American Journal of Epidemiology

Vol. 172, No. 11
DOI: 10.1093/aje/kwq289
Advance Access publication: October 12, 2010

Original Contribution

Prenatal Exposures to Perfluorinated Chemicals and Anthropometric Measures in Infancy

Camilla Schou Andersen*, Chunyuan Fei, Michael Gamborg, Ellen Aagaard Nohr, Thorkild I. A. Sørensen, and Jørn Olsen

* Correspondence to Camilla Schou Andersen, Institute of Preventive Medicine, Øster Søgade 18,1, DK-1357 Copenhagen K, Denmark (e-mail: csl@ipm.regionh.dk).

Initially submitted March 15, 2010; accepted for publication August 3, 2010.

Perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) are persistent chemicals that may affect growth early in life. The authors estimated the associations between maternal plasma levels of PFOS and PFOA and infants' weight, length, and body mass index development during the first year of life. Fourteen hundred women were randomly selected from the Danish National Birth Cohort among those who provided blood samples early in pregnancy and gave birth to liveborn singletons between 1996 and 2002. Weight and length information at 5 and 12 months of age was available for 1,010 children. Multiple linear regression models were used for analyses, and maternal PFOS and PFOA concentrations (ng/mL) were inversely related to children's weight in the first year of life: adjusted regression coefficients: −1.1 g (95% confidence interval (CI): −4.6, 2.3) at 5 months and −5.8 g (95% CI: −10.4, −1.2) at 12 months for PFOS; −10.6 g (95% CI: −30.2, 8.9) at 5 months and −19.7 g (95% CI: −45.9, 6.5) at 12 months for PFOA. A similar pattern was observed for body mass index measurements, and no associations with length were found. After sex stratification, the inverse associations with weight and body mass index were more pronounced in boys, and no clear association was seen for girls.

body mass index; body weight; growth; infant; prenatal exposure delayed effects

Abbreviations: CI, confidence interval; PFC, perfluorinated chemical; PFOA, perfluorooctanoate; PFOS, perfluorooctanesulfonate.

During the last 50 years, the production of synthetic compounds, such as perfluorinated chemicals (PFCs), has increased dramatically because of their usefulness in industry and in consumer products. Perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) have been the most widely used PFCs. PFOS and PFOS-related compounds are widely used as water repellents and stain resistants and for lubricants and waxes (1, 2). PFOA is primarily used as a surfactant and an emulsifier in the production of polytetrafluoroethylene, as well as fluoropolymers and fluoroelastomers. They are man-made compounds or can be formed from environmental and metabolic degradation of precursor compounds. These 2 compounds are essentially nonvolatile and diffuse into the immediate environment where they have been found in air, water, soil, and food samples (3–5). They have been detected worldwide in wildlife and humans. They are readily absorbed by living species but poorly eliminated in human beings (4). As both PFOS and PFOA cross the placental barrier (1), they are present in blood from almost all newborn babies (1, 6). However, in spite of the widespread exposure to PFCs, there remain considerable individual differences in exposure levels (7).

Fetuses are probably more vulnerable to a variety of environmental toxicants than older children and adults (8). Prenatal exposure to PFCs has been associated with reduced birth weight in animals (2, 4, 9), although with less consistency in humans (7). Animal studies have showed that high doses of PFOS and PFOA administrated to dams were associated with postnatal growth impairment of their offspring in a dose-response manner (10–12), even in the absence of exposure during lactation (12). Furthermore, previous experimental studies have suggested various potential sex-differential PFC exposures (13–16). However, it is not clear if PFCs impact early human postnatal growth.

In this study, we investigated if PFOS and PFOA, measured in maternal plasma in early pregnancy, were associated with children's weight, length, and body mass index at 5 months and at 12 months of age and whether the associations were different in boys and girls.

MATERIALS AND METHODS

Study population

The study was based on data from the Danish National Birth Cohort, where 91,827 women were enrolled during the years 1996–2002 (17, 18).

Women were eventually recruited from all over Denmark in the beginning of pregnancy when they came to their first antenatal care visit to their general practitioner, and about 60% of those invited accepted the invitation. Two maternal blood samples were collected in the first and second trimester, respectively, and a blood sample from the child was retrieved from the umbilical cord at birth. The women also participated in 4 computer-assisted telephone interviews twice during pregnancy at approximately week 16 and week 30 (interview 1 and interview 2) and twice after birth at approximately 6 months and 18 months postpartum (interview 3 and interview 4).

As described previously (19, 20), 1,400 mothers were randomly selected among all participants who gave birth to a liveborn singleton without congenital malformations (n = 87,752), provided the first blood sample (n = 80,678), and took part in all 4 telephone interviews (n = 43,045). From the 1,400 women, plasma levels of PFOS and PFOA in the first blood sample were analyzed, and the previous study demonstrated that the PFC level measured early in pregnancy was a good indicator of exposure during pregnancy (19).

For the present study, children of the 1,400 mothers were eligible if they had available information about weight and length measurements at 5 months of age (n = 1,154 and n = 1,147, respectively) or at 12 months of age (n = 1,076 and n = 1,075, respectively).

