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## **Prenatal Exposure to Perfluoroalkyl Compounds and Body Fatness in Girls**

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## Abstract

Background: Perfluoroalkyl compounds (PFCs) are chemicals used to make coatings that resist stains, grease and water. Human exposure occurs via contaminated air, food and water.

Previous analyses have reported an inverse association between prenatal PFC serum concentrations and birth weight.

Methods: Data from a prospective birth cohort study, the Avon Longitudinal Study of Parents and Children in the United Kingdom, was used to examine the association between *in utero* PFC exposure and body fatness in girls at age 9 years. Maternal serum samples, collected during pregnancy in 1991–1992, were analyzed for perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorohexane sulfonate (PFHxS) and perfluorononanoate (PFNA). Body composition at age 9 was measured by dual x-ray emission absorptiometry (DXA) and percent total body fat (%BF) calculated. Multivariable linear regression was used to model associations between each PFC and %BF after adjustment for covariates including mothers' educational status, pre-pregnancy body mass index and smoking (for PFNA only).

Results: Among 359 girls, median (intra-quartile range – IQR) %BF was 27.5 (IQR 21.7-34.6). Median (IQR) concentrations (all ng/ml) were 3.7 (2.9-4.8) for PFOA, 19.8 (15.0-25.3) for PFOS, 1.6 (1.3-2.2) for PFHxS, and 0.5 (0.4-0.7) for PFNA. In the main effects models, maternal PFC concentrations were not significantly associated with daughters' %BF; however, we observed some differences in the associations between maternal PFC concentrations and daughters' %BF by mothers' educational status. For PFHxS, %BF significantly increased by 3.0% ( $p=0.04$ ) and 3.3% ( $p=0.03$ ) for each one unit (ng/ml) increase among girls with mothers in the highest and middle education groups, respectively, but decreased by 3.1% ( $p=0.04$ ) for the corresponding change among girls with mothers in the lowest education group. Similar results were observed for PFOS and PFOA.

Conclusions: Prenatal exposure to some PFCs was associated with increased body fatness in girls but only after consideration of maternal education status.

## Introduction

In 2012, the prevalence of overweight and obesity among girls aged 2-10 years in the United Kingdom (UK) was estimated at 22.8% (1, 2). Increased dietary energy intakes and sedentary behaviors conducive to positive energy balance are well-known risk factors for obesity.

Emerging evidence suggests that there may also be mechanisms through which early life (e.g., in utero, infancy) exposure to a subclass of environmental endocrine-disrupting chemicals (EDCs) may contribute to altered growth and development with long-term effects on recognized risk factors for chronic disease (3-5). For example, certain EDCs could disrupt hormonally regulated ingestive behaviors or metabolic sequelae resulting in a metabolic phenotype with a predisposition to gain weight (4). Excess weight during childhood is associated with adverse effects on circulating blood lipids, measures of insulin resistance, and elevated blood pressure known to persist into adulthood and predict adult cardiometabolic risk factors and chronic disease (6-9).

Perfluoroalkyl compounds (PFCs) are synthetically-made chemicals used as surfactants and surface coatings to decrease staining and sticking. PFCs are used commercially as lubricants, paper and textile coatings, in polishes, and in food packaging materials. Exposure to PFCs is widespread; detectable levels were found in more than 98% of Americans who participated in the U.S. National Health and Nutrition Examination Survey (NHANES) in 2003-2004 (10). Because of their persistence and tendency to bioaccumulate, there is growing interest in the relationship between exposure to PFCs, especially during critical windows of susceptibility like early life, and health effects later on (11). Exposure to PFCs during development could permanently influence risk for chronic disease later in life through long-term effects on risk factors such as weight gain and body fatness (3).

Prenatal exposure to PFCs has been linked with smaller size at birth (12-14). In follow-up analyses of girls at 20 months of age, those with higher prenatal serum concentrations of perfluorooctane sulfonate (PFOS) were heavier despite being smaller at birth (12). The goal of

the present research was to assess the role of prenatal exposure to PFCs on adiposity measured in older girls. Our analyses used existing prospectively collected data from the Avon Longitudinal Study of Parents and Children (ALSPAC) to evaluate the association between maternal prenatal serum concentrations of PFCs and body fatness measured by dual energy absorptiometry (DXA) in girls at age 9 years. To date no other study has evaluated the association between prenatal PFC exposure and body composition measured by DXA in school-age girls.

