5)
Maternal data (n = 114)	
Age, y, mean (SD)	31.5 (4.3)
Para 0, n (%)	63 (55)
Regular smoking, n (%)	2 (2)
Alcohol units per week, median (IQR)	0 (0)
Regular use of micronutrient supplements (≥3 days/week), n (%)	47 (41)
Regular use of fish for dinner (≥ 1 day per week), n (%)	102 (89)

Table 2
Concentrations of metabolic markers and PFAS in infants and mothers.

Parameters, Median (IQR) Total range	Infants, 6 months N = 49/94[a]	Mothers, pregnancy week 18 N = 107	Mothers, 6 months postpartum N = 114	P value[b] Infants vs mothers in pregnancy week 18	P value[b] Infants vs mothers 6 months postpartum
Serum markers of liver function and lipids					
Alanine aminotransferase, U/L	34 (26, 42) 18, 79	14 (11, 20) 5, 83	19 (15, 22) 7, 52	<0.001	<0.001
Gamma-glutamyl transferase, U/L	12 (10, 14) 3, 34	9 (7, 11) 3, 30	12 (9, 15) 4, 70	<0.001	0.21
Alkaline phosphatase, U/L	216 (179, 255) 143, 372	47 (39, 55) 26, 101	74 (65, 89) 42, 173	<0.001	<0.001
Total-cholesterol, mmol/L	4.4 (3.7, 5.2) 2.6, 7.4	5.3 (4.8, 5.9) 3.6, 7.9	4.5 (4.1, 5.1) 3.0, 8.4	<0.001	0.21
LDL-cholesterol, mmol/L	2.5 (1.9, 3.1) 1.1, 4.3	3.0 (2.5, 3.7) 1.5, 5.9	2.8 (2.3, 3.2) 1.6, 5.0	<0.001	0.01
HDL-cholesterol, mmol/L	1.2 (1.0, 1.4) 0.6, 1.8	2.0 (1.8, 2.3) 1.0, 3.2	1.8 (1.5, 2.0) 0.8, 2.9	<0.001	<0.001
Triglycerides, mmol/L	1.50 (0.97, 2.05) 0.60, 4.80	1.23 (0.95, 1.59) 0.60, 3.10	0.62 (0.50, 0.79) 0.22, 2.19	0.05	<0.001
Serum PFAS					
PFOA, ng/mL	3.27 (2.14, 4.23) 0.73, 8.87	1.15 (0.79, 1.49) 0.26, 3.18	0.67 (0.50, 0.87) 0.23, 4.19	<0.001	<0.001
PFNA, ng/mL	0.71 (0.56, 0.91) 0.20, 2.03	0.45 (0.37, 0.55) 0.07, 1.83	0.35 (0.27, 0.46) 0.10, 1.45	<0.001	<0.001
PFDA, ng/mL	0.23 (0.16, 0.30) 0.06, 0.67	0.22 (0.17, 0.29) 0.05, 0.62	0.20 (0.15, 0.25) 0.07, 0.64	0.83	0.14
PFUnDA, ng/mL	0.16 (0.10, 0.21) 0.03, 0.67	0.26 (0.18, 0.34) 0.06, 0.88	0.22 (0.14, 0.30) 0.02, 0.87	<0.001	<0.001
Sum PFCA, ng/mL	4.70 (3.27, 5.95) 1.19, 11.78	2.17 (1.73, 2.67) 0.47, 5.11	1.50 (1.16, 1.98) 0.50, 5.62	<0.001	<0.001
Sum PFHxS, ng/mL	0.68 (0.53, 0.92) 0.20, 2.26	0.54 (0.39, 0.67) 0.17, 1.34	0.45 (0.35, 0.66) 0.15, 1.58	<0.001	<0.001
Sum PFHpS, ng/mL	0.12 (0.08, 0.16) 0.03, 0.46	0.08 (0.05, 0.10) 0, 0.25	0.06 (0.04, 0.08) 0, 0.19	<0.001	<0.001
Sum PFOS, ng/mL	4.71 (3.53, 6.23) 0.94, 10.99	4.30 (3.23, 5.94) 0.70, 11.64	3.53 (2.42, 4.37) 0.71, 8.56	0.36	<0.001
Sum PFSA, ng/mL	5.48 (4.15, 7.30) 1.16, 13.34	5.18 (3.67, 6.69) 0.87, 12.84	4.10 (2.95, 5.21) 0.89, 9.67	0.17	<0.001
Sum PFAS, ng/mL	10.14 (7.80, 13.67) 2.34, 21.42	7.30 (5.72, 9.76) 1.34, 16.81	5.75 (4.28, 7.01) 1.39, 12.25	<0.001	<0.001