All participants provided written informed consent when they were enrolled in the cohort in early pregnancy. The Scientific Ethics Committee in Denmark, the Danish Data Protection Board, and the Danish National Birth Cohort Steering Committee approved the study.

Exposure variables and covariates

Plasma concentrations of PFOS and PFOA were measured by using high-performance liquid chromatography tandem mass spectrometry in the 3M Toxicology Laboratory (21). The laboratory staff was blinded to any information about the subjects. All values of PFOS and PFOA were above the lower limit of quantification (1 ng/mL) at that time, except for 1 PFOA value that was assigned a value of half the lower limit of quantification. Further detailed information about extractions and analytical methods is presented elsewhere (19, 21).

From interview 1, we obtained information about the mother's self-reported prepregnancy weight and height, which were used to calculate prepregnancy body mass index (weight (kg)/height $(m)^2$). Information about maternal age at conception, parity, smoking during pregnancy, and socioeconomic status defined by education and occupation was also available. In interview 3, the mothers were asked to report duration of breastfeeding. Information about birth weight and gestational age was obtained from the National Birth Register. The child's age was derived from the date on which the weight was measured and the child's birth date.

Outcome variables

In interview 4, the mothers were asked to report the weight and length of their child at 5 months and at 12 months of age, measured by the general practitioner and recorded in the child's book kept by the mother. In total, 1,010 children had all 4 anthropometric measurements. We used weight and length measurements to calculate body mass index at 5 months and at 12 months of age as kg/m^2. The average age at measurements was 5.3 months (range, 3.0–7.0) and 12.6 months (range, 10.5–15.0), respectively.

Statistical analysis

Multiple linear regression analyses were used to study associations between maternal levels of PFOS or PFOA and weight of their children. Restricted cubic spline models were fitted to examine trends in data, but no regression coefficients deviated significantly from linear models (all values for $P > 0.1$); modeling was then done with exposure levels as continuous variables. We also reevaluated associations between exposure variables and birth weight. Sex-specific z scores for all outcome variables were calculated on the basis of internal reference values. Stratified analyses were further done for boys and girls separately to investigate possible sex differences.

The following covariates, chosen a priori, were included in the final models for weight, length, and body mass index at 5 months and at 12 months of age: maternal age; parity; prepregnancy body mass index; smoking during pregnancy (no smoking, quit smoking, 1–9 cigarettes/day, or $\geq$10 cigarettes/day); socioeconomic status (high, middle, or low); gestational week at blood drawing; duration of breastfeeding (0–13 weeks, 14–21 weeks, or $\geq$22 weeks); and the child's exact age at measurements. In the analyses for weight, length, or body mass index at both ages, birth weight, birth length, or birth body mass index was also included, respectively. In additional analyses for weight, length, or body mass index at 12 months of age, we also adjusted for weight, length, or body mass index at 5 months of age, respectively. All covariates were included as continuous variables, except smoking during pregnancy, socioeconomic status, and duration of breastfeeding.

In the analyses for birth weight, we included gestational age as linear and quadratic terms to capture the reduced weight gain during the last gestational weeks.

All statistical analyses were performed by using Intercooled STATA, version 9.0, software (StataCorp, College Station, Texas).

RESULTS

A description of the study population is given in Table 1. Maternal levels of PFOS ranged from 6.4 to 106.7 ng/mL and of PFOA from less than the lower limit of quantification to 21.9 ng/mL. The median and interquartile levels of PFOS and

Table 1. Characteristics of Subjects,[a] Danish National Birth Cohort, 1996–2002

	Median	IQR	Range
PFOS, ng/mL	33.4	17.2	6.4–106.7
PFOA, ng/mL	5.21	3.06	0.5–21.9
Maternal age, years	30.2	6.1	18.9–45.2
Prepregnancy body mass index, kg/m^2	23.0	4.8	15.6–50.5
Gestational week at blood drawing	8	3	3–14
Infants' birth weight, g	3,626	740.0	1,060–5,450
Infants' gestational age, days	281	14.0	199–306
Weight at 5 months of age, g	7,745	13.00	4,000–11,700
Length at 5 months of age, cm	68	4.0	56–79
Body mass index at 5 months of age, kg/m^2	16.7	2.2	12.7–23.9
Weight at 12 months of age, g	10,100	15.00	7,085–15,000
Length at 12 months of age, cm	78	4.0	68–90
Body mass index at 12 months of age, kg/m^2	17.0	2.2	12.8–26.0
	No.	**%**	
Parity			
0	625	45	
1	508	36	
2	225	16	
≥3	41	3	
Socioeconomic status			
High	704	51	
Middle	565	40	
Low	121	9	
Smoking			
Nonsmokers	1,051	75	
Quit smoking	131	9	
1–9 cigarettes/day	109	8	
≥10 cigarettes/day	108	8	
Breastfeeding			
None or <14 weeks	420	30	
14–21 weeks	590	42	
>21 weeks	389	28	

Abbreviations: IQR, interquartile range; PFOA, perfluorooctanoate; PFOS, perfluorooctanesulfonate.

[a] Missing data on prepregnancy body mass index ($n = 24$), birth weight ($n = 10$), weight at 5 months ($n = 245$), length at 5 months ($n = 252$), body mass index at 5 months ($n = 253$), weight at 12 months ($n = 323$), length at 12 months ($n = 324$), body mass index at 12 months ($n = 331$), and socioeconomic status ($n = 2$).