## **Methods**

### ***Population***

The ALSPAC is a prospective birth cohort in the United Kingdom (UK) that enrolled 14,541 pregnant women residing in Avon, UK with expected delivery dates between April, 1991 and December, 1992 (15, 16). The goal of ALSPAC was to study the effects of genetics, lifestyle factors and the physical environment on the health, behavior and development of children. The current study includes a subset of mother-daughter dyads from the parent study selected for an ancillary study of maternal serum concentrations of environmental exposures and daughter's puberty characteristics (17). To be considered, girls had to have at least two pubertal assessments to allow for classification of age at menarche. The ancillary study included all girls with early menarche (<11.5 years; n=218) and a random sample of girls without early menarche  $\geq 11.5$  years (n=230)). Informed consent was provided at the time of enrollment by the mothers. Human subjects' protection and ethical approval was provided by the ALSPAC Law and Ethics Committee, the Local Research Ethics Committees and the Centers for Disease Control and Prevention (CDC) Institutional Review Board.

### ***Data Collection***

Mothers reported other demographic (e.g., age, educational status, race/ethnicity), health (e.g., prepregnancy body mass index - BMI kg/m<sup>2</sup>) and lifestyle (e.g., smoking status) information for

themselves at enrollment and later on for their children. Birth characteristics, including weight (grams), length (cm), and gestational age (wks) were abstracted from medical records. Since enrollment, detailed information has been collected on the children using parent or guardian- and self-reported questionnaires that address growth and development, psychological, social and health behaviors, and a variety of health-related outcomes. Trained research assistants reviewed these records with mothers as they were completed. In addition, periodic clinical assessments have collected detailed physiological data, cognitive information and biological samples (15, 18, 19). Measures of total and regional body fat, lean mass and bone mass were made biennially using a Lunar Prodigy DXA scanner (GE Medical Systems Lunar, Madison, WI, USA) beginning at age 9 years. At age 9 a total of 359 girls whose mothers had provided prenatal sera for PFC measurements also contributed DXA scans for assessment of body fatness. The ALSPAC website contains details of all the data that are available through a fully searchable data dictionary available at: <http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>.

### ***Laboratory Analyses***

At enrollment (1991–1992), mothers were asked to provide a single prenatal blood sample which was processed, frozen, and stored for later analysis. Median gestational age at collection was 15 weeks with an interquartile range of 10-28 weeks. Perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS) and perfluorononanoate (PFNA) were measured in 448 stored maternal serum samples from mothers of girls by the National Center for Environmental Health laboratories of the CDC (Atlanta, GA) as described elsewhere (12). Briefly, sera samples were analyzed by on-line solid phase extraction coupled to isotope dilution high-performance liquid chromatography-tandem mass spectrometry. The limit of detection for PFNA was 0.08 ng/mL, for PFOA and PFHxS, 0.10 ng/mL and for PFOS 0.20 ng/mL. Laboratory analyses included low-concentration and high-concentration pooled

standards, reagent blanks, and study samples. Precision of the measurements for the four PFCs was 8–13%.

### ***Statistical Analyses***

The laboratory data were plotted and examined for outliers. Measures of central tendency and distributions were calculated for demographic characteristics of the mother-daughter dyads. Our analyses were conducted on a sample of girls previously selected for a nested case-control study to evaluate the association of PFCs with early age at menarche. PFC concentrations did not appear to be associated with age at menarche in this sample (17); however, to account for the sampling selection probabilities we conservatively constructed stratum-weighted linear regression models to account for the sampling scheme used for participant selection, weighting (weight=15.1) the girls who attained menarche at 11.5 years or older (a random sample of the girls who attained menarche  $\geq$  11.5 years of age). These regression models were used to evaluate the associations of girls' body fatness (%BF) at 9 years of age with each PFC after adjustment for maternal pre-pregnancy BMI (continuous) and educational status (low, medium, high). In this analysis, not attaining any General Certificates of Secondary Education (GCSEs, at 16 years of age) was coded as "low" educational status, obtaining GCSEs as "medium" and completing GCSEs with additional education (e.g., University) was considered "high." PFNA models were also adjusted for maternal smoking status (yes/no any prenatal). A number of other potential confounders were considered including maternal age (continuous), race (Caucasian v. other), parity (continuous), gestational age at blood collection (continuous), previous live birth (yes/no), daughters' preterm delivery (<37 weeks yes/no), birthweight (continuous, gm), breastfed (any v. none), activity level in childhood (very active v. not), exact age at DXA scan, and girls dietary energy and macronutrient intake at age 7 (continuous total energy, percent energy from fat, protein, and carbohydrate). None of these additional variables improved model fit or led to meaningful changes in the relationship between body fatness and PFCs; thus, they were not retained in the final models. Lastly, we considered potential effect

modification by maternal pre-pregnancy BMI, smoking and educational status by including these variables and their cross-product terms with each of the PFCs in their respective models. Statistical analyses were performed using Statistical Analysis Systems (SAS version 9.3) software.

