University of Southern Denmark

Prenatal Exposures to Perfluoroalkyl Acids and Associations with Markers of Adiposity and Plasma Lipids in Infancy: An Odense Child Cohort Study

Jensen, Richard Christian; Skovsager Andersen, Marianne; Larsen, Pia Veldt; Glintborg, Dorte; Dalgård, Christine; Timmermann, Amalie; Nielsen, Flemming; Sandberg, Maria Boysen; Andersen, Helle Raun; Thybo Christesen, Henrik; Grandjean, Philippe; Jensen, Tina Kold

Published in:
Environmental Health Perspectives

DOI:
10.1289/EHP5184

Publication date:
2020

Document version:
Final published version

Citation for pulished version (APA):
Jensen, R. C., Skovsager Andersen, M., Larsen, P. V., Glintborg, D., Dalgård, C., Timmermann, A., Nielsen, F., Sandberg, M. B., Andersen, H. R., Thybo Christesen, H., Grandjean, P., & Jensen, T. K. (2020). Prenatal Exposures to Perfluoroalkyl Acids and Associations with Markers of Adiposity and Plasma Lipids in Infancy: An Odense Child Cohort Study. *Environmental Health Perspectives*, *128*(7), Article 077001. https://doi.org/10.1289/EHP5184

Go to publication entry in University of Southern Denmark's Research Portal

Terms of use
This work is brought to you by the University of Southern Denmark.
Unless otherwise specified it has been shared according to the terms for self-archiving.
If no other license is stated, these terms apply:

- You may download this work for personal use only.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim.
Please direct all enquiries to puresupport@bib.sdu.dk

Download date: 11. Jan. 2025

A Section 508–conformant HTML version of this article
is available at https://doi.org/10.1289/EHP5184.

Prenatal Exposures to Perfluoroalkyl Acids and Associations with Markers of Adiposity and Plasma Lipids in Infancy: An Odense Child Cohort Study

Richard Christian Jensen,[1,2] Marianne S. Andersen,[2] Pia Veldt Larsen,[3] Dorte Glintborg,[2] Christine Dalgård,[1] Clara Amalie Gade Timmermann,[1] Flemming Nielsen,[1] Maria Boysen Sandberg,[4] Helle Raun Andersen,[1] Henrik Thybo Christesen,[5] Philippe Grandjean,[1,6] and Tina Kold Jensen[1,5,7]

[1]Department of Environmental Medicine, University of Southern Denmark, Odense, Denmark
[2]Department of Endocrinology, Odense University Hospital, Odense, Denmark
[3]Telepsychiatric Centre, Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[4]Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark
[5]Odense Child Cohort, Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark
[6]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
[7]Odense Patient data Exploratory Network (OPEN), University of Southern Denmark, Odense, Denmark

Background: Perfluoroalkyl acids (PFAA) are repellants that cross the placental barrier, enabling interference with fetal programming. Maternal PFAA concentrations have been associated with offspring obesity and dyslipidemia in childhood and adulthood, but this association has not been studied in infancy.

Objectives: We investigated associations between maternal PFAA concentrations and repeated markers of adiposity and lipid metabolism in infancy.

Methods: In the prospective Odense Child Cohort, maternal pregnancy serum concentrations of five PFAA: Perfluorohexane sulfonic acid (PFHxS), perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) were measured in 649 women. Offspring were examined at birth ($n=613$) and at 3 months ($n=602$) and 18 months ($n=503$) of age. Total cholesterol, LDL, HDL, and triglyceride were evaluated at 3 months ($n=262$) and 18 months ($n=198$) of age. Mixed effects linear regression models estimated associations between PFAA and standardized (SDS) body mass index (BMI), ponderal index, and waist circumference. Associations between PFAA and body fat% (BF%) and plasma lipids SDS at 3 months and 18 months of age were investigated with linear regression models.

Results: PFNA and PFDA were associated with higher BMI SDS [adjusted $\beta=0.26$; 95% confidence interval (CI): 0.03, 0.49 and $\beta=0.58$; 95% CI: –0.03, 1.19, respectively, for 1-ng/mL increases] and ponderal index SDS ($\beta=0.36$; 95% CI: 0.13, 0.59 and $\beta=1.02$; 95% CI: 0.40, 1.64, respectively) at 3 and 18 months of age (pooled) in girls. Corresponding estimates for boys were closer to the null but not significantly different from estimates for girls. In boys and girls (combined), PFNA and PFDA were associated with BF% at age 3 months (for 1-ng/mL PFDA, $\beta=0.40$; 95% CI: 0.04, 0.75), and PFDA was associated with total cholesterol SDS at 18 months ($\beta=1.06$; 95% CI: 0.08, 2.03) ($n=83$).

Discussion: Prenatal PFAA were positively associated with longitudinal markers of adiposity and higher total cholesterol in infancy. These findings deserve attention in light of rising rates of childhood overweight conditions and dyslipidemia. https://doi.org/10.1289/EHP5184

Introduction

Perfluoroalkyl acids (PFAA) are persistent chemicals used as surface repellants in fabrics and food packaging due to water-, stain-, and grease-resistant properties (ATSDR 2018). Prevalent routes of PFAA exposure are mainly dietary and, in some populations, also through drinking water. PFAA can be measured in the majority of humans with elimination half-lives ranging from 4 to 8 y (ATSDR 2018). Two of the previously most used and studied PFAA, perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), have been phased out by some of the major manufacturers (ATSDR 2018; Glynn et al. 2012). Nonetheless, other PFAA, such as perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA), are still in production, and these PFAA are less studied.

PFAA cross the placental barrier (Monroy et al. 2008), and PFAA have been detected in human amniotic fluid (Stein et al. 2012) and umbilical cord blood (Monroy et al. 2008). Some PFAA have endocrine-disrupting abilities and may influence the fetal endocrine programing related to growth patterns and lipid metabolism (Buhrke et al. 2013; Wolf et al. 2012; Ye et al. 2012; Yu et al. 2009; Zhao et al. 2011). Data from previous infancy studies investigating associations between PFAA concentrations and anthropometry differed in sample size, and anthropometric outcomes were obtained at different stages of infancy and from various sources (Table S1) (Alkhalawi et al. 2016; Andersen et al. 2010; Gyllenhammar et al. 2018; Karlsen et al. 2017; Maisonet et al. 2012; Manzano-Salgado et al. 2017; Shoaff et al. 2018; Starling et al. 2019). Three prospective studies suggested that increased maternal PFAA concentrations was linked to higher weight at 3 months of age (Gyllenhammar et al. 2018), significantly increased percent fat mass at 5 months of age in boys (Starling et al. 2019), and significantly higher weight gain z-scores [$\beta=0.13$; (95% CI: 0.01, 0.26); with a doubling of PFOA] at 6 months of age in boys (Manzano-Salgado et al. 2017). However, a Danish study found that a one-unit increase (1-ng/mL) in maternal pregnancy concentrations of PFOS was associated with small reductions in 12-month-old offspring in body mass index (BMI) z-score [$\beta=0.007$; (95% CI: -0.011, -0.002)] (Andersen et al. 2010). Two studies demonstrated that higher maternal concentration of PFOS was associated in late infancy with higher BMI z-scores and overweight risk in Faroese children 18 months old (Karlsen et al. 2017) and with increased weight in British girls

Address correspondence to R.C. Jensen, Research Unit of Environmental Medicine, Department of Public Health, University of Southern Denmark., J.B. Winsløws Vej 17A, 2. 5000 Odense C – Denmark. Telephone: +45 65 50 49 17. Email: rcjensen@health.sdu.dk

Supplemental Material is available online (https://doi.org/10.1289/EHP5184).

P.G. is supported by a grant from the National Institutes of Health (ES026596). All other authors declare they have no actual or potential competing financial interests.

Received 13 February 2019; Revised 4 June 2020; Accepted 10 June 2020; Published 6 July 2020.

Note to readers with disabilities: *EHP* strives to ensure that all journal content is accessible to all readers. However, some figures and Supplemental Material published in *EHP* articles may not conform to 508 standards due to the complexity of the information being presented. If you need assistance accessing journal content, please contact ehponline@niehs.nih.gov. Our staff will work with you to assess and meet your accessibility needs within 3 working days.

20 months old (Maisonet et al. 2012). No significant association was demonstrated between PFAA and repeated pooled measurements of ponderal index (Alkhalawi et al. 2016) during the first year of infancy, whereas there were indications of negative associations between PFOA and pooled BMI z-scores from 4 wk to 2 years of age (Shoaff et al. 2018); however, during this period, the rate of change in anthropometry was not modified by PFAA (Shoaff et al. 2018). In relation to lipid metabolism, PFOS and PFOA concentrations have been associated with hyperlipidemia in adults from the general population (Nelson et al. 2010; Steenland et al. 2009). Moreover, prenatal PFAA concentrations could affect metabolic function in offspring girls and boys differently, and five studies analyzing sex-dimorphic anthropometry found significant associations for females only in three studies (Halldorsson et al. 2012; Høyer et al. 2015; Mora et al. 2017) and for males only in two studies (Andersen et al. 2010; Manzano-Salgado et al. 2017). Five of the eight infancy studies investigated associations between PFAA exposure and repeated anthropometric measurements throughout infancy (Alkhalawi et al. 2016; Andersen et al. 2010; Gyllenhammar et al. 2018; Maisonet et al. 2012; Shoaff et al. 2018), whereas others measured anthropometry only at a single time point during infancy (Karlsen et al. 2017; Manzano-Salgado et al. 2017; Starling et al. 2019). Moreover, some studies were restricted to outcomes that were either self-reported (Andersen et al. 2010) or obtained from medical records (Alkhalawi et al. 2016; Gyllenhammar et al. 2018; Manzano-Salgado et al. 2017), whereas others collected data from regular clinical examinations (Karlsen et al. 2017; Maisonet et al. 2012; Shoaff et al. 2018; Starling et al. 2019). In general, the PFAA studies during infancy were of a sample size <447 children (Alkhalawi et al. 2016; Gyllenhammar et al. 2018; Karlsen et al. 2017; Maisonet et al. 2012; Shoaff et al. 2018; Starling et al. 2019). To the best of our knowledge, no study has investigated associations between maternal pregnancy PFAA concentrations and lipid metabolism in infancy.

We hypothesized that prenatal PFAA exposure may induce metabolic dysfunction, resulting in increased markers of adiposity and lipid metabolism observed in infancy. To our knowledge, this is the first study to prospectively explore associations of maternal PFHxS, PFOS, PFOA, PFNA, and PFDA concentrations in early pregnancy with repeated markers of adiposity and lipid metabolism in infancy.