[a] Serum markers of liver function and lipids concentrations were measured in 49 infants and serum PFAS concentrations in 94 infants.
[b] Serum markers of liver function and lipids and serum PFAS in infants versus mothers in pregnancy week 18 and 6 months postpartum were compared by the Mann-Whitney test.

were replaced by LOD*i* divided by 2. Statistical analyses were performed only for PFAS with detection rate > 90 %. PFAS with detection rate < 90 % were included in the PFAS sum concentration, as well as sum PFCA and sum PFSA (perfluoroalkyl sulfonic acids).

The SPSS statistical program (version 29) and the packages "mgcv" in R, version 4.4.1 (The R Foundation for Statistical Computing) were used for the statistical analyses. Two-sided *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. Demographics

All infants (n = 114) were healthy, born at term, with an appropriate for gestational age weight, mean 3573 (SD 418) grams and 53 % (60/114) were males (Table 1). At age six months, the weight had increased by mean 125 % (SD 30) to a mean weight of 7969 (SD 987) grams. Mean duration of exclusive breastfeeding was 3.8 (SD 1.5) months. At four months, 61 % (70/114) of the infants had been introduced to solid food. All infants still received breastmilk at six months, but only four infants (3.5 %) were then exclusively breastfed.

The majority of the women (55 %) were Para 0, indicating she has never carried a pregnancy beyond 20 weeks, while 29 % were Para 1 (giving birth once), 12 % Para 2 (twice) and 4 % were Para 3 (three times). Mean prepregnancy weight was 64.9 (SD 9.7) kg and it increased by 20 % to 78.0 (9.7) kg at birth. The mean weight after giving birth was 69.1 (SD 9.1) kg and it decreased by 6 % to 65.1 (9.4) kg at 6 months.

All the women reported having an omnivore diet and 89 % had fish for dinner at least once a week. Fish for dinner ≥ 3 days per week was reported by 17 women (15 %) in pregnancy week 18. Throughout the study period, the number of high fish consumers (≥3 days per week) varied somewhat, the lowest number was seen in pregnancy week 36 (16 women, 14 %) and the highest at four months postpartum (26 women, 23 %). The high fish consumers were slightly older, median age 33 (IQR 31, 36) years compared to the women who ate less fish, median age 31 (IQR 28, 34) years, p = 0.05. There were however no differences in education, parity, body mass index, use of tobacco or alcohol between the high and low fish-eating groups (p > 0.11). The most common choice of fish for dinner was farmed salmon (69 %), followed by lean fish (21 %) and other types of fatty fish (10 %).

3.2. Serum PFAS concentrations in infants and mothers

All PFAS concentrations (apart from PFDA) were significantly higher in the infants than in their mothers six months postpartum (Table 2).

Women who were high fish consumers in pregnancy week 18 (n =

17, 15 %) had significantly higher serum median levels of sum PFCA (2.89 ng/mL (IQR 2.07, 3.05) versus 2.07 ng/mL (1.71, 2.50), p = 0.02) and sum PFSA (6.26 ng/mL (IQR 4.28, 7.90) versus 4.81 ng/mL (3.51, 6.48), p = 0.05) compared to women who ate less fish often.

3.3. Infant growth parameters in relation to maternal PFAS status in pregnancy week 18

All maternal serum PFAS concentrations in pregnancy week 18 were negatively associated with infant birth weight, length and head circumference. The strongest associations were seen for maternal PFOA to birth weight; rho: −0.22, p = 0.02, and to length; rho: −0.21, p = 0.03 in unadjusted Spearman correlations. Infants born to mothers with sum PFCA concentrations above the median (2.18 ng/mL) in pregnancy week 18, had significantly lower mean birth weight 3493 (SD 400) gram compared to infants born to mothers with lower sum PFCA concentrations, mean weight 3662 (SD 424) gram, p = 0.03. No significant differences were seen for birth length and head circumference according to maternal PFAS concentrations.