PFOA were slightly lower for those without data on weight at 12 months—PFOS: median, 33.3 ng/mL (interquartile level, 17.1 vs. 33.8 and 17.5); PFOA: median, 5.1 ng/mL (interquartile level, 2.8 vs. 5.2 and 3.1) compared with those having data. One outlying high value of PFOA (41.5 ng/mL) significantly decreased the estimates for weight and body mass index and increased the estimates for height in the analyses for all children and for the boys. Therefore, this value was excluded from all analyses.

Almost half of the mothers were giving birth for the first time and breastfed their child for 14–21 weeks. Before pregnancy, 22% of the mothers were overweight (body mass index, 25–29.9 kg/m^2), and 8% were obese (body mass index, ≥30 kg/m^2) according to international standards (22). Among the children ($n = 1{,}154$), 2% had a birth weight of <2,500 g, and 4% were born preterm (<259 days).

PFOS was inversely associated with children's weight measurements at birth and during infancy, and the association was statistically significant at 12 months of age (Table 2). This association remained after excluding birth weight or including weight at 5 months of age. There were consistent inverse associations between PFOA and weight at all assessed ages, but only the association with birth weight was statistically significant (Table 2). The change in estimates between crude and adjusted results was mainly due to including maternal age and parity in the models. The same pattern of inverse associations was seen with body mass index at 5 months and at 12 months of age, where the association between PFOS and body mass index at 12 months of age was the only statistically significant estimate (Table 2). Excluding body mass index at birth or including body mass index at 5 months of age in the adjusted analyses did not change the estimates notably. There were positive but nonsignificant associations between both exposure variables and length measurements during infancy (Table 2).

Interaction analyses, adjusted for the same set of covariates as in the multiple linear regression analyses, showed that sex might modify the additive association between PFOA and weight at 5 months ($P = 0.02$), body mass index at 5 months ($P = 0.01$), weight at 12 months ($P = 0.04$), and body mass index at 12 months of age ($P = 0.04$). Therefore, all multiple regression analyses were also performed separately for boys and girls. Overall, weight and body mass index measurements in boys were inversely related to both PFOS and PFOA, with the adjusted associations for PFOS at 5 months of age being the only nonsignificant estimates (Table 3). In additional adjusted analyses for 5 months of age, where birth weight or birth body mass index was excluded, the estimates did not change markedly. However, in supplementary adjusted analyses for weight or body mass index at 12 months of age, the estimates significantly decreased when including weight or body mass index at 5 months of age, respectively, as expected if the effect decreases with age. For the girls, PFOS and PFOA were both inversely associated with weight at birth, but the associations with weight and body mass index disappeared after birth, and no clear pattern was observed at 5 and 12 months of age (Tables 3 and 4). Overall, both boys and girls showed inverse associations between exposure variables and length during infancy, but none was statistically significant (Tables 3 and 4).

We also analyzed data according to a longitudinal growth model and found that results were very similar to what is

Table 2. Associations Between Maternal PFOS and PFOA Concentrations (ng/mL) and Their Children's Weight, Length, and Body Mass Index During Infancy (*z* Score and β Coefficients), Danish National Birth Cohort, 1996–2002[a]

	No.	PFOS				PFOA[b]			
		β for *z* Scores	95% CI	β for Weight, g[c]	95% CI	β for *z* Scores	95% CI	β for Weight, g[c]	95% CI
Birth weight[d]									
Crude model[e]	1,144	−0.001	−0.005, 0.003	−0.8	−2.8, 1.2	−0.04	−0.061, −0.019***	−21.2	−32.5, −9.9***
Adjusted model[f]	1,118	−0.002	−0.006, 0.002	−1	−3.1, 1.0	−0.024	−0.046, −0.002*	−12.8	−24.5, −1.2*
Weight at 5 months									
Crude model[e]	1,154	0.002	−0.002, 0.006	1.4	−2.9, 5.6	−0.003	−0.028, 0.021	−4	−27.4, 19.4
Adjusted model[f]	1,110	−0.001	−0.005, 0.003	−0.8	−4.2, 2.6	−0.009	−0.031, 0.012	−9.4	−28.6, 9.9
Height at 5 months									
Crude model[e]	1,147	0.002	−0.002, 0.007	0.006	−0.006, 0.017	0.002	−0.022, 0.027	0.006	−0.057, 0.069
Adjusted model[f]	1,104	0.002	−0.002, 0.006	0.006	−0.004, 0.017	0.017	−0.007, 0.040	0.044	−0.017, 0.105
Body mass index at 5 months									
Crude model[e]	1,146	0.001	−0.003, 0.006	0.002	−0.005, 0.009	−0.003	−0.026, 0.021	−0.003	−0.043, 0.036
Adjusted model[f]	1,101	−0.001	−0.006, 0.003	−0.002	−0.010, 0.005	−0.015	−0.040, 0.010	−0.025	−0.067, 0.017
Weight at 12 months									
Crude model[e]	1,076	−0.002	−0.006, 0.003	−1.9	−7.2, 3.4	−0.006	−0.031, 0.019	−7.8	−37.0, 21.4
Adjusted model[f]	1,034	−0.005	−0.009, −0.001*	−5.8	−10.4, −1.2*	−0.015	−0.038, 0.007	−19.0	−44.9, 6.8
Height at 12 months									
Crude model[e]	1,075	0.004	−0.0003, 0.009	0.013	−0.001, 0.026	0.019	−0.006, 0.004	0.056	−0.018, 0.130
Adjusted model[f]	1,033	0.003	−0.001, 0.008	0.010	−0.003, 0.023	0.016	−0.009, 0.042	0.049	−0.026, 0.124
Body mass index at 12 months									
Crude model[e]	1,068	−0.005	−0.010, −0.001*	−0.008	−0.016, −0.001	−0.02	−0.045, 0.005	−0.034	−0.075, −0.007
Adjusted model[f]	1,026	−0.007	−0.011, −0.002*	−0.011	−0.019, −0.003	−0.025	−0.052, 0.002	−0.042	−0.086, 0.002