Materials and Methods

Study Population

The present exploratory study is part of Odense Child Cohort (OCC) ($n = 2,874$), a longitudinal birth cohort conducted in Denmark (Kyhl et al. 2015). Eligible women were those residing in the Municipality of Odense, Region of Southern Denmark, and recruited in early pregnancy [gestational age (GA) <16] between 2010 and 2012. Following enrollment, the pregnant women were asked to donate a blood sample for PFAA assessment ($n = 649$) and to respond to a questionnaire on current general health. Infant anthropometric measurements were conducted at birth, and children were invited to a clinical examination, including anthropometry, at 3 months and 18 months of age (Figure 1). All parents of children participating at the clinical examination at 3 and 18 months were approached to consent for blood sample collection from the child for lipid assessment (Figure 1).

In this study, we excluded multiple pregnancy ($n = 56$), miscarriage ($n = 103$), stillbirth ($n = 10$), and mothers with no serum PFAA ($n = 2,056$) (Figure 1). Of the eligible 649 mother–child pairs with PFAA concentrations, 4 women were pregnant more than once within the inclusion period (only first pregnancy included in data set), 27 children born preterm ($GA < 37$) were excluded, and 5 children had missing anthropometric data from birth (Figure 1). Anthropometric measurements of children were performed at birth ($n = 613$), at a median age of 3.2 months [interquartile range (IQR): 2.8, 3.7] ($n = 602$) and 19.2 months (IQR: 18.6, 19.6) ($n = 530$). Among these, 84 children (51% boys, 49% girls) had a blood sample drawn from both clinical visits at 3 and 18 months of age (Figure 1).

PFAA Assessment

Assessment of maternal serum PFAA concentrations included the following compounds: PFHxS, PFOS, PFOA, PFNA, and PFDA. Serum PFAA concentrations were assessed based on blood samples obtained at inclusion [median GA (IQR): 11.3 (9.9, 14.3) weeks] in a subsample of 649 pregnant women. Of the 649 women with serum PFAA concentrations, 200 blood samples were randomly selected, and the remaining 449 blood samples were chosen based on obtainability of data from birth records, questionnaires and a clinical examination of the children at 3 months of age. PFAA concentrations were estimated using online solid phase extraction followed by liquid chromatography and triple quadruple mass spectrometry (LC-MS/MS) at the Department of Environmental Medicine, University of Southern Denmark (Jensen et al. 2015). The analyses were performed between September 2011 and September 2013. The within-batch coefficients of variation (CVs) were $<3\%$ and the between-batch CVs were $<5.2\%$. The Limit of Quantification (LOQ) was 0.03 ng/mL for all compounds. PFOS, PFOA, PFNA, and PFDA were detectable in all samples in this study ($LOQ > 0.03$ ng/mL), but 7 (1.1%) of the participants had a PFHxS concentration below the LOQ that was reported as LOQ/2.

Markers of Adiposity

Birth weight, length, and waist circumference (WC) were registered by midwives after parturition, and data were obtained from birth records. Weight, length, WC, and skinfold thickness were assessed at clinical examinations at ages 3 months and 18 months. Three health care professionals performed the clinical examination blinded to the prenatal PFAA concentrations. Weight was measured without clothing using an electronic scale (Seca 717; Seca), and recumbent length was determined to the nearest millimeter (Seca 416; Seca). WC was assessed as an indirect measure of central adiposity (Cornier et al. 2011) using a plastic measuring tape (Seca 212, Seca) to the nearest millimeter around a horizontal plane midway between the lower lateral rib border and the upper lateral hip crest border. BMI and ponderal index were proxies for total body adiposity (Hetherington-Rauth et al. 2017). BMI (in kg/m^2) was calculated as weight (kg) divided by the length squared (m^2), and ponderal index (in kg/m^3) was calculated as weight (kg) divided by the length cubed (m^3). Triceps and subscapular skinfold thicknesses were each measured three times with a Harpenden skinfold caliper (C.M.S. Weighing Equipment Ltd.) to the nearest 0.1 mm, and measures were averaged. Body fat percentage (BF%) was calculated according to Slaughter et al.'s formula (Slaughter et al. 1988) applying triceps and subscapular skinfolds according to sex.

Age- (month-by-month) and sex-specific standard deviation score (SDS) for BMI were calculated according to 2014 Danish reference data (Tinggaard et al. 2014), and age- (month-by-month) and sex-specific SDS for waist circumference and BF% SDS were calculated according to a Danish mother–child reference cohort (Wohlfahrt-Veje et al. 2014). Age- (month-by-month) and sex-specific SDS for ponderal index was calculated on basis of cohort specific internal reference values from the OCC.

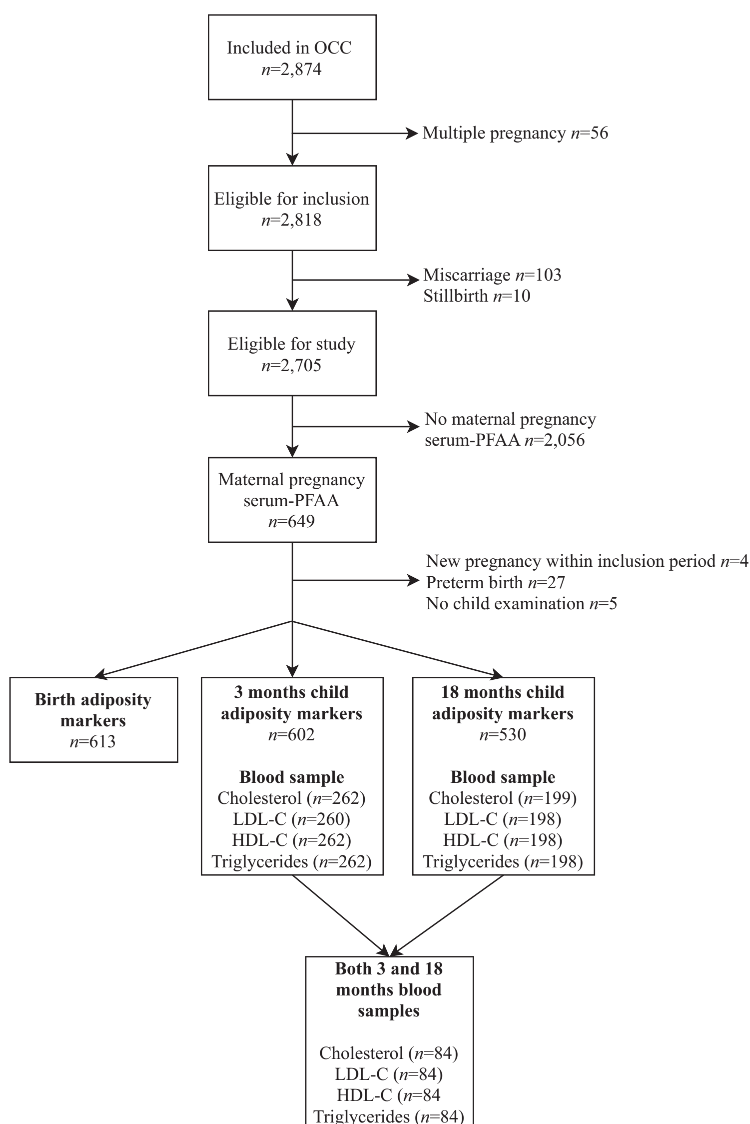

Figure 1. Flowchart of mother–child pairs.

SDS expresses the number of standard deviations a given measurement of interest lies below or above the sample mean from an age- and sex-specific reference population.

Lipid Assessment

Lipid assays were completed on nonfasting blood samples collected at 3 months and 18 months of age. Plasma total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and triglyceride (TG) concentrations were assayed using ARCHITECT (Abbott). When TG concentrations were less than $4\,mmol/L$, LDL results were calculated using the Friedewald equation (Friedewald et al. 1972). The quality of the lipid analyses was assured by participation in external quality control programs from The Reference Institute for Bioanalytics (RfB), Bonn, Germany, using "Clinical chemical analytes in serum" (8/y) and "Lipoproteins" (4/y).

Age- (month-by-month) and sex-specific SDS for biomarkers of lipid status were calculated on basis of cohort specific internal reference values from the OCC.

Covariates

Maternal age at delivery and parity were derived from hospital records using maternal civil registration numbers. Prepregnancy BMI, smoking status (yes; no) during pregnancy, breastfeeding duration (months) for the current pregnancy, and educational level (high school or less; high school + 1–4 y; high school + > 4 y) were extracted from questionnaires. If educational information was missing in questionnaires, they were retrieved from hospital records. Maternal ethnicity (European; non-European) was based on information on her mother's country of birth obtained from Odense Municipality. Characteristics of the children, including gestational age at birth and sex, were obtained from hospital records.

Ethical Approval

The study was performed in accordance with the Helsinki Declaration II and approved by the Regional Scientific Ethical Review Committee for Southern Denmark (Project ID S-20090130) and the Danish Data Protection Agency (J. No. 18/33119). All participants received written and oral information and provided their written consent for participation in the study.

Statistical Analyses

Maternal pregnancy serum PFAA concentrations were reported as median (5th–95th percentiles) in subgroups according to maternal and child characteristics. Kruskal-Wallis and Wilcoxon rank sum tests were used to compare PFAA concentrations between subgroups, and pairwise Spearman correlations were calculated for each pair of PFAA. Characteristics of included mother–child pairs in the study were compared with those of the rest of the women in the OCC using Wilcoxon rank sum tests for BMI and gestational age, and *t*-test for age, and a chi square test for smoking, ethnicity, parity, child sex, and educational level.

Random mixed effects linear regression models were used to investigate associations between maternal pregnancy PFAA concentrations and longitudinal offspring markers of adiposity, including BMI SDS, ponderal index SDS, and WC SDS, from 3 months and 18 months of age and adjusting for outcome at birth (baseline) to take baseline imbalance into account. Mother–child pairs were included as random effects to account for the repeated measurements of the children. For the outcomes BMI SDS, ponderal index SDS, and WC SDS, we modeled interaction terms between maternal PFAA concentrations and an indicator for study visit (3 months or 18 months) in the random mixed effects regression models to investigate differences in associations with the outcomes according to age and report pooled estimates for associations with outcomes at 3 months and 18 months of age (combined) when the difference in slopes was not significant ($p > 0.05$), in addition to estimates for visit-specific outcomes from the same models. The random mixed effects linear regression models estimated the difference (β-estimates) in offspring markers of adiposity (pooled and visit-specific) per 1-ng/mL increase in the maternal PFAA concentration.