## Results

Table 1 presents sample demographic characteristics, median maternal prenatal PFC serum concentrations and median percent body fatness for daughters. Overall, the sample was primarily Caucasian (>90% of mothers and girls). The majority (64%) of mothers were considered normal weight prior to pregnancy and nearly half of mothers reported a previous live birth. There were few girls who were preterm or of low birthweight. Of the PFCs measured, concentrations of PFOS were the highest (median 19.8; interquartile range (IQR) = 15.0–25.3 ng/ml) and PFNA concentrations were the lowest (median 0.5; IQR = 0.4–0.7). Spearman correlation coefficients between the PFCs ranged between 0.25 for PFNA and PFHxS to 0.71 for PFOA and PFOS (data not presented). Median %BF for daughters was 27.5 (IQR = 21.7–34.6).

In multivariable regression analyses (Table 2) mothers' PFCs were not associated with daughters' %BF overall (main effects); however, we observed some differences in the associations between maternal PFC concentrations and daughters' %BF by mothers' educational status. Daughters' %BF increased by 3% for each one unit increase in mothers PFHxS among girls with mothers in the highest and middle education groups, but was associated with a similar percent decrease among girls with mothers in the lowest education group. A similar pattern of association was observed for PFOA with significant results only for the middle education group. There were no significant associations observed for PFOS. Lastly, among less-educated mothers, each one unit increase in PFNA was associated with a 12.7% increase in %BF among daughters. Mothers' pre-pregnancy BMI and smoking status did not

significantly modify the associations between maternal PFC concentrations and daughters' %BF.

## **Discussion**

Our results suggest that prenatal exposure to some PFCs is associated with increased body fatness among this cohort of British girls but only after consideration of maternal education status. Obesity is a multifactorial and complex disease and a number of dynamic genetic, environmental, lifestyle and social interactions likely contribute to its etiology (20). It is plausible that educational status is serving as a proxy for some other factor(s) that influence the associations between maternal PFC concentrations and %BF among daughters. For example, educational attainment is a well-known marker for socioeconomic status where disparities have been observed for maternal health-related behaviors and childhood obesity (21, 22). In addition, disparities may exist for exposures to PFCs. In the early 1990's when the ALSPAC prenatal blood collection took place, one important source of PFC exposure is thought to have occurred through contact with new furnishings and carpets in home and office settings; thus, participants of higher socioeconomic status might have experienced the highest exposures. Interestingly, concentrations of maternal PFCs in this data tend to be positively associated with educational status (23-25). In this data, daughters of less educated (lower socioeconomic status) moms may have experienced more complex dynamic combinations of environmental, lifestyle and social stressors over time (20). Maternal education status is generally positively associated with diet quality during pregnancy and childhood but inversely associated with childhood obesity (22, 26). Families with more limited resources experience greater variability in some well-known contributors to childhood adiposity including diet composition, diet quality and acute and chronic food security which are challenging to measure accurately (i.e., self-reported) in epidemiologic research (27). This could at least in part contribute to the inconsistencies we observed by maternal educational status.

Previous observational epidemiologic studies that have examined the role of PFCs in childhood weight have yielded divergent results overall and within studies results have lacked consistency across the PFCs measured, not unlike the results in the current study. Andersen and colleagues (28) evaluated the role of prenatal exposure to PFOA and PFOS on measures of body fatness in 811 7-yr old children whose mothers participated in the Danish National Birth Cohort during 1996–2002. In contrast to the ALSPAC population, PFOA and PFOS plasma concentrations were not associated with lower weight in infancy in the Danish cohort (29). Similarly, maternal plasma PFCs were not significantly associated with BMI and waist circumference among 7-yr old girls or boys or in the group as a whole. It is noteworthy that both PFOA (median 5.3 ng/mL) and PFOS (median 33.8 ng/mL) concentrations were higher in Danish prenatal samples than we observed in ALSPAC (Table 1). Halldorsson et al. (30) assessed the association between prenatal PFC serum concentrations and weight among 665 offspring (n=320 males; 345 females) of mothers recruited into the Aarhus Denmark birth cohort (1988-1989). Median maternal PFC concentrations in this study were similar to ours (Table 1): PFOA was 3.7 ng/mL, PFOS was 21.5 ng/mL, and PFNA was 0.3 ng/mL. In the Aarhus study maternal PFOA concentrations were positively and significantly associated with BMI and waist circumference among females at 20 years of age. Similar, but weaker, associations were observed for PFOS and PFNA among girls. None of the PFCs were associated with BMI or waist circumference among males (30). Heyer et al. (31) analyzed PFOA and PFOS from the sera of 1022 pregnant women from Greenland and the Ukraine enrolled in the INUENODO cohort between 2002–2004. Median concentrations of maternal PFOA and PFOS were higher among the Greenland sample, (median PFOA=1.8 ng/mL; median PFOS 20.2 ng/mL) and more similar to our population (Table 1), than those from the Ukraine sample (median PFOA=1.0 ng/mL; median PFOS=5.0 ng/mL). The investigators reported adjusted relative risk (RR (95% CI)) of offspring overweight (defined as >85 percentile for age and sex) and unfavorable offspring waist-to-height ratio (>0.5) for continuous (natural log transformed) and tertiles of