Abbreviations: CI, confidence interval; PFOA, perfluorooctanoate; PFOS, perfluorooctanesulfonate.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (P values are 2 sided).

[a] Models for weight at 5 or 12 months included birth weight, models for length at 5 or 12 months included birth length, and models for body mass index at 5 or 12 months included birth body mass index.

[b] One outlier was excluded from analyses.

[c] The change in the offspring's weight (in grams), corresponding to 1-ng/mL increase in the maternal level of PFOS or PFOA.

[d] The crude and adjusted model for birth weight includes gestational age as a linear and quadratic term.

[e] Crude models were adjusted for the child's exact age at measurement.

[f] Adjusted models included maternal age, parity, prepregnancy body mass index, smoking, socioeconomic status, gestational age at blood drawing, and breastfeeding.

presented in Tables 3 and 4. The adjusted analyses for weight showed significant effect measure modification for gender and age. For boys, the adjusted regression coefficients of PFOS were −0.005 (95% confidence interval (CI): −0.011, 0.000) at 5 months and −0.008 (95% CI: −0.013, −0.002) at 12 months. For girls, they were 0.003 (95% CI: −0.002, 0.008) at 5 months and −0.002 (95% CI: −0.008, 0.003) at 12 months. For boys, the adjusted results of PFOA were 0.033 (95% CI: −0.064, −0.001) at 5 months and −0.031 (95% CI: −0.063, 0.001) at 12 months. For girls, similar results were 0.016 (95% CI: −0.013, 0.045) at 5 months and 0.003 (95% CI: −0.027, 0.033) at 12 months.

DISCUSSION

In this study, maternal plasma levels of PFOS and PFOA were inversely related to the children's weight and body mass index at 5 and 12 months of age in boys, even after adjustment for birth weight and body mass index at birth. Associations between prenatal exposure to PFCs and weight in girls were less consistent, with exposure to PFOS and PFOA associated with decreased weight at birth, but no apparent association was observed after that. Our findings suggested that associations between prenatal exposure to PFCs and anthropometric measurements may persist during infancy in boys. However, for a given weight or body mass index at 5 months of age, these associations diminished in the analyses for 12 months of age in the boys. The possible influence from prenatal exposure to PFCs may therefore weaken after the first months of life. The sex difference in fetal growth related to PFOS has also been reported, showing a decrease in birth weight in girls (13). One study in mice did indicate different effects in males and females (14). These authors showed that, up to postnatal day 22, an inverse association was found between prenatal exposure to PFOA and body weight in both genders, but after postnatal day 85, males recovered from the prenatal growth deficit

Table 3. Associations Between Maternal PFOS and PFOA Concentrations (ng/mL) and the Boys' Weight, Length, and Body Mass Index During Infancy (*z* Scores and β Coefficients), Danish National Birth Cohort, 1996–2002[a]

	No.	PFOS				PFOA[b]			
		β for *z* Scores	95% CI	β for Weight, g[c]	95% CI	β for *z* Scores	95% CI	β for Weight, g[c]	95% CI
Birth weight[d]									
Crude model[e]	570	0.003	−0.003, 0.009	1.6	−1.4, 4.5	−0.046	−0.077, −0.014*	−23.7	−40.2, −7.2*
Adjusted model[f]	556	0.003	−0.003, 0.008	1.3	−1.6, 4.2	−0.018	−0.051, 0.015	−9.5	−26.6, 7.6
Weight at 5 months									
Crude model[e]	575	−0.0001	−0.006, 0.006	−0.1	−6.0, 5.8	−0.034	−0.069, 0.001	−31.9	−65.2, 1.3
Adjusted model[f]	552	−0.004	−0.009, 0.001	−3.7	−8.7, 1.3	−0.032	−0.063, −0.001*	−30.2	−59.3, −1.1*
Height at 5 months									
Crude model[e]	572	0.002	−0.004, 0.008	0.005	−0.011, 0.021	−0.003	−0.039, 0.032	−0.008	−0.098, 0.081
Adjusted model[f]	551	0.0004	−0.006, 0.006	0.001	0.014, 0.016	0.0015	−0.020, 0.050	0.039	−0.050, 0.127
Body mass index at 5 months									
Crude model[e]	571	−0.001	−0.007, 0.006	−0.001	−0.012, 0.009	−0.035	−0.070, 0.001	−0.057	−0.115, 0.001
Adjusted model[f]	549	−0.004	−0.011, 0.002	−0.007	−0.018, 0.003	−0.04	−0.078, −0.003*	−0.067	−0.129, −0.004*
Weight at 12 months									
Crude model[e]	533	−0.004	−0.010, 0.003	−4.4	−12.3, 3.5	−0.036	−0.073, 0.001	−43.4	−87.5, 0.6
Adjusted model[f]	510	−0.008	−0.013, −0.002*	−9	−15.9, −2.2*	−0.036	−0.069, −0.003*	−43.1	−82.9, −3.3*
Height at 12 months									
Crude model[e]	533	0.004	−0.003, 0.010	0.011	−0.008, 0.031	0.007	−0.030, 0.043	0.021	−0.088, 0.129
Adjusted model[f]	511	0.003	−0.004, 0.009	0.008	−0.011, 0.027	0.011	−0.027, 0.048	0.032	−0.079, 0.143
Body mass index at 12 months									
Crude model[e]	529	−0.007	−0.014, −0.001*	−0.013	−0.024, −0.001*	−0.048	−0.084, −0.011*	−0.081	−0.143, −0.019*
Adjusted model[f]	507	−0.01	−0.017, −0.003**	−0.017	−0.028, −0.005**	−0.046	−0.086, −0.006*	−0.078	−0.144, −0.011*