Multiple linear regression models were used to examine associations between maternal pregnancy PFAA concentrations and markers of adiposity (BMI SDS, ponderal index SDS, and WC SDS) at birth. Because BF% SDS and lipid data SDS were available only at 3 months and 18 months of age, random mixed effects regression modeling could not be performed, when also adjusting for baseline (3 months) to take baseline imbalance into account, as explained below. Thus, multiple linear regression models were conducted to exploratively investigate associations between maternal PFAA concentrations and BF% SDS and lipid concentration SDS at ages 3 months and 18 months, because data for these outcomes were not available at birth. The multiple linear regression models estimated the difference (β-estimates) in markers of adiposity and lipid metabolism in children per 1-ng/mL increase in the maternal PFAA concentration. Thus, it was not possible to evaluate differences by visit for BF% and lipid concentrations, and visit-specific estimates by default were reported for these outcomes.

To address potential baseline imbalance of prenatal growth measures, the random mixed effects linear regression models at 3 months and 18 months of age were adjusted for the birth measurement of the respective outcome (BMI SDS, ponderal index SDS, and WC SDS) (Vickers and Altman 2001). Additionally, this adjustment will correct for any effect of exposures on growth until birth. The multiple linear regression models with BF% and markers of lipid metabolism as outcome of interest at 18 months of age were adjusted for the baseline measurement at 3 months of age (Vickers and Altman 2001). Confounders and intermediate factors were identified based on *a priori* review of published evidence and using directed acyclic graphs (DAGs) (Figure S1). PFAA concentrations have been reported to change across categories of parity (Brantsæter et al. 2013), age (Bjerregaard-Olesen et al. 2016), education (Bjerregaard-Olesen et al. 2016), offspring sex (Frisbee et al. 2010), BMI (Brantsæter et al. 2013), and smoking (Bjerregaard-Olesen et al. 2016). These covariates have also been associated with childhood adiposity and lipid metabolism (Woo Baidal et al. 2016). Thus, in mixed effects linear regression models we *a priori* included the following potential confounders: maternal age at delivery (continuous), parity (nulliparous; parous), prepregnancy BMI (continuous), maternal educational level (high school or less; high school + 1–4 y; high school + > 4 y), maternal smoking (yes; no), offspring sex (girl; boy), visit (three months; 18 months), and adiposity measurements at birth (continuous). The adjusted linear regression models at birth and 3 months of age included the potential confounders: maternal age at delivery, parity, prepregnancy BMI, maternal educational level, maternal smoking, and offspring sex. The linear regression models at 18 months of age were additionally adjusted for the outcome at 3 months. As a sensitivity analysis, lipid outcomes at ages 3 months and 18 months were additionally adjusted for offspring BMI SDS at respective ages.

In all adjusted statistical models, maternal prepregnancy BMI was additionally included as a second-degree polynomial to allow for nonlinear associations. Moreover, effect modification by child sex on the associations between PFAA concentrations and markers of adiposity and lipid metabolism was evaluated by including an interaction term (between PFAA concentration and sex) in all the adjusted models. These models were used to obtain sex-specific results.

Model assumptions of all models were validated through thorough residual analyses, and multicollinearity was assessed using variance inflation factors. Missing data were assumed to occur at random, and all statistical analyses were based on complete cases. A two-sided significance level of 5% was used in all analyses, including evaluation of effect modifiers. Data were analyzed using STATA/IC version 15.1 (StataCorp).

Results

Of the 613 mother–child pairs, mothers were predominantly nulliparous (57.9%) with a mean age of 30.2 y (± 4.5 y) y at the time of parturition; 97.7% were of European origin, 18.4% were in the highest educational group (completed high school + > 4 y), and 3.4% smoked during pregnancy (Table 1). Included mother–child pairs did not differ statistically from the rest of the OCC with regard to major characteristics, but were more often nulliparous, of European origin, smoked less, and had a higher prepregnancy BMI (Table S2). The included children were evenly distributed by sex (47% girls and 53% boys) with a mean BMI SDS of 0.02 (± 1.01), 0.07 (± 0.97), and -0.20 (± 1.01) at birth, 3 months, and 18 months of age, respectively (Table S3). The subgroup of children with lipid outcomes at both 3 months and 18 months of age ($n = 84$) did not differ in relation to major maternal or child characteristics when compared with the subset of mother–child pairs with anthropometric measurements but were more often nulliparous, of European origin, smoked less, and had a higher prepregnancy BMI when compared with the rest of the OCC (Table S2).

All pregnant women had detectable serum concentrations of at least four PFAA, but 1.1% of the women had a PFHxS concentration below the LOQ (Table S4). The five maternal PFAA concentrations were weakly to strongly intercorrelated with Spearman's correlation coefficients ranging from 0.33 (PFHxS and PFDA) to 0.74 (PFNA and PFDA) (Table S5). Concentrations of all five PFAA were higher among nulliparous vs. parous women and among women giving birth at 37–40 wk vs. ≥40 wk of gestational age (Table 1). PFOS and PFOA decreased with increasing maternal age and higher educational level, PFNA and PFDA decreased with higher prepregnancy BMI; and PFHxS, PFOA, and PFNA

Table 1. Maternal pregnancy serum PFAA concentration according to maternal and offspring characteristics.

Variables	n (%)	Median (5th, 95th percentile)				
		PFHxS (ng/mL)	PFOS (ng/mL)	PFOA (ng/mL)	PFNA (ng/mL)	PFDA (ng/mL)
Total	613 (100)	0.30 (0.08, 0.66)	8.04 (3.82, 15.46)	1.62 (0.67, 4.03)	0.66 (0.33, 1.52)	0.26 (0.15, 0.53)
Maternal characteristics						
Maternal age (y)						
<25	61 (10.0)	0.27 (0.13, 0.56)	8.68 (4.98, 14.80)	1.87 (0.73, 4.50)	0.72 (0.29, 1.75)	0.26 (0.15, 0.44)
25–29	220 (35.9)	0.30 (0.06, 0.66)	8.36 (3.65, 17.25)	1.84 (0.73, 4.34)	0.72 (0.32, 1.63)	0.28 (0.13, 0.59)
30–34	222 (36.2)	0.29 (0.08, 0.59)	7.82 (4.22, 15.17)	1.56 (0.67, 3.85)	0.63 (0.37, 1.32)	0.26 (0.16, 0.46)
>35	110 (17.9)	0.30 (0.10, 0.72)	7.16 (3.61, 13.24)	1.28 (0.54, 3.98)	0.62 (0.27, 1.33)	0.24 (0.14, 0.64)
p-Value		0.92	0.01	<0.01	0.08	0.21
Prepregnancy BMI (kg/m^2)						
<18.5	15 (2.4)	0.34 (0.03, 0.78)	8.36 (3.41, 16.72)	1.87 (0.31, 3.28)	0.84 (0.27, 1.52)	0.29 (0.12, 0.58)
18.5–25.0	357 (58.2)	0.30 (0.07, 0.66)	8.14 (3.79, 15.46)	1.67 (0.67, 4.49)	0.69 (0.34, 1.50)	0.28 (0.15, 0.56)
≥25.0	241 (39.3)	0.29 (0.09, 0.59)	7.73 (3.83, 15.30)	1.57 (0.73, 3.81)	0.62 (0.31, 1.52)	0.25 (0.15, 0.43)
p-Value		0.26	0.49	0.87	0.08	0.02
Parity						
Nulliparous	355 (57.9)	0.36 (0.12, 0.70)	8.85 (4.23, 16.81)	2.01 (0.86, 4.61)	0.73 (0.37, 1.64)	0.28 (0.16, 0.59)
Parous	258 (42.1)	0.24 (0.05, 0.52)	6.80 (3.60, 14.23)	1.16 (0.54, 3.13)	0.57 (0.29, 1.16)	0.24 (0.14, 0.48)
p-Value		<0.01	<0.01	<0.01	<0.01	<0.01
Smoking						
Yes	21 (3.4)	0.30 (0.09, 0.59)	8.71 (5.50, 12.30)	1.94 (1.20, 2.82)	0.62 (0.41, 1.10)	0.23 (0.16, 0.45)
No	592 (96.6)	0.30 (0.08, 0.66)	7.85 (3.79, 15.67)	1.60 (0.67, 4.14)	0.66 (0.33, 1.52)	0.26 (0.15, 0.53)
p-Value		0.93	0.23	0.09	0.90	0.26
Educational level						
High school or less	184 (30.0)	0.28 (0.09, 0.59)	8.51 (3.91, 16.46)	1.83 (0.74, 4.78)	0.67 (0.32, 1.74)	0.26 (0.14, 0.58)
High school+1–4 y	308 (50.2)	0.29 (0.07, 0.63)	8.13 (3.82, 15.31)	1.53 (0.63, 3.85)	0.65 (0.34, 1.47)	0.26 (0.14, 0.47)
High school+ > 4 y	113 (18.4)	0.32 (0.10, 0.70)	7.23 (3.65, 15.67)	1.58 (0.65, 3.78)	0.71 (0.35, 1.47)	0.28 (0.15, 0.53)
Missing	8 (1.4)					
p-Value		0.18	0.02	0.01	0.20	0.36
Ethnicity						
European	599 (97.7)	0.30 (0.08, 0.63)	8.07 (3.83, 15.67)	1.63 (0.69, 4.01)	0.66 (0.33, 1.51)	0.26 (0.15, 0.52)
Non-European	14 (2.3)	0.21 (0.03, 0.85)	5.07 (1.25, 13.44)	1.12 (0.31, 9.71)	0.71 (0.27, 4.40)	0.33 (0.12, 1.75)
p-Value		0.38	0.01	0.22	0.77	0.23
Child characteristics						
Child sex						
Boys	325 (53 0)	0.31 (0.12, 0.63)	8.47 (4.07, 15.46)	1.70 (0.74, 4.61)	0.70 (0.35, 1.55)	0.27 (0.14, 0.59)
Girls	288 (47.0)	0.28 (0.07, 0.66)	7.51 (3.61, 15.17)	1.57 (0.58, 3.70)	0.63 (0.30, 1.45)	0.26 (0.15, 0.47)
p-Value		0.04	0.07	<0.01	0.03	0.27
Gestational age (weeks)						
37–40	244 (39.8)	0.31 (0.12, 0.63)	8.51 (3.94, 17.18)	1.80 (0.71, 4.14)	0.70 (0.35, 1.58)	0.27 (0.15, 0.53)
>40	369 (60.2)	0.28 (0.07, 0.66)	7.78 (3.65, 14.33)	1.52 (0.67, 3.98)	0.64 (0.31, 1.43)	0.26 (0.14, 0.52)
p-Value		0.01	<0.01	<0.01	0.03	0.04
Exclusive breastfeeding (months)						
0	100 (16.3)	0.33 (0.09, 0.71)	8.30 (4.14, 16.24)	1.71 (0.69, 3.81)	0.67 (0.38, 1.57)	0.25 (0.15, 0.60)
>0–3	222 (36.2)	0.28 (0.07, 0.61)	8.53 (3.94, 16.50)	1.82 (0.78, 4.90)	0.70 (0.30, 1.57)	0.27 (0.15, 0.57)
3–6	182 (29.7)	0.30 (0.09, 0.62)	7.73 (3.82, 15.67)	1.47 (0.66, 3.58)	0.63 (0.34, 1.31)	0.26 (0.15, 0.47)
>6	31 (5.1)	0.29 (0.13, 0.60)	8.11 (3.58, 13.24)	1.44 (0.54, 3.70)	0.70 (0.31, 1.84)	0.28 (0.15, 0.43)
Missing	78 (12.7)					
p-Value		0.44	0.17	0.02	0.27	0.36
Birth weight						
<2,500 g	2 (0.3)	0.53 (0.33, 0.72)	8.95 (7.80, 10.11)	2.48 (2.33, 2.63)	0.71 (0.58, 0.84)	0.26 (0.22, 0.30)
2,500–4,499 g	587 (95.8)	0.30 (0.08, 0.66)	8.06 (3.82, 15.67)	1.65 (0.67, 4.03)	0.67 (0.33, 1.52)	0.26 (0.15, 0.53)
>4,499 g	24 (3.9)	0.28 (0.07, 0.54)	7.38 (4.21, 14.23)	1.28 (0.70, 2.39)	0.64 (0.40, 0.99)	0.27 (0.17, 0.36)
p-Value		0.34	0.68	0.02	0.84	0.99