PFCs between ages 5–9 years. In country-specific and in pooled analyses, neither PFOA nor PFOS was significantly associated with offspring risk of overweight (31). In the pooled analysis, continuous PFOS concentration was positively associated with offspring waist-to-height ratio (RR=1.38; CI=1.05-1.82); however, in gender-stratified analyses results were statistically significant only for girls (RR=1.54; CI=1.06-2.23) and not boys (RR=1.24; CI=0.82-1.87). There were no statistically significant findings for the association of tertiles of maternal PFCs with youth waist-to-height ratios (31). Lastly, in the Cincinnati-based HOME Study, Braun and colleagues (32) evaluated associations of prenatal PFC concentrations (PFOA, PFOS, PFHxS and PFNA) with BMI, waist circumference, and percent body fat (measured by a Tanita body fat monitor) among a modestly sized sample of 8-year old children of both genders (n=204). Median prenatal PFOA concentration in HOME was 5.3 ng/mL, more than 1.5 times as high as in our population (median 3.7 ng/mL). This study reported positive associations between PFOA and BMI z-score trajectories, waist circumference and percent body fat. Results were not reported by gender; however, the results stated that gender did not modify the associations. No associations were observed for the other PFCs measured (PFOS, PFHxS and PFNA). The investigators noted that their study was limited by the use of less-refined measures of body fatness and that future studies should take advantage of more comprehensive measures such as DXA (32).

In a recent review, Vandenberg and colleagues (33) discuss mechanisms for a variety of observed responses to low dose exposure to endocrine disrupting chemicals. Prenatal PFC exposure might influence childhood body fatness among girls through a number of potential mechanisms (3, 5, 34). According to a recent Scientific Statement on Endocrine-Disrupting Chemicals (EDCs) issued by the Endocrine Society (35), EDCs have broad effects on numerous endocrine endpoints *in vivo* and may act through an array of mechanisms including actions on estrogen and androgen receptors and through thyroid effects. In animal models, a growing body of research suggests that exposure to EDCs can increase the number and size of

adipocytes, alter insulin metabolism, and disrupt energy balance (36). While the molecular mechanisms involved are unclear, some research suggests that EDCs can interfere with epigenetic programming of gene regulation through activation of fat-regulating nuclear receptors like peroxisome proliferator-activated receptor gamma, which can lead to weight gain (37-39). Other potential mechanisms could include effects on neurocognitive development that could alter the processing of sensory information related to ingestive behaviors throughout life (40).

There are a number of strengths to our analyses. All the data for the present study were collected prospectively by trained staff under tightly controlled conditions. PFCs were measured at the National Center for Environmental Health laboratories of the CDC, the laboratory that measures PFCs for NHANES. Concentrations of PFCs in the prenatal samples in our study are similar to those reported in recent analysis of samples from the 2009–2010 NHANES; thus, our results are potentially of relevance to current U.S. populations. Body fatness (composition) was measured by DXA which provides a more accurate estimate of fat mass than BMI or waist circumference (41). There are also some potential limitations. PFCs were measured only once during pregnancy and daughters' PFC concentrations measured postnatally are not available. Generalizability of our findings was reduced by the demographic characteristics (mainly Caucasian) and geography (only UK) of our cohort. However, concentrations of PFCs in the prenatal samples in our study are similar to those reported in the United States in the 2009–2010 NHANES (42). Our analyses were conducted on a sample of mother-daughter dyads selected for an ancillary study of pubertal development; weighted linear regression models were used to adjust for the sampling scheme. A subset of the daughters included in the ancillary study completed DXA scans for the assessment of body fatness. If the girls included in our analyses were not representative of all ancillary study participants or of the parent study then our results could be biased. However, we do not believe that selection bias played an important role in our findings. As reported previously, maternal characteristics for girls included in the ancillary sample were similar to the group of girls enrolled in the cohort (12) and based on the

available data for characteristics of mothers and daughters, our sample with complete data for both prenatal PFCs and youth DXA scans was representative of the overall ancillary sample. Finally, similar to previous investigations, our results do not show a consistent pattern of association across the PFCs measured.