Abbreviations: CI, confidence interval; PFOA, perfluorooctanoate; PFOS, perfluorooctanesulfonate.

* $P < 0.05$; ** $P < 0.01$ (P values are 2 sided).

[a] Models for weight at 5 or 12 months included birth weight, models for length at 5 or 12 months included birth length, and models for body mass index at 5 or 12 months included birth body mass index.

[b] One outlier was excluded from analyses.

[c] The change in the offspring's weight (in grams), corresponding to 1-ng/mL increase in the maternal level of PFOS or PFOA.

[d] The crude and adjusted model for birth weight includes gestational age as a linear and quadratic term.

[e] Crude models were adjusted for the child's exact age at measurement.

[f] Adjusted models included maternal age, parity, prepregnancy body mass index, smoking, socioeconomic status, gestational age at blood drawing, and breastfeeding.

whereas females continued to have a decreased body weight (14). One possible explanation for effect measure modification by sex is the endocrine-disrupting potential of PFOS and PFOA. It has been shown that PFCs may have estrogen-like properties in some experimental models (15, 23, 24), decreasing the level of testosterone and increasing the level of estradiol in male rats (16, 25). However, sex hormones may play a minor role for growth at this stage, and disruption of thyroid hormones may be another mechanism. Toxicologic studies have reported that decreased total and free thyroid hormones in serum were observed in the animals with high doses of PFOS (10, 12). PFOA was positively associated with triiodothyronine levels in occupationally exposed workers (26) and thyroid disease in the general population (27). Similar to our study, the latter study showed that exposure to both PFOS and PFOA was associated with thyroid disease in male adults, but in female adults the association was observed only with higher exposure to PFOA (27).

Evidence from animal studies has suggested that PFCs may interfere with lipid metabolism because of its ability to act as a peroxiome proliferators-activated receptor agonist (28, 29). These receptor agonists are widely distributed in various mammalian tissues and play important roles in lipid and glucose metabolism, energy homeostasis, and adipocyte differentiation (30). If PFCs bind to the peroxiome proliferators-activated receptor, it may induce enhanced transcription of peroxisomal fatty acyl-coenzyme A oxidase, thereby increasing the beta-oxidation of fatty acids and decreasing the level of serum lipids (28, 31). Less is known about the biologic mechanisms involving these chemicals in the human body, but epidemiologic studies have consistently shown that PFOA and PFOS were positively associated with total and/or non-high-density-lipoprotein cholesterol (32–36). Only one study found, however, no association between cord serum lipids and PFCs (37), and the association between PFCs and fetal growth deficits was independent of lipid levels.

Table 4. Associations Between Maternal PFOS and PFOA Concentrations (ng/mL) and the Girls' Weight, Length, and Body Mass Index During Infancy (*z* Score and β Coefficients), Danish National Birth Cohort, 1996–2002[a]