All maternal PFAS concentrations in pregnancy week 18 were positively correlated to percent weight gain from birth to six months. The strongest correlations were seen for lin PFHxS (rho: 0.25, p = 0.009), lin PFHpS (rho: 0.24, p = 0.02) and sum PFCA (rho: 0.23, p = 0.02). No significant correlations were seen between maternal PFAS and percentage increase in length or head circumference from birth to six months.

The strongest predictor for infant percent weight gain from birth to six months was birth weight (Standardized Coeffisient Beta: −0.47, p < 0.001), followed by gender (Beta −0.25, p = 0.003), maternal sum PFCA in week 18 (Beta 0.20, p = 0.04) and maternal sum PFSA in week 18 (Beta −0.06, p = 0.55) in multiple linear regression models.

3.4. Infant growth parameters in relation to maternal intake of fish in pregnancy week 18

Overall, maternal fish for dinner intake in week 18 was negatively, but not significantly, correlated to infant weight, length and head circumference at birth (P > 0.17), but it was significantly positively correlated to percent weight increase from birth to six months (rho: 0.22, p = 0.02). Mean difference in birth weight was −182 g, p = 0.10, and at six months + 200 g, p = 0.44, between infants born to mothers who had fish for dinner ≥ 3 days per week (n = 17) compared to those who ate less (n = 91). Median percent weight increase was significantly higher 151 % (IQR 115, 156) in infants born to high fish consumers compared to infants born to mothers with a lower fish intake, median 117 % (IQR 100, 145), p = 0.01.

3.5. Infant liver and lipid status and relation to growth pattern and PFAS at age six months

Infants had higher serum median ALT, ALP and triglycerides and lower LDL- and HDL-cholesterol concentrations than postpartum women, while no differences were seen for γ-GT and total-cholesterol (Table 2).

Positive correlations were observed between percent weight gain from birth to six months and infant serum ALT (rho: 0.29, p = 0.04), ALP (rho: 0.29, p = 0.04) and γ-GT (rho: 0.42, p = 0.003). No correlations were seen between percent weight gain and cholesterol or triglyceride concentrations (p > 0.3).

Infant serum ALT was significantly positively correlated to infant serum sum PFCA (rho: 0.37, p = 0.009), but not to sum PFSA (p > 0.30). No significant correlations were seen for infant serum γ-GT and ALP and PFAS (p > 0.22).

Serum total cholesterol was significantly positively correlated to sum PFCA (rho: 0.31, p = 0.03), but not to sum PFSA. No significant correlations were seen between LDL- and HDL-cholesterol and triglycerides and PFAS (p > 0.22).

In a multiple linear regression model, which additionally included gender and weight at six months, infant PFCAs, particularly PFOA, were strong positive determinants for serum ALT, total- and LDL-cholesterol (Table 3). In this model, infant sum PFCA was also a positive determinant for serum ALP (unstandardized coefficient B: 8, p = 0.03). Fig. 1 shows the relationship between infant sum PFOA and ALT, total- and LDL-cholesterol concentrations, adjusted for gender and weight at six months. No significant relations were observed between PFCAs and γ-GT, HDL-cholesterol and triglyceride concentrations, and no relations were seen between infant PFSAs and metabolic markers (Table 3).

Maternal sum PFCA concentration in pregnancy week 18 was significantly positively correlated to infant total cholesterol concentrations at six months (rho: 0.36, p = 0.01). In a linear regression model, which additionally included gender and infant weight at six months, maternal sum PFCA and particularly PFOA concentrations were significant predictors of infant total-cholesterol at six months (unstandardized coefficient B for PFCA: 0.41, p = 0.02 and for sum PFOA: 0.74, p = 0.006). No other significant relations were seen between maternal PFAS status and infant liver and lipid markers.