Note: BMI, body mass index; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid. p-Value, when comparing PFAA concentrations between subgroups according to maternal and child characteristics using Kruskal-Wallis or Wilcoxon rank sum tests.

were higher in women with male offspring in comparison with women with female offspring.

At birth, 1-ng/mL increases in PFOS and PFHxS were associated with increases in the ponderal index SDS of 0.03 (95% CI: 0.01, 0.05) and 0.24 (95% CI: 0.01, 0.47), respectively, after confounder adjustment (Table 2). In the adjusted random mixed effects linear regression models including the whole study group, interaction terms (p_{int}) between PFAA and visit indicated no significant differences in the slopes at 3 months and 18 months of age for offspring BMI SDS (all $p_{int} \geq 0.42$), ponderal index SDS ($p_{int} \geq 0.43$), and WC SDS ($p_{int} \geq 0.06$). In adjusted analyses at 3 months and 18 months of age (pooled), 1-ng/mL increases in PFOA, PFNA, and PFDA were associated with average increases in the ponderal index SDS of 0.07 (95% CI: 0.01, 0.13), 0.24 (95% CI: 0.08, 0.41), and 0.60 (95% CI: 0.18, 1.02), respectively. Likewise, 1-ng/mL increases in PFNA, PFDA, and PFOA at 3 months and 18 months of age were associated with average increases in the BMI SDS of 0.18 (95% CI: 0.02, 0.34), 0.42 (95% CI: 0.01, 0.84), and 0.04 (95% CI: −0.01, 0.10), respectively. When stratified according to child sex, in girls at 3 months and 18 months of age, PFNA and PFDA concentrations were associated with increased BMI SDS [PFNA: 0.26 (95% CI: 0.03, 0.49), PFDA: 0.58 (95% CI: −0.03, 1.19)] and ponderal index SDS [PFNA: 0.36 (95% CI: 0.13, 0.59), PFDA: 1.02 (95% CI:

Table 2. Average difference (β) in marker of adiposity in offspring at 3 and 18 months of age pooled, and at respective visits for 1-unit (ng/mL) increase in maternal pregnancy serum PFAA concentration.

	BMI SDS			Ponderal index SDS			Waist circumference SDS		
Compound (ng/mL)	β (95% CI)	p	p_{int}[a]	β (95% CI)	p	p_{int}[a]	β (95% CI)	p	p_{int}[a]
PFHxS pooled 3 and 18 months									
Crude[b]	0.04 (−0.16, 0.25)	0.68		0.07 (−0.13, 0.28)	0.48		−0.01 (−0.20, 0.18)	0.94	
Adjusted[c]	0.04 (−0.16, 0.24)	0.67	0.90	0.08 (−0.12, 0.29)	0.43	0.69	0.01 (−0.18, 0.19)	0.95	0.62
Respective visits									
Birth[d]	0.19 (−0.04, 0.43)	0.11		0.24 (0.01, 0.47)	0.05		0.13 (−0.11, 0.36)	0.28	
3 months[e]	0.05 (−0.18, 0.28)	0.66		0.10 (−0.14, 0.33)	0.42		0.03 (−0.18, 0.25)	0.76	
18 months[e]	0.04 (−0.19, 0.26)	0.76		0.05 (−0.18, 0.29)	0.67		−0.02 (−0.24, 0.20)	0.84	
PFOS pooled 3 and 18 months									
Crude[b]	−0.01 (−0.03, 0.01)	0.46		−0.01 (−0.03, 0.02)	0.62		−0.01 (−0.03, 0.004)	0.12	
Adjusted[c]	−0.01 (−0.03, 0.01)	0.53	0.84	−0.004 (−0.03, 0.02)	0.77	0.85	−0.01 (−0.03, 0.01)	0.31	0.18
Respective visits									
Birth[d]	0.02 (−0.01, 0.04)	0.15		0.03 (0.01, 0.05)	0.02		0.001 (−0.02, 0.02)	0.95	
3 months[e]	−0.01 (−0.03, 0.02)	0.63		−0.005 (−0.03, 0.016)	0.63		−0.02 (−0.04, 0.004)	0.13	
18 months[e]	−0.01 (−0.03, 0.02)	0.52		−0.003 (−0.03, 0.020)	0.78		−0.001 (−0.02, 0.02)	0.93	
PFOA pooled 3 and 18 months									
Crude[b]	0.03 (−0.03, 0.08)	0.35		0.05 (−0.003, 0.11)	0.06		−0.01 (−0.06, 0.04)	0.73	
Adjusted[c]	0.04 (−0.01, 0.10)	0.14	0.42	0.07 (0.01, 0.13)	0.02	0.43	0.01 (−0.04, 0.07)	0.62	0.06
Respective visits									
Birth[d]	0.02 (−0.04, 0.09)	0.50		0.05 (−0.01, 0.12)	0.10		−0.02 (−0.08, 0.05)	0.59	
3 months[e]	0.03 (−0.03, 0.10)	0.29		0.06 (−0.004, 0.12)	0.07		−0.01 (−0.07, 0.05)	0.72	
18 months[e]	0.06 (−0.01, 0.13)	0.09		0.09 (0.02, 0.16)	0.02		0.05 (−0.02, 0.12)	0.13	
PFNA pooled 3 and 18 months									
Crude[b]	0.13 (−0.04, 0.30)	0.13		0.20 (0.03, 0.36)	0.02		0.03 (−0.12, 0.18)	0.70	
Adjusted[c]	0.18 (0.02, 0.34)	0.03	0.74	0.24 (0.08, 0.41)	<0.01	0.82	0.09 (−0.06, 0.24)	0.25	0.62
Respective visits									
Birth[d]	−0.04 (−0.23, 0.15)	0.65		0.03 (−0.16, 0.21)	0.79		−0.10 (−0.30, 0.09)	0.28	
3 months[e]	0.17 (−0.01, 0.35)	0.07		0.23 (0.05, 0.42)	0.01		0.07 (−0.11, 0.24)	0.45	
18 months[e]	0.20 (0.01, 0.39)	0.04		0.25 (0.06, 0.45)	0.01		0.12 (−0.07, 0.30)	0.22	
PFDA pooled 3 and 18 months									
Crude[b]	0.33 (−0.10, 0.76)	0.13		0.53 (0.11, 0.96)	0.02		0.03 (−0.37, 0.42)	0.90	
Adjusted[c]	0.42 (0.01, 0.84)	0.05	0.89	0.60 (0.18, 1.02)	<0.01	0.92	0.10 (−0.28, 0.49)	0.60	0.97
Respective visits									
Birth[d]	0.08 (−0.40, 0.56)	0.74		0.20 (−0.27, 0.67)	0.41		−0.07 (−0.55, 0.41)	0.78	
3 months[e]	0.41 (−0.04, 0.87)	0.08		0.61 (0.14, 1.07)	0.01		0.10 (−0.34, 0.54)	0.66	
18 months[e]	0.38 (−0.12, 0.88)	0.12		0.59 (0.07, 1.10)	0.03		0.11 (−0.36, 0.57)	0.65	

Note: BMI, body mass index; CI, confidence interval; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; SDS, standard deviation scores.
[a]Interaction between the compound and visit (3 months or 18 months), tested with the likelihood-ratio test.
[b]Mixed modeling ($n = 600$ for BMI SDS and ponderal index SDS, $n = 596$ for waist circumference SDS).
[c]Mixed modeling: Adjusted for maternal age, parity, prepregnancy BMI, prepregnancy BMI^2, educational level, smoking, sex, visit, and adiposity marker at birth. ($n = 593$ for BMI SDS and ponderal index SDS, $n = 589$ for waist circumference SDS).
[d]Linear regression: Adjusted for maternal age, parity, prepregnancy BMI, prepregnancy BMI^2, educational level, smoking, and sex. ($n = 593$ for BMI SDS and ponderal index SDS, $n = 589$ for waist circumference SDS).
[e]Mixed modeling: Adjusted for maternal age, parity, prepregnancy BMI, prepregnancy BMI^2, educational level, smoking, sex, and adiposity marker at birth. ($n = 593$ for BMI SDS and ponderal index SDS; $n = 589$ for waist circumference SDS).

0.40, 1.64)] (Table 3). Corresponding estimates for boys were closer to the null (e.g., for PFNA and BMI SDS, 0.10; 95% CI: –0.12, 0.33), but were not significantly different from estimates for girls (p_{int} 0.07–0.42).

As BF% SDS and lipid concentration SDS were available only at 3 months and 18 months of age, it was not feasible to evaluate differences by visit and also adjust for baseline (3 months of age). By default, we report separate effect estimates for age-specific BF% SDS and lipid concentration SDS only.

PFNA and PFDA were positively associated with BF% SDS at 3 months of age (adjusted $\beta = 0.20$; 95% CI: 0.06, 0.34 and $\beta = 0.40$; 95% CI: 0.04, 0.75 for 1-ng/mL increases, respectively), but not at 18 months of age (Table 4). Associations between maternal PFAA and BF% were similar in girls and boys (all $p_{int} \geq 0.50$) (Table 4).