	No.	PFOS				PFOA[b]			
		β for *z* Scores	95% CI	β for Weight, g[c]	95% CI	β for *z* Scores	95% CI	β for Weight, g[c]	95% CI
Birth weight[d]									
Crude model[e]	574	−0.005	−0.011, −0.0002*	−3.0	−5.9, −0.2*	−0.035	−0.064, −0.007*	−18.9	−34.3, −3.6*
Adjusted model[f]	562	−0.006	−0.011, −0.001*	−3.2	−6.0, −0.3*	−0.03	−0.058, 0.001	−15.2	−31.1, 0.7
Weight at 5 months									
Crude model[e]	579	0.004	−0.002, 0.010	3.5	−1.9, 8.9	0.024	−0.010, 0.057	20.9	−8.5, 50.3
Adjusted model[f]	558	0.002	−0.004, 0.007	1.3	−3.3, 5.9	0.009	−0.020, 0.038	7.9	−17.7, 33.4
Height at 5 months									
Crude model[e]	575	0.002	−0.004, 0.009	0.007	−0.010, 0.023	0.007	−0.027, 0.040	0.018	−0.072, 0.107
Adjusted model[f]	553	0.004	−0.001, 0.010	0.011	−0.004, 0.026	0.018	−0.014, 0.049	0.047	−0.038, 0.132
Body mass index at 5 months									
Crude model[e]	575	0.003	−0.003, 0.009	0.006	−0.004, 0.016	0.026	−0.006, 0.058	0.044	−0.009, 0.098
Adjusted model[f]	552	0.001	−0.005, 0.007	0.002	−0.008, 0.012	0.007	−0.027, 0.041	0.012	−0.045, 0.069
Weight at 12 months									
Crude model[e]	543	0.0003	−0.006, 0.006	0.3	−6.3, 6.9	0.021	−0.013, 0.054	21.9	−13.9, 57.9
Adjusted model[f]	524	−0.003	−0.009, 0.003	−3.3	−9.3, 2.7	0.002	−0.029, 0.034	2.5	−30.9, 36.0
Height at 12 months									
Crude model[e]	542	0.005	−0.002, 0.011	0.014	−0.005, 0.033	0.029	−0.005, 0.063	0.086	−0.015, 0.187
Adjusted model[f]	522	0.004	−0.002, 0.010	0.011	−0.007, 0.030	0.021	−0.013, 0.056	0.064	−0.039, 0.166
Body mass index at 12 months									
Crude model[e]	539	−0.003	−0.009, 0.003	−0.004	−0.014, 0.006	0.004	−0.029, 0.038	0.007	−0.047, 0.061
Adjusted model[f]	519	−0.005	−0.011, 0.002	−0.007	−0.018, 0.003	−0.006	−0.043, 0.030	−0.01	−0.068, 0.048

Abbreviations: CI, confidence interval; PFOA, perfluorooctanoate; PFOS, perfluorooctanesulfonate.

* $P < 0.05$ (P values are 2 sided).

[a] Models for weight at 5 or 12 months included birth weight, models for length at 5 or 12 months included birth length, and models for body mass index at 5 or 12 months included birth body mass index.

[b] One outlier was excluded from analyses.

[c] The change in the offspring's weight (in grams), corresponding to 1-ng/mL increase in the maternal level of PFOS or PFOA.

[d] The crude and adjusted model for birth weight includes gestational age as a linear and quadratic term.

[e] Crude models were adjusted for the child's exact age at measurement.

[f] Adjusted models included maternal age, parity, prepregnancy body mass index, smoking, socioeconomic status, gestational age at blood drawing, and breastfeeding.

Most studies to date investigating the possible adverse effect of prenatal exposure to PFCs have reported only results on birth weight. Most of these studies, although not all (34, 38, 39), found that PFOS (13, 37, 40, 41) and PFOA concentrations (19, 20, 37) were inversely related to birth weight, although not all found statistically significant associations, which is expected for small samples. Our population had slightly higher maternal plasma levels of PFOA and PFOS than some other pregnant populations (40, 42, 43), which may indicate differences in time periods of blood drawings or laboratory techniques. There may also be geographic differences in exposure levels.

Factors not included in this study could affect the association between PFCs and the offspring's weight development, the most important being lack of postnatal exposure data. We have shown a strong correlation between prenatal maternal blood levels of PFOA and PFOS and concentrations in cord blood. We expect this correlation to alternate over time when other sources of exposure play a role. Lactation may affect the effect of prenatal exposure by transporting PFC to the child early in life, especially for those who are exclusively breastfed (42), but inclusion of duration of breastfeeding did not produce noteworthy changes in the estimates. This is further supported by a study in rodents, where lactational exposure alone did not produce significant effects in the offspring, but prenatal PFOA exposure altered growth with effects persisting into the postnatal stage (14). One human study also indicated no association between levels of PFOS and PFOA in breast milk and infant weight (44), but the sample was very small ($n = 19$). Because mothers and infants live in the same or similar environment, the postnatal exposure levels may correlate with

prenatal exposure and provide reasonable estimates of postnatal exposure, but future studies should collect longitudinal data on the concentrations of PFCs in children, together with detailed growth measures.

The study has several advantages. Data were from a well-described, nationwide cohort (17), and we used high-standard laboratory techniques to measure the values of PFOS and PFOA. Additionally, although the outcomes were based on self-reported information, the measurements were reliable because health professionals performed the measurements, and the general practitioners in Denmark follow a standard procedure. Furthermore, the mothers did not have to remember the values themselves but could just repeat them from the child's book. Any misclassification would most likely be nondifferential and bias the association toward the null.

In summary, our study suggests that prenatal exposure to PFOS and PFOA may be inversely associated with weight and body mass index in boys during infancy. Furthermore, length did not seem to be associated with prenatal PFC exposure.

ACKNOWLEDGMENTS

Author affiliations: Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen, Denmark (Camilla Schou Andersen, Michael Gamborg, Thorkild I. A. Sørensen); Department of Epidemiology, University of California, Los Angeles, California (Chunyuan Fei, Jørn Olsen); and Department of Epidemiology, Institute of Public Health, University of Aarhus, Aarhus, Denmark (Ellen Aagaard Nohr).