4. Discussion

Our findings demonstrate reduced birth weight and increased weight gain during the first six months of life in infants exposed to prenatal and postnatal PFAS, particularly in infants born to mothers with a high fish intake. In addition, infant PFCA status was positively associated with ALT and total- and LDL-cholesterol concentrations at six months.

4.1. Birth weight and weight gain in relation to maternal PFAS status

Our knowledge of the PFAS-induced mechanisms causing reduced fetal growth is still incomplete, but several articles report an association between PFAS and changes in both fetal and postfetal growth (Gundacker et al. 2022; Lee et al. 2021; Rogers et al. 2023).

The observed reduced birth weight and increased weight gain during the first six months of life in infants exposed to prenatal and postnatal PFAS, are in agreement with other published studies (Chen et al. 2023; Gyllenhammar et al. 2018; Kashino et al. 2020; Liew et al. 2018; Maisonet et al. 2012; Starling et al. 2019). We observed negative associations between all maternal PFAS in pregnancy week 18 and birth weight and length, significant for PFOA and sum PFCA. An inverse relation between PFOA and birth weight and length has been reported from the Danish National Birth Cohort (Fei et al. 2008), and between cord blood PFOS and PFOA and birth weight in an American study (Apelberg et al. 2007), while no significant associations between maternal PFAS concentrations and birth outcomes were seen in a Spanish cohort (Manzano-Salgado et al. 2017) and either positive or no associations were seen between cord PFAS concentrations and birth weight, length and head circumference in multi-ethnic Singaporean mother-offspring cohort study (Chen et al. 2024).

Data from *in vitro* and *in vivo* studies have related PFAS reduced birth weight to oxidative stress and cellular damage. PFAS may induce reactive-oxygen species (ROS), which triggers increased peroxisome proliferator-activated receptor (PPAR) γ-expression and activation of growth signaling pathways leading to hyperdifferentiation of a lower number of pre-adipocytes reported to reduce birth weight (Gundacker et al. 2022). Additionally, PFAS induced endocrine effects have been related to changes in growth (Gundacker et al. 2022). *In vivo* studies have reported increased oestrogen and decreased testosterone levels, as well as changes in the steroidogenesis cytochrome enzyme levels after PFAS exposure (Gundacker et al. 2022; Qiu et al. 2020; Zhang et al. 2020). *In vitro* studies indicate that PFAS can interfere with thyroid hormone transport, bind to thyroid hormone receptors, inhibit iodine uptake and thyroperoxidase activity, thereby changing thyroid function which affects body weight (Buckalew et al. 2020; Gundacker et al. 2022;

Table 3
Infant serum PFAS as determinants of liver parameters and lipid concentrations at age six months by multiple linear regression (n = 49).

Infant serum variables included in the model	Serum alanine aminotransferase, U/L		Serum total cholesterol, mmol/L		Serum LDL cholesterol, mmol/L		Serum HDL cholesterol, mmol/L		Serum triglycerides, mmol/L	
	B[a]	95 % CI	B[a]	95 % CI	B[a]	95 % CI	B[a]	95 % CI	B[a]	95 % CI
PFOA	4.5	2.3, 6.7	0.25	0.05, 0.46	0.16	0.01, 0.31	−0.01	−0.06, 0.05	0.06	−0.11, 0.23
PFNA	14.9	4.3, 25.6	0.99	0.06, 1.91	0.90	0.25, 1.56	0.03	−0.22, 0.28	0.25	−0.51, 1.01
PFDA	28.3	2.1, 54.4	1.70	−0.55, 3.94	1.85	0.27, 3.43	−0.07	−0.66, 0.52	0.72	−1.08, 2.53
PFUnDA	8.9	−17.7, 35.6	1.84	−0.33, 4.00	1.75	0.21, 3.29	−0.08	−0.65, 0.49	1.36	−0.36, 3.08
Sum PFCA	3.0	1.4, 4.6	0.18	0.40, 0.33	0.14	0.03, 0.24	−0.002	−0.04, 0.04	0.05	−0.07, 0.17
Sum PFHxS	0.6	−15.5, 16.7	0.11	−1.24, 1.46	−0.48	−1.45, 0.49	0.31	−0.02, 0.64	0.10	−0.96, 1.16
Sum PFHpS	25.4	−50.9, 101.6	3.67	−2.66, 10.00	0.56	−4.10, 5.23	0.85	−0.77, 2.47	1.25	−3.80, 6.29
Sum PFOS	0.5	−1.4, 2.4	0.08	−0.08, 0.24	0.00	−0.12, 0.12	0.02	−0.03, 0.06	0.07	−0.06, 0.19
Sum PFSA	0.4	−1.2, 2.1	0.07	−0.07, 0.21	−0.01	−0.11, 0.10	0.02	−0.20, 0.05	0.06	−0.06, 0.17

Each regression model included one PFAS, as well as gender and weight at six months.
[a] Unstandardized coefficient.