Maternal PFDA and PFNA were associated with higher total cholesterol SDS in offspring at 18 months (adjusted $\beta = 1.06$; 95% CI: 0.08, 2.03 and $\beta = 0.37$; 95% CI: -0.05, 0.79 for 1-ng/mL increases, respectively) but not at 3 months of age (Table 5). In addition, there was a positive association between maternal PFDA and TG SDS at 18 months of age (adjusted $\beta = 0.92$; 95% CI: –0.11, 1.95 for 1-ng/mL increase). Gender-specific associations between maternal PFAA and lipid outcomes were based on data for 125–126 girls and 133–134 boys at 3 months of age, and 40 girls and 43 boys at 18 months of age; therefore, estimates are imprecise and should be interpreted with caution, especially for outcomes measured at 18 months of age (Table 6). There were no clear differences between girls and boys for associations with lipid outcomes at 3 months of age, with the exception of HDL SDS, which showed inverse associations among girls and positive associations among boys for PFHxS, PFOS, PFNA, and PFDA ($p_{int} = 0.02$–0.08). For LDL SDS in offspring at 18 months, associations with PFOA, PFNA, and PFDA were positive for girls and inverse for boys (p_{int} of 0.01, 0.07,

Table 3. Adjusted average difference (β) in adiposity marker in offspring at 3 and 18 months of age (pooled data) for 1-unit (ng/mL) increase in maternal pregnancy serum PFAA concentration stratified according to sex obtained from random mixed effects linear regression models.

Compound (ng/mL)	BMI SDS			Ponderal index SDS			Waist circumference SDS		
	Girls ($n = 275$) β (95% CI)	Boys ($n = 318$) β (95% CI)	p_{int} [a]	Girls ($n = 275$) β (95% CI)	Boys ($n = 318$) β (95% CI)	p_{int} [a]	Girls ($n = 274$) β (95% CI)	Boys ($n = 315$) β (95% CI)	p_{int} [a]
PFHxS									
Adjusted[b]	0.03 (−0.19, 0.24)	0.13 (−0.34, 0.60)	0.70	0.02 (−0.14, 0.82)	0.34 (−0.14, 0.82)	0.24	0.02 (−0.19, 0.22)	−0.05 (−0.49, 0.39)	0.80
PFOS									
Adjusted[b]	−0.01 (−0.04, 0.02)	−0.004 (−0.03, 0.02)	0.84	−0.01 (−0.04, 0.02)	−0.001 (−0.03, 0.03)	0.64	−0.01 (−0.04, 0.01)	−0.01 (−0.03, 0.02)	0.80
PFOA									
Adjusted[b]	0.06 (−0.02, 0.14)	0.03 (−0.04, 0.11)	0.67	0.09 (0.004, 0.17)	0.06 (−0.02, 0.13)	0.58	−0.01 (−0.09, 0.07)	0.03 (−0.04, 0.11)	0.40
PFNA									
Adjusted[b]	0.26 (0.03, 0.49)	0.10 (−0.12, 0.33)	0.33	0.36 (0.13, 0.59)	0.13 (−0.10, 0.36)	0.16	0.14 (−0.08, 0.35)	0.04 (−0.17, 0.25)	0.52
PFDA									
Adjusted[b]	0.58 (−0.03, 1.19)	0.24 (−0.31, 0.80)	0.42	1.02 (0.40, 1.64)	0.25 (−0.32, 0.82)	0.07	0.07 (−0.50, 0.65)	0.13 (−0.38, 0.64)	0.89

Note: BMI, body mass index; CI, confidence interval; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; SDS, standard deviation scores.

[a]Interaction between the compound and sex, tested with the likelihood-ratio test.

[b]Adjusted for maternal age, parity, prepregnancy BMI, prepregnancy BMI^2, educational level, smoking, visit, and adiposity marker at birth.

and <0.01, respectively), whereas associations between the same PFAA and triglyceride SDS at 18 months of age were positive for boys and close to the null for girls (all $p_{int} < 0.01$). PFNA and PFDA were positively associated with total cholesterol SDS at 18 months of age in boys and girls, without significant differences by gender (p_{int} 0.59 and 0.41, respectively). Associations between maternal PFAA and lipid outcomes at 3 months and 18 months of age did not markedly change when additionally adjusted for BMI SDS at the same ages (Tables S6–S7).

Discussion

Maternal PFNA and PFDA concentrations during pregnancy were associated with offspring having higher BMI SDS and ponderal index SDS at 3 months and 18 months of age, and higher BF% SDS at 3 months of age. PFNA and PFDA concentrations were positively associated with BMI SDS and ponderal index SDS in girls at 3 months and 18 months of age. In boys, corresponding associations were also positive, but estimates were closer to the null, and they were not significantly different from estimates for girls.

In the present study, maternal pregnancy PFNA concentrations were comparable with findings reported in a Spanish study (Manzano-Salgado et al. 2017), whereas prenatal maternal PFOS and PFOA concentrations were generally lower than those reported in previous studies (Andersen et al. 2010; Braun et al. 2016; Maisonet et al. 2012; Mora et al. 2017). These differences may reflect temporal and/or spatial differences in PFAA exposures.

Our results support the study hypothesis that prenatal PFAA exposure may induce metabolic dysfunction resulting in increased markers of adiposity in infancy, and the findings expand and are in line with observations from other infancy studies. Also, for study participants at 3 months of age, a recent Swedish study demonstrated nonsignificant positive associations between maternal concentrations of PFHxS, PFOS, PFNA, and PFOA and weight SDS in infants (Gyllenhammar et al. 2018). Moreover, maternal plasma PFOA concentration was associated with greater weight gain until 6 months of age in Spanish boys, but not in girls (Manzano-Salgado et al. 2017). Maternal serum PFOS concentration was associated with increased BMI SDS and overweight risk in 18-month-old Faroese children (Karlsen et al. 2017) and with increased weight in British girls 20 months of age (Maisonet et al. 2012). It is interesting to note that we found that higher maternal pregnancy PFNA and PFDA concentrations were associated with increased BF% SDS at 3 months of age, but not at 18 months of age. Likewise, a recent American study reported that higher maternal pregnancy concentrations of PFNA and PFOA were associated with greater fat mass in boys at 5 months of age, but they had only one fat mass measurement during infancy (Starling et al. 2019). We still demonstrated positive associations between PFNA and PFDA concentrations and BMI SDS and ponderal index SDS at 18 months of age. This finding may reflect that our markers of adiposity are sensitive to different compartments of body composition, because BMI and ponderal index are proxies for total adiposity, with restricted ability to detect specific changes in fat percentage throughout infancy in comparison with the skinfold thickness BF% marker (Rodríguez et al. 2005). Moreover, early infancy represents a period of rapid changes and unequal growth rates. The postnatal weight gain is primarily due to the increase in the infant's fat mass, which peaks around 6 months of age (Demerath and Fields 2014; Wohlfahrt-Veje et al. 2014). This increase is followed by a slowed growth rate of fat mass in comparison with the increasing growth rate of fat-free mass, resulting in a declined BF% (Demerath and Fields 2014; Wohlfahrt-Veje et al. 2014). This decline in percentage body fat after 6 months in infants could

Table 4. Adjusted difference (β) in body fat % (BF%) in offspring at 3 months and 18 months of age for 1-unit (ng/mL) increase in maternal pregnancy serum PFAA concentration obtained from linear regression models.

Compound (ng/mL)	BF% SDS All β (95% CI)	BF% SDS Girls β (95% CI)	BF% SDS Boys β (95% CI)	p_{int}[a]
PFHxS				
3 months[b]	0.04 (−0.14, 0.22)	0.04 (−0.15, 0.23)	0.03 (−0.39, 0.44)	0.96
18 months[c]	−0.08 (−0.27, 0.11)	−0.08 (−0.29, 0.12)	−0.07 (−0.53, 0.39)	0.95
PFOS				
3 months[b]	−0.0004 (−0.02, 0.02)	−0.001 (−0.02, 0.02)	−0.003 (−0.02, 0.02)	0.99
18 months[c]	0.01 (−0.01, 0.03)	0.01 (−0.01, 0.04)	0.01 (−0.02, 0.02)	0.69
PFOA				
3 months[b]	0.05 (−0.002, 0.10)	0.06 (−0.03, 0.14)	0.07 (−0.002, 0.13)	0.50
18 months[c]	0.02 (−0.04, 0.07)	0.03 (−0.05,0.11)	0.002 (−0.08, 0.08)	0.61
PFNA				
3 months[b]	0.20 (0.06, 0.34)	0.20 (0.002, 0.40)	0.19 (−0.004, 0.39)	0.94
18 months[c]	0.05 (−0.12, 0.21)	0.03 (−0.19, 0.26)	0.06 (−0.17, 0.29)	0.89
PFDA				
3 months[b]	0.40 (0.04, 0.75)	0.41 (−0.13, 0.94)	0.39 (−0.09, 0.86)	0.96
18 months[c]	0.10 (−0.33, 0.54)	−0.04 (−0.65, 0.57)	0.24 (−0.37, 0.85)	0.52

Note: BF%, body fat %; CI, confidence interval; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; SDS, standard deviation scores.
[a]Interaction between the compound and sex, adjusted as described under [b] or [c], tested with the Wald test.
[b]Adjusted for maternal age, parity, prepregnancy BMI, prepregnancy BMI^2, educational level, smoking, and sex (not in sex-specific analyses) (All: $n=585$, girls: $n=272$, boys: $n=313$).
[c]Adjusted for maternal age, parity, prepregnancy BMI, prepregnancy BMI^2, educational level, smoking, sex (not in sex-specific analyses), and BF% at age 3 months (All: $n=473$, girls: $n=218$, boys: $n=255$).

potentially have attenuated our associations between PFNA and PFDA concentrations and BF% SDS at 18 months of age. In addition, as the infant grows, the impact of prenatal PFAA exposure on the measured markers of adiposity at 18 months of age may decline, and the child's own exposure to environmental factors, such as PFAA, may start to have a greater influence.

We estimated that higher maternal serum PFNA and PFDA concentrations were associated with increased total cholesterol SDS at 18 months of age in girls and boys, but estimates were based on a subset of observations [$n=83$ (40 girls and 43 boys)]. Previous reports on associations between PFAA concentrations and lipid metabolism in childhood and adolescence (Frisbee et al. 2010; Geiger et al. 2014; Manzano-Salgado et al. 2017; Zeng et al. 2015) included only a single time point measurement of lipid metabolism (Frisbee et al. 2010; Geiger et al. 2014; Manzano-Salgado et al. 2017; Zeng et al. 2015) or were of a cross-sectional design (Frisbee et al. 2010; Geiger et al. 2014; Zeng et al. 2015), thus limiting an extensive assessment of dyslipidemia over time. However, a recent prospective Spanish study (Manzano-Salgado et al. 2017) reported that maternal PFHxS concentrations were associated with increased TG SDS in children 4 years of age ($n=627$). In comparison with our study population, the mean maternal pregnancy PFHxS concentration was two-fold higher in the Spanish study (Manzano-Salgado et al. 2017).