The Danish National Research Foundation donated a major grant and established the Danish Epidemiology Science Centre that created the Danish National Birth Cohort. Additional support was obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustinus Foundation, and the Health Foundation. This study is part of the Danish Obesity Research Centre and has been supported by the Lundbeck Foundation (267/06), the Danish Graduate School in Public Health Science, and the Danish Agency for Science, Technology, and Innovation (271-06-0421).

The 3M Toxicology Laboratory led by Dr. David J. Ehresman performed all laboratory analyses and is acknowledged for its work.

Conflict of interest: none declared.

REFERENCES

1. Jensen AA, Leffers H. Emerging endocrine disrupters: perfluoroalkylated substances. *Int J Androl*. 2008;31(2):161–169.
2. Butenhoff JL, Kennedy GL Jr, Frame SR, et al. The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. *Toxicology.* 2004;196(1-2):95–116.
3. Halldorsson TI, Fei C, Olsen J, et al. Dietary predictors of perfluorinated chemicals: a study from the Danish National Birth Cohort. *Environ Sci Technol*. 2008;42(23):8971–8977.
4. Lau C, Butenhoff JL, Rogers JM. The developmental toxicity of perfluoroalkyl acids and their derivatives. *Toxicol Appl Pharmacol*. 2004;198(2):231–241.
5. Schecter A, Colacino J, Haffner D, et al. Perfluorinated compounds, polychlorinated biphenyls, and organochlorine pesticide contamination in composite food samples from Dallas, Texas, USA. *Environ Health Perspect*. 2010;118(6):796–802.
6. Apelberg BJ, Goldman LR, Calafat AM, et al. Determinants of fetal exposure to polyfluoroalkyl compounds in Baltimore, Maryland. *Environ Sci Technol*. 2007;41(11):3891–3897.
7. Olsen GW, Butenhoff JL, Zobel LR. Perfluoroalkyl chemicals and human fetal development: an epidemiologic review with clinical and toxicological perspectives. *Reprod Toxicol*. 2009;27(3-4):212–230.
8. Grandjean P, Bellinger D, Bergman A, et al. The faroes statement: human health effects of developmental exposure to chemicals in our environment. *Basic Clin Pharmacol Toxicol*. 2008;102(2):73–75.
9. Case MT, York RG, Christian MS. Rat and rabbit oral developmental toxicology studies with two perfluorinated compounds. *Int J Toxicol*. 2001;20(2):101–109.
10. Lau C, Thibodeaux JR, Hanson RG, et al. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. II: postnatal evaluation. *Toxicol Sci.* 2003;74(2):382–392.
11. Lau C, Thibodeaux JR, Hanson RG, et al. Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. *Toxicol Sci.* 2006;90(2):510–518.
12. Luebker DJ, York RG, Hansen KJ, et al. Neonatal mortality from in utero exposure to perfluorooctanesulfonate (PFOS) in Sprague-Dawley rats: dose-response, and biochemical and pharamacokinetic parameters. *Toxicology.* 2005;215(1-2):149–169.
13. Washino N, Saijo Y, Sasaki S, et al. Correlations between prenatal exposure to perfluorinated chemicals and reduced fetal growth. *Environ Health Perspect*. 2009;117(4):660–667.
14. Wolf CJ, Fenton SE, Schmid JE, et al. Developmental toxicity of perfluorooctanoic acid in the CD-1 mouse after cross-foster and restricted gestational exposures. *Toxicol Sci.* 2007;95(2):462–473.
15. Liu C, Du Y, Zhou B. Evaluation of estrogenic activities and mechanism of action of perfluorinated chemicals determined by vitellogenin induction in primary cultured tilapia hepatocytes. *Aquat Toxicol*. 2007;85(4):267–277.
16. Shi Z, Zhang H, Liu Y, et al. Alterations in gene expression and testosterone synthesis in the testes of male rats exposed to perfluorododecanoic acid. *Toxicol Sci.* 2007;98(1):206–215.
17. Olsen J, Melbye M, Olsen SF, et al. The Danish National Birth Cohort—its background, structure and aim. *Scand J Public Health*. 2001;29(4):300–307.
18. Nohr EA, Frydenberg M, Henriksen TB, et al. Does low participation in cohort studies induce bias? *Epidemiology.* 2006;17(4):413–418.
19. Fei C, McLaughlin JK, Tarone RE, et al. Perfluorinated chemicals and fetal growth: a study within the Danish National Birth Cohort. *Environ Health Perspect*. 2007;115(11):1677–1682.
20. Fei C, McLaughlin JK, Tarone RE, et al. Fetal growth indicators and perfluorinated chemicals: a study in the Danish National Birth Cohort. *Am J Epidemiol*. 2008;168(1):66–72.
21. Ehresman DJ, Froehlich JW, Olsen GW, et al. Comparison of human whole blood, plasma, and serum matrices for the determination of perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA), and other fluorochemicals. *Environ Res.* 2007;103(2):176–184.