Ren et al. 2016).

Animal and human studies have suggested an association between PFAS exposure and increased risk of overweight or obesity later in life also in infants and young children (Braun et al. 2016). In our study population, all maternal PFAS concentrations in pregnancy week 18 were positively correlated to percent weight gain from birth to six months, the strongest correlations involved both PFCA and PFSA. An American study found positive associations between maternal PFOA and PFNA concentrations in pregnancy week 20–34 and adiposity in male, but not female, infants at five months (Starling et al. 2019). Concentrations of PFOA, PFNA and PFHxS in Swedish women at delivery were positive associated with BMI in the children at age 3 and 4 years (Gyllenhammar et al. 2018).

4.2. Birth weight and weight gain in relation to maternal fish intake

Fish consumption is reported to be a major source of human PFAS exposure(Casals-Casas and Desvergne 2011; Crawford et al. 2024; Langberg et al. 2024; Langberg et al. 2020). A recent study state that even consumption of small amounts of fish can lead to exceedance of PFAS safety thresholds(Langberg et al. 2024). Infants born to mothers who had fish for dinner ≥ 3 days per week in pregnancy week 18 had 34 % higher median percent weight gain during the first six months of life compared to infants born to mothers with a lower fish intake. High fish intake during pregnancy (>3 times/week) has also been associated with rapid infant growth and childhood obesity in a large multicentre, population-based birth cohort study including more than 26 000 pregnant women (Stratakis et al. 2016).

Fish is a source of several persistent organic pollutants (POPs), including PFAS (Casals-Casas and Desvergne 2011; Crawford et al. 2024), and dioxins and dioxin-like-polychlorinated biphenyls (PCBs) (Panseri et al. 2019). Hence, maternal fish intake exposes the fetus to a mixture of toxins with well-known negative health effects (Braun and Gray 2017; Panseri et al. 2019). Several studies report a relation between POPs and obesity (Caspersen et al. 2016; Karlsen et al. 2017; Meeker 2012) and a *meta*-analysis within 12 European Birth Cohorts showed that low-level exposure to PCBs was inversely associated with fetal growth (Govarts et al. 2012).

4.3. PFAS and liver status in the infant at six months

Infants at six months had higher serum concentrations of liver enzymes if they had a higher percent weight gain after birth and if they had higher serum sum PFCA concentrations. Higher concentrations of liver enzymes in plasma are indications of liver damage (Senior 2012) and there are consistent findings regarding the effect of PFAS on higher ALT concentrations, as indicators of liver disease in adults (Zhang et al. 2024), in adolescents (Attanasio 2019) and in children (median age, 8 years (IQR 6.6–9.1)(Stratakis et al. 2020). A recent review found evidence for PFAS hepatotoxicity in rodent studies and in epidemiological studies in humans (Costello et al. 2022). Both individual and combined PFAS are shown to induce dose-dependent cytotoxicity in human liver cells(Ojo et al. 2021), to interact with hepatocyte transporters to influence PFAS toxicokinetics in animal studies (Vujic et al. 2024), to change mRNA expression of the bile acid transporter and activate the PPARα (Zhang et al. 2018), thereby triggering oxidative stress, increasing proinflammatory cytokine tumor necrosis factor (TNF-α) secretion and induce cytochrome P450 enzymes in the mouse liver (Cheng and Klaassen 2008). However, animal species differ in endogenous metabolic pathways that may confound human relevancy of PFAS exposure outcomes based on rodent data (Vujic et al. 2024).