## **Conclusions**

In conclusion, in this British cohort we did not observe an overall association between maternal PFC exposure and %BF among girls. Prenatal exposure to some PFCs was associated with increased body fatness among girls, but only after consideration of maternal education status.. The role of environmental chemicals, like PFCs, in the development of overweight and obesity at different life stages is an important topic of emerging research and these results warrant additional follow-up.

**Table 1. Sample Characteristics for Mothers of Girls and Girls at 9 Years of Age with PFCs and DXA (n=359)**

<b>Variable</b>	<b>N</b>	<b>Median</b>	<b>IQR</b>
PFOA (ng/ml)	359	3.7	(2.9, 4.8)
PFOS (ng/ml)	359	19.8	(15.0, 25.3)
PFHxS (ng/ml)	359	1.6	(1.3, 2.2)
PFNA (ng/ml)	358	0.5	(0.4,0.7)
Gestational age at blood collection (wks.)	359	15	(10, 28)
Maternal age at collection (yrs.)	359	28.8	(25.6,32.1)
Girls DXA-derived body fat at age 9 (%)	359	27.5	(21.7, 34.6)
Girls BMI Z-Score at age 9	328	0.68	(-0.06,1.47)
Girls dietary intake at age 7	340		
Energy (kcal)		1649	(1426, 1857)
Fat (% energy)		36.7	(33.5, 39.7)
Carbohydrate (% energy)		53.5	(50.0, 57.1)
Protein (% energy)		13.0	(11.5, 14.5)
<b>Variable</b>	<b>N</b>	<b>%</b>	
Maternal prepregnancy BMI (kg/m <sup>2</sup> )			
Underweight (<18.5)	16	4	
Normal (18.5-24.9)	229	64	
Overweight (25-29.9)	54	15	
Obese (≥30)	25	7	
Missing	35	10	
Maternal education			
Low	61	16	
Medium	115	32	
High	170	47	
Missing	13	4	
Maternal race / Girls' race			
Caucasian	336 / 332	94 / 92	
Other	10 / 13	3 / 4	
Missing	13 / 14	4 / 4	
maternal smoking (#, % any prenatal)	72	20	
Previous life birth (#, % yes)	176	49	
Preterm delivery (#, % < 37 wks.)	12	3	
Low birth weight (#, % <2500 grams)	15	4	
Breastfed (#, % any)	278	77	

Girls activity level (#, % very active)	173	48
Menarche by age 9 (#, %yes)	4	1.1

**Table 2. Regression coefficients ( $\beta$ ) for the relationship between perfluoroalkyl compounds and DXA-derived total body fatness (%) overall and by educational status (low, medium, high)**

Analyte	$\beta$	95% CI	p-value
PFOS (ng/ml)			
Overall**	-0.07	-0.16, 0.02	0.12
Low Education	0.02	-0.18, 0.22	0.81
Medium	0.07	-0.20, 0.33	0.62
High	-0.21	-0.45, 0.02	0.08
PFOA (ng/ml)			
Overall**	-0.30	-0.76, 0.16	0.20
Low Education	-1.03	-2.35, 0.29	0.13
Medium	2.44	0.68, 4.20	0.007
High	0.45	-0.97, 1.87	0.54
PFHxS (ng/ml)			
Overall**	-0.06	-0.21, 0.09	0.47
Low Education	-3.09	-6.04, -0.13	0.04
Medium	3.26	0.28, 6.24	0.03
High	3.00	0.04, 5.96	0.04
PFNA (ng/ml)			
Overall**	1.71	-1.29, 4.71	0.26
Low Education	12.73	0.11, 25.36	0.04
Medium	-9.30	-22.91, 4.31	0.18
High	-12.61	-25.67, 0.45	0.06

\*Models adjusted for sampling design, prepregnancy body mass index (BMI kg/m<sup>2</sup>) and maternal educational status. PFNA models were also adjusted for maternal smoking status.

\*\*Main effect model without the interaction terms.

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