Evidence from experimental studies suggests that PFAA may affect complex metabolic pathways relevant to childhood adiposity and lipid metabolism by interfering with peroxisome proliferator–

Table 5. Adjusted difference (β) in lipid outcome in offspring at 3 months and 18 months of age for 1-unit (ng/mL) increase in maternal pregnancy serum PFAA concentration obtained from linear regression models.

	Total cholesterol SDS		LDL SDS		HDL SDS		Triglyceride SDS	
Compound (ng/mL)	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
PFHxS								
3 months[a]	−0.08 (−0.33, 0.17)	0.54	0.01 (−0.24, 0.26)	0.93	−0.08 (−0.34, 0.18)	0.55	0.18 (−0.07, 0.44)	0.16
18 months[b]	−0.06 (−0.32, 0.21)	0.68	−0.06 (−0.35, 0.22)	0.65	0.02 (−0.23, 0.27)	0.89	−0.24 (−0.51, 0.04)	0.09
PFOS								
3 months[a]	0.01 (−0.03, 0.04)	0.66	0.02 (−0.02, 0.05)	0.41	0.003 (−0.04, 0.04)	0.89	−0.01 (−0.05, 0.02)	0.50
18 months[b]	0.02 (−0.05, 0.08)	0.60	0.04 (−0.03, 0.10)	0.28	−0.03 (−0.09, 0.02)	0.26	0.001 (−0.06, 0.07)	0.99
PFOA								
3 months[a]	−0.08 (−0.18, 0.03)	0.14	−0.02 (−0.13, 0.08)	0.65	−0.07 (−0.17, 0.04)	0.22	−0.03 (−0.13, 0.08)	0.61
18 months[b]	0.07 (−0.07, 0.22)	0.32	0.04 (−0.12, 0.20)	0.63	−0.05 (−0.19, 0.09)	0.48	0.10 (−0.05, 0.26)	0.19
PFNA								
3 months[a]	−0.15 (−0.44, 0.13)	0.30	−0.06 (−0.35, 0.23)	0.67	−0.04 (−0.34, 0.26)	0.78	−0.10 (−0.39, 0.20)	0.52
18 months[b]	0.37 (−0.05, 0.79)	0.08	0.24 (−0.21, 0.70)	0.29	−0.001 (−0.41, 0.40)	0.98	0.18 (−0.26, 0.63)	0.41
PFDA								
3 months[a]	−0.23 (−0.90, 0.43)	0.49	−0.05 (−0.73, 0.62)	0.87	0.004 (−0.68, 0.69)	0.99	−0.21 (−0.88, 0.47)	0.55
18 months[b]	1.06 (0.08, 2.03)	0.03	0.64 (−0.43, 1.71)	0.24	−0.13 (−1.08, 0.83)	0.79	0.92 (−0.11, 1.95)	0.08

Note: CI, confidence interval; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; SDS, standard deviation scores.
[a]Adjusted for maternal age, parity, prepregnancy BMI, prepregnancy BMI^2, educational level, smoking, and sex ($n=260$ for total cholesterol SDS, HDL SDS, and triglyceride SDS; and $n=258$ for LDL SDS).
[b]Adjusted for maternal age, parity, prepregnancy BMI, prepregnancy BMI^2, educational level, smoking, sex, and lipid outcome at age 3 months ($n=83$ for all markers of lipid metabolism).

Table 6. Adjusted difference (β) in lipid concentration in offspring at 3 months and 18 months of age for 1-unit (ng/mL) increase in maternal pregnancy serum PFAA concentration stratified according to sex, obtained from linear regression models.

Compound (ng/mL)	Total cholesterol SDS Girls β (95% CI)	Total cholesterol SDS Boys β (95% CI)	p_{int} [a]	LDL SDS Girls β (95% CI)	LDL SDS Boys β (95% CI)	p_{int} [a]	HDL SDS Girls β (95 % CI)	HDL SDS Boys β (95% CI)	p_{int} [a]	Triglyceride SDS Girls β (95% CI)	Triglyceride SDS Boys β (95% CI)	p_{int} [a]
PFHxS												
3 months[b]	−0.11 (−0.37, 0.16)	0.13 (−0.58, 0.85)	0.53	0.05 (−0.22, 0.32)	−0.28 (−1.01, 0.44)	0.39	−1.19 (−0.46, 0.08)	0.73 (0.001, 1.47)	0.02	0.21 (−0.06, 0.48)	−0.02 (−0.75, 0.71)	0.56
18 months[c]	−0.05 (−0.32, 0.21)	−0.10 (−1.41, 1.21)	0.95	−0.08 (−0.37, 0.21)	0.37 (−1.02, 1.76)	0.53	0.01 (−0.25, 0.27)	0.15 (−1.10, 1.41)	0.82	−0.22 (−0.50, 0.06)	−0.62 (−1.95,0.70)	0.56
PFOS												
3 months [b]	0.01 (−0.04, 0.06)	0.01 (−0.04, 0.06)	0.99	0.04 (−0.01, 0.09)	−0.01 (−0.06, 0.04)	0.22	−0.03 (−0.09, 0.02)	0.04 (−0.02, 0.09)	0.07	−0.01 (−0.06, 0.04)	−0.02 (−0.07, 0.04)	0.86
18 months[c]	0.01 (−0.07, 0.09)	0.03 (−0.06, 0.12)	0.67	0.04 (−0.04, 0.13)	0.03 (−0.07, 0.12)	0.76	−0.07 (−0.14, 0.01)	0.01 (−0.08, 0.09)	0.18	−0.04 (−0.12,0.05)	0.05 (−0.05, 0.14)	0.18
PFOA												
3 months[b]	−0.07 (−0.22, 0.08)	−0.08 (−0.23, 0.06)	0.88	−0.02 (−0.17, 0.13)	−0.02 (−0.17, 0.12)	0.99	−0.11 (−0.26, 0.05)	−0.03 (−0.18, 0.12)	0.48	0.01 (−0.14, 0.16)	−0.06 (−0.21, 0.08)	0.52
18 months[c]	0.14 (−0.03, 0.31)	−0.12 (−0.39, 0.16)	0.10	0.16 (−0.02, 0.34)	−0.29 (−0.58, −0.003)	0.01	−0.05 (−0.22, 0.12)	−0.05 (−0.32, 0.21)	0.98	−0.02 (−0.19, 0.15)	0.43 (0.16, 0.70)	<0.01
PFNA												
3 months[b]	−0.08 (−0.49, 0.33)	−0.22 (−0.62, 0.18)	0.64	0.08 (−0.34, 0.49)	−0.20 (−0.61, 0.21)	0.35	−0.35 (−0.77, 0.08)	0.25 (−0.16, 0.67)	0.05	0.09 (−0.33, 0.51)	−0.28 (−0.69, 0.13)	0.22
18 months[c]	0.40 (−0.07, 0.87)	0.25 (−0.68, 1.19)	0.59	0.45 (−0.05, 0.95)	−0.58 (−1.59, 0.42)	0.07	−0.11 (−0.58, 0.36)	0.36 (−0.56, 1.29)	0.38	−0.11 (−0.59 , 0.36)	1.39 (0.44, 2.35)	<0.01
PFDA												
3 months[b]	−0.39 (−1.43, 0.66)	−0.12 (−1.00, 0.75)	0.71	−0.01 (−1.07, 1.04)	−0.09 (−0.97, 0.80)	0.92	−0.83 (−1.96, 0.29)	0.64 (−0.56, 1.85)	0.08	0.002 (−0.97, 0.97)	−1.32 (−3.18, 0.49)	0.21
18 months[c]	1.29 (0.17, 2.42)	0.27 (−1.86, 2.40)	0.41	1.51 (0.34, 2.68)	−2.33 (−4.54, −0.11)	<0.01	−1.36 (−1.49, 0.77)	0.61 (−1.49, 2.71)	0.43	−0.10 (−1.18, 0.99)	4.44 (2.37, 6.53)	<0.01

Note: CI, confidence interval; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; SDS, standard deviation scores.
[a]Interaction between the compound and sex, adjusted as described under [b] or [c], tested with the Wald test.
[b]Adjusted for maternal age, parity, prepregnancy BMI, prepregnancy BMI^2, educational level, and smoking (For total cholesterol SDS, HDL SDS, and triglyceride SDS $n = 126$ girls and $n = 134$ boys; and for LDL SDS $n = 125$ girls and $n = 133$ boys).
[c]Adjusted for maternal age, parity, prepregnancy BMI, prepregnancy BMI^2, educational level, smoking, and lipid outcome at age 3 months (For all lipid outcomes $n = 40$ girls, and $n = 43$ boys).

activated receptors (PPAR), cortisol and thyroid metabolism, and sex hormone receptors (Buhrke et al. 2013; Wolf et al. 2012; Ye et al. 2012; Yu et al. 2009; Zhao et al. 2011). Rodent and human *in vitro* studies demonstrated that PFAA are able to activate the PPARα and PPARγ, which are involved in lipid and glycogen metabolism (Buhrke et al. 2013; Wolf et al. 2008; Wolf et al. 2012). Non-PPAR–mechanistic pathways have been suggested, because *in vitro* studies in both rat and human cells have shown PFAA as potent inhibitors of both 11β-hydroxysteroid dehydrogenase 1 (Ye et al. 2012) and 2 (Zhao et al. 2011), thus potentially influencing available cortisol to the fetus. In a recent prospective cohort study, we demonstrated that PFOS concentration in early pregnancy was significantly inversely associated with diurnal urinary concentrations of cortisone in late pregnancy, indicating reduced activity of 11β-hydroxysteroid dehydrogenase 2 (Dreyer et al. 2020). A rodent study (Yu et al. 2009) indicated that both prenatal exposure and postnatal PFOS exposure were associated with decreased thyroxine levels (T4) in offspring, which is linked to decreased basal metabolic rate and increased BMI in humans (Knudsen et al. 2005). Finally, findings from this study and others (Halldorsson et al. 2012; Høyer et al. 2015; Manzano-Salgado et al. 2017; Mora et al. 2017) provide some evidence of differences in associations by sex in regard to the association between *in utero* PFAA exposure and anthropometry measurements, where females appear to be more susceptible (Halldorsson et al. 2012; Høyer et al. 2015; Mora et al. 2017). However, we also found evidence of positive associations in girls between PFAA exposure and LDL SDS at 18 months of age that were accompanied by even stronger inverse associations in boys; however, lipid data should be interpreted with caution due to the small sample size by gender at 18 months of age. An *in vitro* study (Kjeldsen and Bonefeld-Jørgensen 2013) on human cells demonstrated that PFAA induced estrogenic and antiandrogenic activities, but the sensitivity to the effects of PFAA between the two sexes may hypothetically differ due to the natural androgen–estrogen homeostasis (Jensen et al. 2020; Kuijper et al. 2013).