PFAS exposure has been associated with non-alcoholic fatty liver disease (NAFLD) in children (Jin et al. 2020), possibly through alterations of the epigenome (Foulds et al. 2017; Perng et al. 2023). NAFLD is considered to be hepatic manifestations of metabolic syndrome and has been related to an increased risk for later cardiovascular disease, adverse lipid profile, obesity and insulin resistance (Angulo and Lindor 2002). NAFLD in young adults aged 18–24 years was seen after rapid weight gain during the first three months of life, not related to small size at birth per se(Breij et al. 2014).

4.4. Lipid changes in the infant at six months

Cholesterol concentrations in children are considered a risk factor for later hyperlipidemia and cardiovascular disease (Daniels et al. 2008; Khalil et al. 2018). Most studies report data from adults, adolescents and older children (Canova et al. 2021; Geiger et al. 2014; Khalil et al. 2018; Zheng et al. 2023), but there are very few observations in infants. Our data show that already at age six months, both prenatal PFAS exposure and infant PFCA concentrations were associated with an adverse lipid profile. Maternal PFOA in pregnancy week 18 was a significant positive predictor of infant total-cholesterol concentrations at six months, while infant PFOA and PFNA significantly predicted both total- and LDL-cholesterol, but not HDL-cholesterol or triglycerides. Our results are in accordance with most published data (Rappazzo et al. 2017), but a recent review including a total of 58 articles also found evidence for PFAS exposure and a positive association to HDL-cholesterol and a negative association to triglycerides (Ho et al. 2022). One longitudinal study in children found no associations between PFAS (PFDA, PFNA and PFOS) and cholesterol at birth, but strong associations at age nine years (Blomberg et al. 2021). A Korean study reported inverse relations between maternal PFAS in pregnancy week 12–16 and total-, LDL and HDL-cholesterols and triglycerides in cord blood at birth (Tian et al. 2021), which is the opposite of what we find for total-and LDL-cholesterol at six months. These results may however depend on the proportion of arterial and venous cord blood collected in the study, as venous blood

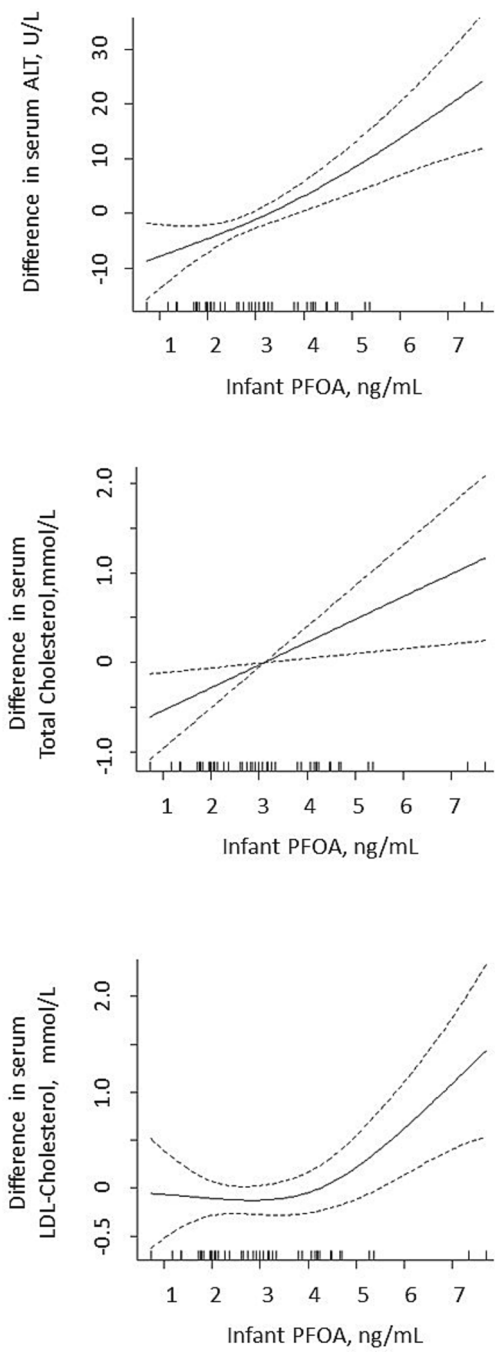

Fig. 1. Infant serum Alanine aminotransferase (ALT), Total- and Low Density Lipoprotein (LDL)-Cholesterol (n = 49) in relation to infant serum PFOA concentration at age six months, corrected for weight at six months and gender, by generalized additive models (GAM). The values on the y-axes are given as difference from the respective mean values. The lines indicate the 25th and 75th percentiles.