22. World Health Organization. *Obesity: Preventing and Managing the Global Epidemic*. Geneva, Switzerland: World Health Organization; 2000.
23. Ishibashi H, Ishida H, Matsuoka M, et al. Estrogenic effects of fluorotelomer alcohols for human estrogen receptor isoforms alpha and beta in vitro. *Biol Pharm Bull.* 2007;30(7):1358–1359.
24. Wei Y, Dai J, Liu M, et al. Estrogen-like properties of perfluorooctanoic acid as revealed by expressing hepatic estrogen-responsive genes in rare minnows (*Gobiocypris rarus*). *Environ Toxicol Chem.* 2007;26(11):2440–2447.
25. Biegel LB, Liu RC, Hurtt ME, et al. Effects of ammonium perfluorooctanoate on Leydig cell function: in vitro, in vivo, and ex vivo studies. *Toxicol Appl Pharmacol*. 1995;134(1): 18–25.
26. Olsen GW, Burlew MM, Burris JM, et al. *A Cross-Sectional Analysis of Serum Perfluorooctanesulfonate (PFOS) and Perfluorooctanoate (PFOA) in Relation to Clinical Chemistry, Thyroid Hormone, Hematology and Urinalysis Results from Male and Female Employee Participants of the 2000 Antwerp and Decatur Fluorochemical Medical Surveillance Program*. 3M Company. Final report. October 11, 2001. US EPA Administrative Record, AR-226-1087. Washington, DC: US Environmental Protection Agency; 2001.
27. Melzer D, Rice N, Depledge MH, et al. Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the U.S. National Health and Nutrition Examination Survey. *Environ Health Perspect*. 2010;118(5):686–692.
28. Kennedy GL Jr, Butenhoff JL, Olsen GW, et al. The toxicology of perfluorooctanoate. *Crit Rev Toxicol*. 2004;34(4): 351–384.
29. Loveless SE, Finlay C, Everds NE, et al. Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO). *Toxicology.* 2006;220(2-3):203–217.
30. Peraza MA, Burdick AD, Marin HE, et al. The toxicology of ligands for peroxisome proliferator-activated receptors (PPAR). *Toxicol Sci.* 2006;90(2):269–295.
31. Sohlenius AK, Andersson K, Bergstrand A, et al. Effects of perfluorooctanoic acid—a potent peroxisome proliferator in rat—on Morris hepatoma 7800C1 cells, a rat cell line. *Biochim Biophys Acta*. 1994;1213(1):63–74.
32. Gilliland FD, Mandel JS. Serum perfluorooctanoic acid and hepatic enzymes, lipoproteins, and cholesterol: a study of occupationally exposed men. *Am J Ind Med*. 1996;29(5): 560–568.
33. Nelson JW, Hatch EE, Webster TF. Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general U.S. population. *Environ Health Perspect*. 2010;118(2):197–202.
34. Olsen GW, Burris JM, Burlew MM, et al. Epidemiologic assessment of worker serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations and medical surveillance examinations. *J Occup Environ Med*. 2003;45(3): 260–270.
35. Steenland K, Fletcher T, Savitz D. *Status Report: Association of Perfluorooctanic Acid (C8/PFOA) and Perfluoroctanesulfonate (PFOS) with Lipids Among Children in the Mid-Ohio Valley.* Morgantown, WV: West Virginia University; 2009. (http://www.c8sciencepanel.org/pdfs/Status_Report_C8_and_lipids_in_children_28Oct2009.pdf).
36. Steenland K, Tinker S, Frisbee S, et al. Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant. *Am J Epidemiol*. 2009;170(10):1268–1278.
37. Apelberg BJ, Witter FR, Herbstman JB, et al. Cord serum concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in relation to weight and size at birth. *Environ Health Perspect*. 2007;115(11):1670–1676.
38. Grice MM, Alexander BH, Hoffbeck R, et al. Self-reported medical conditions in perfluorooctanesulfonyl fluoride manufacturing workers. *J Occup Environ Med*. 2007;49(7): 722–729.
39. Nolan LA, Nolan JM, Shofer FS, et al. The relationship between birth weight, gestational age and perfluorooctanoic acid (PFOA)-contaminated public drinking water. *Reprod Toxicol*. 2009;27(3-4):231–238.
40. Inoue K, Okada F, Ito R, et al. Perfluorooctane sulfonate (PFOS) and related perfluorinated compounds in human maternal and cord blood samples: assessment of PFOS exposure in a susceptible population during pregnancy. *Environ Health Perspect*. 2004;112(11):1204–1207.
41. Stein CR, Savitz DA, Dougan M. Serum levels of perfluorooctanoic acid and perfluorooctane sulfonate and pregnancy outcome. *Am J Epidemiol*. 2009;170(7): 837–846.
42. Kärrman A, Ericson I, van Bavel B, et al. Exposure of perfluorinated chemicals through lactation: levels of matched human milk and serum and a temporal trend, 1996-2004, in Sweden. *Environ Health Perspect*. 2007;115(2): 226–230.
43. Midasch O, Drexler H, Hart N, et al. Transplacental exposure of neonates to perfluorooctanesulfonate and perfluorooctanoate: a pilot study. *Int Arch Occup Environ Health*. 2007;80(7): 643–648.
44. So MK, Yamashita N, Taniyasu S, et al. Health risks in infants associated with exposure to perfluorinated compounds in human breast milk from Zhoushan, China. *Environ Sci Technol*. 2006;40(9):2924–2929.