The major strength of the study is the prospective follow-up design, with a sizable number of mother–child pairs for most of the outcomes. Maternal PFAA concentrations were determined in early pregnancy, and we presume that the results reflect the PFAA concentration during much of the pregnancy due to the long half-lives of PFAA (ATSDR 2018). Three trained health care professionals blinded to the PFAA concentrations carried out the consecutive clinical examinations, hence minimizing misclassification bias with respect to the outcomes. Repeated objective standardized markers of adiposity and lipid metabolism were obtained in offspring.

The study also has some limitations. Included mothers were more often nulliparous, of European origin, smoked less, and had a higher prepregnancy BMI in comparison with the rest of the women in the OCC. Potential confounding by parity, smoking, and prepregnancy BMI was addressed by adjustment in the analyses. However, residual confounding by other covariates related to prenatal PFAA concentrations and markers of adiposity and lipid metabolism in infancy cannot be dismissed; these covariates include family cholesterol levels and exposure to other unmeasured correlated endocrine disrupting chemicals during pregnancy and in infancy. Moreover, the possibility of unmeasured or residual confounding by diet cannot be ruled out, because diet may be a common cause of both PFAA exposure (Vestergren et al. 2012) and markers of adiposity and lipids in infancy (Emmett and Jones 2015). Unfortunately, data on maternal and child diet were not available in this study. The observed trends of reduced maternal pregnancy PFAA concentrations with increasing maternal prepregnancy BMI could suggest that fat biopsies may be a matrix

of interest, even though PFAA do not tend to accumulate in fatty compartments (Pérez et al. 2013). Fat biopsies were not collected in the present study; however, that information may be a focus for future studies. Because the study hypothesis was tested across several markers of adiposity and lipid metabolism, multiple comparison bias should be considered. We acknowledge the variability in the magnitude of the associations between PFAA and markers of lipid metabolism. The variability may depend on age at blood sampling, infant sex, and other intrinsic factors, such as hormones. As concentrations of androgens and gonadotropins differ between girls and boys during minipuberty in early childhood (Jensen et al. 2020; Kuiri-Hänninen et al. 2014), it cannot be excluded that the investigated associations between PFAA and markers of lipid metabolism may be influenced by sex differences in hormones. In addition, the results on maternal PFAA concentrations and markers of offspring lipid metabolism at 18 months of age, especially the gender-specific estimates, warrants cautious interpretation due to the small sample size limiting the statistical precision. However, the study had an exploratory approach in the analysis of associations between maternal pregnancy serum PFAA concentrations and infancy metabolism investigated from multiple angles, including adiposity measurements and lipid status.

Collectively, our longitudinal data suggest that fetal life is a sensitive period for exposure to maternal PFAA concentrations with future implications on markers of adiposity and lipid metabolism already in infancy. Childhood obesity is increasing dramatically (Kumar and Kelly 2017); in addition, childhood overweight and abnormal lipid metabolism are predictive of obesity (Singh et al. 2008) and cardiovascular risk factors (Juonala et al. 2011; Nicklas et al. 2002) in adulthood, including dyslipidemia, hypertension, and type 2 diabetes, conditions considered to be major challenges to human health (Unnikrishnan et al. 2017).

Conclusions

Maternal PFOA, PFNA, and PFDA concentrations in pregnancy serum were associated with increased BMI SDS and ponderal index SDS in the offspring at 3 months and 18 months of age, and with higher BF% SDS at 3 months. The PFDA concentration was also associated with increased total cholesterol SDS at age 18 months of age.

The possible impact of developmental PFAA exposure on metabolic dysfunction in childhood and in later life deserves attention.

Acknowledgments

The families in the OCC are acknowledged for their participation and commitment to the study. The health care professionals at the Hans Christian Andersen Children's Hospital and the technicians at the Department of Environmental Medicine are acknowledged for their careful examination of the children and analysis of PFAA concentrations in serum samples, respectively. The authors thank J. Tinggaard and C. Wohlfart-Veje for providing detailed references for the calculation of standard deviation scores.

This work was supported by the Danish Council for Independent Research, Medical Sciences (4004-00352B and 8020-00123B); Odense University Hospital, the Region of Southern Denmark; the Municipality of Odense; the Mental Health Service of the Region of Southern Denmark; the Danish Council for Strategic Research, Program Commission on Health, Food and Welfare (2101-08-0058); Odense University Hospital Research Foundation; Odense Patient data Exploratory Network (OPEN); Novo Nordisk Foundation (grants NNF15OC00017734 and NNF17OC0029404); the Foundation for Research Collaboration between Rigshospitalet and Odense University Hospital; and the Health Foundation (Helsefonden).

References

ATSDR (Agency for Toxic Substances and Disease Registry). 2018. *Toxicological Profile for Perfluoroalkyls*. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Alkhalawi E, Kasper-Sonnenberg M, Wilhelm M, Völkel W, Wittsiepe J. 2016. Perfluoroalkyl acids (PFAAs) and anthropometric measures in the first year of life: results from the Duisburg Birth Cohort. J Toxicol Environ Health Part A 79(22–23):1041–1049, PMID: 27924715, https://doi.org/10.1080/15287394.2016.1219552.

Andersen CS, Fei C, Gamborg M, Nohr EA, Sørensen TI, Olsen J. 2010. Prenatal exposures to perfluorinated chemicals and anthropometric measures in infancy. Am J Epidemiol 172(11):1230–1237, PMID: 20940176, https://doi.org/10.1093/aje/kwq289.

Bjerregaard-Olesen C, Bach CC, Long M, Ghisari M, Bech BH, Nohr EA, et al. 2016. Determinants of serum levels of perfluorinated alkyl acids in Danish pregnant women. Int J Hyg Environ Health 219(8):867–875, PMID: 27451073, https://doi.org/10.1016/j.ijheh.2016.07.008.

Brantsæter AL, Whitworth KW, Ydersbond TA, Haug LS, Haugen M, Knutsen HK, et al. 2013. Determinants of plasma concentrations of perfluoroalkyl substances in pregnant Norwegian women. Environ Int 54:74–84, PMID: 23419425, https://doi.org/10.1016/j.envint.2012.12.014.

Braun JM, Chen A, Romano ME, Calafat AM, Webster GM, Yolton K, et al. 2016. Prenatal perfluoroalkyl substance exposure and child adiposity at 8 years of age: the HOME Study. Obesity (Silver Spring, MD) 24(1):231–237, PMID: 26554535, https://doi.org/10.1002/oby.21258.

Buhrke T, Kibellus A, Lampen A. 2013. In vitro toxicological characterization of perfluorinated carboxylic acids with different carbon chain lengths. Toxicol Lett 218(2):97–104, PMID: 23391484, https://doi.org/10.1016/j.toxlet.2013.01.025.

Cornier MA, Després JP, Davis N, Grossniklaus DA, Klein S, Lamarche B, et al. 2011. Assessing adiposity: a scientific statement from the American Heart Association. Circulation 124(18):1996–2019, PMID: 21947291, https://doi.org/10.1161/CIR.0b013e318233bc6a.

Demerath EW, Fields DA. 2014. Body composition assessment in the infant. Am J Hum Biol 26(3):291–304, PMID: 24424686, https://doi.org/10.1002/ajhb.22500.

Dreyer AF, Jensen RC, Glintborg D, Schmedes AV, Brandslund I, Nielsen F, et al. 2020. Perfluoroalkyl substance exposure early in pregnancy was negatively associated with late pregnancy cortisone levels. J Clin Endocrinol Metab, PMID: 32436946, https://doi.org/10.1210/clinem/dgaa292.

Emmett PM, Jones LR. 2015. Diet, growth, and obesity development throughout childhood in the Avon Longitudinal Study of Parents and Children. Nutr Rev 73 (suppl 3):175–206, PMID: 26395342, https://doi.org/10.1093/nutrit/nuv054.

Friedewald WT, Levy RI, Fredrickson DS. 1972. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18(6):499–502, PMID: 4337382, https://doi.org/10.1093/clinchem/18.6.499.

Frisbee SJ, Shankar A, Knox SS, Steenland K, Savitz DA, Fletcher T, et al. 2010. Perfluorooctanoic acid, perfluorooctanesulfonate, and serum lipids in children and adolescents: results from the C8 Health Project. Arch Pediatr Adolesc Med 164(9):860–869, PMID: 20819969, https://doi.org/10.1001/archpediatrics.2010.163.

Geiger SD, Xiao J, Ducatman A, Frisbee S, Innes K, Shankar A. 2014. The association between PFOA, PFOS and serum lipid levels in adolescents. Chemosphere 98:78–83, PMID: 24238303, https://doi.org/10.1016/j.chemosphere.2013.10.005.

Glynn A, Berger U, Bignert A, et al. 2012. Perfluorinated alkyl acids in blood serum from primiparous women in Sweden: serial sampling during pregnancy and nursing, and temporal trends 1996–2010. Environ Sci Technol 46(16):9071–9079, https://doi.org/10.1021/es301168c.

Gyllenhammar I, Diderholm B, Gustafsson J, Berger U, Ridefelt P, Benskin JP, et al. 2018. Perfluoroalkyl acid levels in first-time mothers in relation to offspring weight gain and growth. Environ Int 111:191–199, PMID: 29223808, https://doi.org/10.1016/j.envint.2017.12.002.

Halldorsson TI, Rytter D, Haug LS, Bech BH, Danielsen I, Becher G, et al. 2012. Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective cohort study. Environ Health Perspect 120(5):668–673, PMID: 22306490, https://doi.org/10.1289/ehp.1104034.

Hetherington-Rauth M, Bea JW, Lee VR, Blew RM, Funk J, Lohman TG, et al. 2017. Comparison of direct measures of adiposity with indirect measures for assessing cardiometabolic risk factors in preadolescent girls. Nutr J 16(1):15, PMID: 28231807, https://doi.org/10.1186/s12937-017-0236-7.

Høyer BB, Ramlau-Hansen CH, Vrijheid M, Valvi D, Pedersen HS, Zviezdai V, et al. 2015. Anthropometry in 5- to 9-year-old Greenlandic and Ukrainian children in relation to prenatal exposure to perfluorinated alkyl substances. Environ Health Perspect 123(8):841–846, PMID: 25809098, https://doi.org/10.1289/ehp.1408881.

Jensen TK, Andersen LB, Kyhl HB, Nielsen F, Christesen HT, Grandjean P. 2015. Association between perfluorinated compound exposure and miscarriage in Danish pregnant women. PLoS One 10(4):e0123496, PMID: 25848775, https://doi.org/10.1371/journal.pone.0123496.