from the mother carry nutrients (and PFAS) to the infant, while arterial blood from the fetus carry waste products to the mother. No relations were seen between lipid concentrations and birth weight or percent weight gain in our study, but there are several reports relating low birth weight with an increased risk of a negative lipid profile in later life (Wen et al. 2010).

Animal studies have generally not indicated a mechanism that fully can explain the positive correlation between PFAS and serum cholesterol concentrations in humans, however, PFOA and PFOS activate PPARα (Vanden Heuvel et al. 2006), and currently PPARα activation is accepted as the primary mediator of the lipidemic effects (Andersen et al. 2021).

4.5. Low birth weight and the associated risk of an unfavourable metabolic profile

It is well-known that a low birth weight is associated with an increased weight gain after birth (Ong and Loos 2006), and rapid weight gain in infancy has consistently been associated with an increased risk of later obesity (Monteiro and Victora 2005). The mean reduction in birth weight in our PFAS exposed infants, resemble the reported 170 g reduction in birth weight reported to be the result of another harmful factor, namely maternal smoking in pregnancy (Butler et al. 1972). Just as prenatal PFAS exposure, also maternal smoking during pregnancy is associated with a dose-dependent increased risk of rapid weight gain in early infancy (Mine et al. 2017), and at the same time linked to obesity in childhood (Florath et al. 2014) with an increased risk of cardiovascular disease and type 2 diabetes later in early adulthood (Ekelund et al. 2007; Leunissen et al. 2009). However, a low birth weight per se is obviously not enough to cause changes in the lipid profile. Small for gestational age (SGA) infants are known to have a rapid weight gain after birth, but only those who were born to smoking mothers had an elevated risk of hypercholesterolemia in adulthood (Wen et al. 2010).

The mechanisms behind the changes in fetal growth caused by prenatal PFAS exposure or maternal smoking are currently not known. A low birth weight is considered to be a proxy for genetic and environmental factors that cause adult diseases (Gillman 2002) and this is in line with recent data showing epigenetic changes associated with prenatal PFAS exposure in loci involved in growth and development, lipid metabolism, and nutrient metabolism (Perng et al. 2023).

4.6. Strengths and limitation

Pediatric blood sampling is difficult, particularly in young infants, so PFAS analyses were available for only 94 of the 114 infants, due to unsuccessful venepuncture, and biochemical parameters were only available for 49 of the 114 infants at six months, due to lack of sample volume.

One of the limitations of this study is the relatively small sample size and the possibility of residual confounding such as maternal education, socioeconomic status and body composition. They had however no association with PFAS and were therefore not included in the regression models.

5. Conclusion

In published studies, PFAS exposure has been associated with changes in growth patterns and biochemical parameters resembling metabolic syndrome in older children and adults. Our data show that such changes are visible already in infants at age six months. Maternal PFAS status and fish intake in early pregnancy are associated with changes in fetal and infant growth patterns, and infant PFAS status is associated with higher levels of liver enzymes and cholesterol at age six months. As PFAS are readily transferred from mother to child, PFAS exposure to women of fertile age should be reduced to protect the next generation from metabolic disease.

Author contributions.

K. Varsi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Investigation, Writing – original draft.

Sandra Huber; Methodology, Analysis (chemical), Investigation, Writing – review & editing.

Maria Averina; Methodology, Investigation, Writing – review & editing.

Jan Brox: Methodology, Investigation, Writing – review & editing.

Bjørn Bolann: review & editing.

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Supervision.

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Anne-Lise Bjørke-Monsen: Writing – review & editing, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kristin Holstad:** Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sandra Huber:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Maria Averina:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Bjørn Bolann:** Writing – review & editing, Validation. **Jan Brox:** Writing – review & editing, Methodology, Data curation.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.109121.

Data availability

Data will be made available on request.

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