Jensen RC, Glintborg D, Gade Timmermann CA, Nielsen F, Kyhl HB, Frederiksen H, et al. 2020. Prenatal exposure to perfluorodecanoic acid is associated with lower circulating concentration of adrenal steroid metabolites during mini puberty in human female infants. The Odense Child Cohort. Environ Res 182:109101, PMID: 32069767, https://doi.org/10.1016/j.envres.2019.109101.

Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, et al. 2011. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med 365(20):1876–1885, PMID: 22087679, https://doi.org/10.1056/NEJMoa1010112.

Karlsen M, Grandjean P, Weihe P, Steuerwald U, Oulhote Y, Valvi D. 2017. Early-life exposures to persistent organic pollutants in relation to overweight in preschool children. Reprod Toxicol 68:145–153, PMID: 27496715, https://doi.org/10.1016/j.reprotox.2016.08.002.

Kjeldsen LS, Bonefeld-Jørgensen EC. 2013. Perfluorinated compounds affect the function of sex hormone receptors. Environ Sci Pollut Res Int 20(11):8031–8044, PMID: 23764977, https://doi.org/10.1007/s11356-013-1753-3.

Knudsen N, Laurberg P, Rasmussen LB, Bülow I, Perrild H, Ovesen L, et al. 2005. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab 90(7):4019–4024, PMID: 15870128, https://doi.org/10.1210/jc.2004-2225.

Kuijper EA, Ket JC, Caanen MR, Lambalk CB. 2013. Reproductive hormone concentrations in pregnancy and neonates: a systematic review. Reprod Biomed Online 27(1):33–63, PMID: 23669015, https://doi.org/10.1016/j.rbmo.2013.03.009.

Kuiri-Hänninen T, Sankilampi U, Dunkel L. 2014. Activation of the hypothalamic-pituitary-gonadal axis in infancy: minipuberty. Horm Res Paediatr 82(2):73–80, PMID: 25012863, https://doi.org/10.1159/000362414.

Kumar S, Kelly AS. 2017. Review of childhood obesity: from epidemiology, etiology, and comorbidities to clinical assessment and treatment. Mayo Clin Proc 92(2):251–265, PMID: 28065514, https://doi.org/10.1016/j.mayocp.2016.09.017.

Kyhl HB, Jensen TK, Barington T, Buhl S, Norberg LA, Jørgensen JS, et al. 2015. The Odense Child Cohort: aims, design, and cohort profile. Paediatr Perinat Epidemiol 29(3):250–258, PMID: 25756293, https://doi.org/10.1111/ppe.12183.

Maisonet M, Terrell ML, McGeehin MA, Christensen KY, Holmes A, Calafat AM, et al. 2012. Maternal concentrations of polyfluoroalkyl compounds during pregnancy and fetal and postnatal growth in British girls. Environ Health Perspect 120(10):1432–1437, PMID: 22935244, https://doi.org/10.1289/ehp.1003096.

Manzano-Salgado CB, Casas M, Lopez-Espinosa MJ, Ballester F, Iñiguez C, Martinez D, et al. 2017. Prenatal exposure to perfluoroalkyl substances and cardiometabolic risk in children from the Spanish INMA Birth Cohort Study. Environ Health Perspect 125(9):097018, PMID: 28934720, https://doi.org/10.1289/EHP1330.

Monroy R, Morrison K, Teo K, Atkinson S, Kubwabo C, Stewart B, et al. 2008. Serum levels of perfluoroalkyl compounds in human maternal and umbilical cord blood samples. Environ Res 108(1):56–62, PMID: 18649879, https://doi.org/10.1016/j.envres.2008.06.001.

Mora AM, Oken E, Rifas-Shiman SL, Webster TF, Gillman MW, Calafat AM, et al. 2017. Prenatal exposure to perfluoroalkyl substances and adiposity in early and mid-childhood. Environ Health Perspect 125(3):467–473, PMID: 27352404, https://doi.org/10.1289/EHP246.

Nelson JW, Hatch EE, Webster TF. 2010. Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general U.S. population. Environ Health Perspect 118(2):197–202, PMID: 20123614, https://doi.org/10.1289/ehp.0901165.

Nicklas TA, von Duvillard SP, Berenson GS. 2002. Tracking of serum lipids and lipoproteins from childhood to dyslipidemia in adults: The Bogalusa Heart Study. Int J Sports Med 23(suppl 1):S39–S43, PMID: 12012261, https://doi.org/10.1055/s-2002-28460.

Pérez F, Nadal M, Navarro-Ortega A, Fàbrega F, Domingo JL, Barceló D, et al. 2013. Accumulation of perfluoroalkyl substances in human tissues. Environ Int 59:354–362, PMID: 23892228, https://doi.org/10.1016/j.envint.2013.06.004.

Rodríguez G, Moreno LA, Blay MG, Blay VA, Fleta J, Sarría A, et al. 2005. Body fat measurement in adolescents: comparison of skinfold thickness equations with dual-energy X-ray absorptiometry. Eur J Clin Nutr 59(10):1158–1166, PMID: 16047030, https://doi.org/10.1038/sj.ejcn.1602226.

Shoaff J, Papandonatos GD, Calafat AM, Chen A, Lanphear BP, Ehrlich S, et al. 2018. Prenatal exposure to perfluoroalkyl substances: infant birth weight and early life growth. Environ Epidemiol 2(2):e010, PMID: 30272047, https://doi.org/10.1097/EE9.0000000000000010.

Singh AS, Mulder C, Twisk JW, van Mechelen W, Chinapaw MJ. 2008. Tracking of childhood overweight into adulthood: a systematic review of the literature. Obes Rev 9(5):474–488, PMID: 18331423, https://doi.org/10.1111/j.1467-789X.2008.00475.x.

Slaughter MH, Lohman TG, Boileau RA, Horswill CA, Stillman RJ, Van Loan MD, et al. 1988. Skinfold equations for estimation of body fatness in children and youth. Hum Biol 60(5):709–723, PMID: 3224965.

Starling AP, Adgate JL, Hamman RF, Kechris K, Calafat AM, Dabelea D. 2019. Prenatal exposure to per- and polyfluoroalkyl substances and infant growth and adiposity: The Healthy Start Study. Environ Int 131:104983, PMID: 31284113, https://doi.org/10.1016/j.envint.2019.104983.

Steenland K, Tinker S, Frisbee S, Ducatman A, Vaccarino V. 2009. Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant. Am J Epidemiol 170(10):1268–1278, PMID: 19846564, https://doi.org/10.1093/aje/kwp279.

Stein CR, Wolff MS, Calafat AM, Kato K, Engel SM. 2012. Comparison of polyfluoroalkyl compound concentrations in maternal serum and amniotic fluid: a pilot study. Reprod Toxicol 34(3):312–316, PMID: 22613200, https://doi.org/10.1016/j.reprotox.2012.05.039.

Tinggaard J, Aksglaede L, Sørensen K, Mouritsen A, Wohlfahrt-Veje C, Hagen CP, et al. 2014. The 2014 Danish references from birth to 20 years for height, weight and body mass index. Acta Paediatr 103(2):214–224, PMID: 24127859, https://doi.org/10.1111/apa.12468.

Unnikrishnan R, Pradeepa R, Joshi SR, Mohan V. 2017. Type 2 diabetes: demystifying the global epidemic. Diabetes 66(6):1432–1442, PMID: 28533294, https://doi.org/10.2337/db16-0766.

Vestergren R, Berger U, Glynn A, Cousins IT. 2012. Dietary exposure to perfluoroalkyl acids for the Swedish population in 1999, 2005 and 2010. Environ Int 49:120–127, PMID: 23018201, https://doi.org/10.1016/j.envint.2012.08.016.

Vickers AJ, Altman DG. 2001. Statistics notes: analysing controlled trials with baseline and follow up measurements. BMJ 323(7321):1123–1124, PMID: 11701584, https://doi.org/10.1136/bmj.323.7321.1123.

Wohlfahrt-Veje C, Tinggaard J, Winther K, Mouritsen A, Hagen CP, Mieritz MG, et al. 2014. Body fat throughout childhood in 2647 healthy Danish children: agreement of BMI, waist circumference, skinfolds with dual X-ray absorptiometry. Eur J Clin Nutr 68(6):664–670, PMID: 24473457, https://doi.org/10.1038/ejcn.2013.282.

Wolf CJ, Schmid JE, Lau C, Abbott BD. 2012. Activation of mouse and human peroxisome proliferator-activated receptor-alpha (PPARα) by perfluoroalkyl acids (PFAAs): Further investigation of C4-C12 compounds. Reprod Toxicol 33(4):546–551, PMID: 22107727, https://doi.org/10.1016/j.reprotox.2011.09.009.

Wolf CJ, Takacs ML, Schmid JE, Lau C, Abbott BD. 2008. Activation of mouse and human peroxisome proliferator-activated receptor alpha by perfluoroalkyl acids of different functional groups and chain lengths. Toxicol Sci 106(1):162–171, PMID: 18713766, https://doi.org/10.1093/toxsci/kfn166.

Woo Baidal JA, Locks LM, Cheng ER, Blake-Lamb TL, Perkins ME, Taveras EM. 2016. Risk factors for childhood obesity in the first 1,000 days: a systematic review. Am J Prev Med 50(6):761–779, PMID: 26916261, https://doi.org/10.1016/j.amepre.2015.11.012.

Ye L, Zhao B, Cai XH, Chu Y, Li C, Ge RS. 2012. The inhibitory effects of perfluoroalkyl substances on human and rat 11β-hydroxysteroid dehydrogenase 1. Chem Biol Interact 195(2):114–118, PMID: 22178014, https://doi.org/10.1016/j.cbi.2011.11.007.

Yu WG, Liu W, Jin YH, Liu XH, Wang FQ, Liu L, et al. 2009. Prenatal and postnatal impact of perfluorooctane sulfonate (PFOS) on rat development: a cross-foster study on chemical burden and thyroid hormone system. Environ Sci Technol 43(21):8416–8422, PMID: 19924978, https://doi.org/10.1021/es901602d.

Zeng XW, Qian Z, Emo B, Vaughn M, Bao J, Qin XD, et al. 2015. Association of polyfluoroalkyl chemical exposure with serum lipids in children. Sci Total Environ 512–513:364–370, PMID: 25638651, https://doi.org/10.1016/j.scitotenv.2015.01.042.

Zhao B, Lian Q, Chu Y, Hardy DO, Li XK, Ge RS. 2011. The inhibition of human and rat 11β-hydroxysteroid dehydrogenase 2 by perfluoroalkylated substances. J Steroid Biochem Mol Biol 125(1–2):143–147, PMID: 21237268, https://doi.org/10.1016/j.jsbmb.2010.12.017.